# MEDICAL TECHNOLOGIES
Assessment and Choice

## EDITORIAL COLUMN
**Opening Remarks**

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Dear colleagues and friends!

There is the first English-language supplement issue of the journal “Medical Technologies. Assessment and Choice” in front of you, which contains selected articles published in the journal in 2010—2011. The journal is dedicated to development and implementation of the health technology assessment (HTA) principles in the Russian Federation and the former Soviet Union.

At the moment medical environment is overwhelmed with a vast amount of data relating to drugs, new methods of treatment and diagnostics, various advices and recommendations. It is becoming more and more difficult for physicians, researchers, managers and other experts not to be drowned in the ocean-wide amount of information. The task of learning how to deal with information resources and how to adopt them to everyday practice is rising now in front of the global medical community. For today we discuss these issues in our journal.

The system of HTA has been widely used outside of Russia and finally it is also inevitably coming to us. Over 60 countries have established agencies and research centers for HTA to optimize and reallocate state funds rationally and increase decision-making transparency. It is necessary to form certain game rules so that mutual understanding between experts, representatives of regulatory bodies and business authorities will be reached. From one side these rules should determine parameters of submitting information about the new technology, from another side — should include understandable and transparent assessment criteria. Our journal is devoted to this problem: how to make the State to take into consideration the arguments of the practitioners’ and experts’ communities.

In the modern world in the healthcare decision making process there is a tendency toward involvement of more experts as well as members of the patient associations and business representatives. All this requires not only knowledge of the subject but also development and implementation of the specific decision making tools. Some technologic approaches and their role in the diversified and complex decision making process are also described in our journal.

The main journal’s objective is to help all healthcare specialists to understand the necessity of the specially developed approaches to the new technology assessment and providing the most efficient conditions for their implementation into practice. What kind of approaches and how they function — you can read about it in our journal.

At present there is a lot of discussion about social and economic impact of diseases, methods of evidence-based medicine and pharmacoconomics, real-life patient care and pharmacoepidemiology in Russia. All of this can be (and must be) considered as tools for the development of objective decisions regarding HTA. What kind of tools, when and how they should be used — we discuss all these issues in the journal.

Systematic approaches to organizing medical technology assessment research and their separate elements, review of the novel technologies and their role in the public health system, experience of foreign countries and leading Russian regions — this is an incomplete list of the topics represented in the journal.

The journal is aimed at healthcare administrators, representatives of a legislative branch in the field of healthcare, managers and specialists of medical and pharmaceutical organizations, representatives of the pharmaceutical and medicine manufacturing industry, researchers, students, insurance and investment companies.

We invite you to participate in this project and to submit results of your research, reports on the research methods and administration techniques in healthcare, reviews — in one word, everything regarding the instruments and elements of the HTA system.

We hope for your consideration and interest — argue or agree with us, write and read.

We wish you all the best and a great success for all of us!

Sincerely,
Editorial Board
Evidence-Based Medicine

Indirect Comparisons in Health Technology Assessment

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The article describes the general aspects of indirect comparison of medical technologies, a relatively new method of generating evidence in decision-making process. The use of the method is illustrated by indirect comparison of pegylated interferons in the treatment of hepatitis C.

KEYWORDS: indirect comparisons, evaluation of medical technologies, hepatitis C, pegylated interferon.

A medical practitioner faces the daily task of choosing the most appropriate treatment for each patient, including prescription of appropriate medicinal drugs. This is not a matter of following practical guidelines that offer algorithms for making the right decision given the type of disease, its severity, individual characteristics of the patient, etc, but rather of choosing one out of several treatments indicated to the same group of patients. For instance, there are more than ten ACE inhibitors available in clinical practice, and this treatment is the “gold standard” of antihypertensive therapy. But which of them should be prescribed to a patient with newly diagnosed hypertension? With co-morbidities? To patients over 70?

Investors providing financial resources for a particular medical technology often ask themselves the same questions. The scientific approach to making such decisions is to perform a clinical and economic analysis, which compares two or more treatments (e.g. two drugs) both in terms of their clinical efficacy and safety, and in terms of their cost. Considering the increasing importance of clinical and economic studies for health technology assessment (inclusion of drugs in limited lists, implementation of new technologies, etc), the demand for comparative studies of drug efficacy is also growing apace.

High-quality randomized controlled trials (RCT) are widely recognized as the best source of evidence for health technology assessment, since they produce the most objective data applicable above all to clinical practice. However, different RCTs that investigate the same drugs in the same patient population may sometimes lead to different or even conflicting conclusions regarding the effect size or even its direction. Using the method of meta-analysis, it is possible to pool (combine through a statistical analysis) the results of several clinical trials and thus obtain an integrated estimate of the efficacy of a particular drug.

Despite this, often the existing RCTs and meta-analyses are insufficient to solve clinical or clinico-economic tasks. The main reason is that for the most part RCTs compare only two drugs, while more than two medications may be used in clinical practice for the treatment of the same disease, and in this case it may be of interest to perform a type of comparison which is not possible in head-to-head clinical trials (Fig. 1-1). Moreover, even now a new drug is usually compared in clinical trials to placebo or standard therapy, while a comparison with the competing new drugs are much less common than practical considerations would lead us to expect. The reasons are quite obvious: practically all clinical trials are sponsored by manufacturers, who are not interested in comparing their product with potential competitors.

The second problem is that the results of completed RCTs may refer to a population of patients different from the group for which a medical technology is evaluated, for example if the efficacy of drugs has been compared in middle-aged patients, while the issue discussed is their use in the elderly.

The third serious problem concerns the quality of evidence. The methodological rigor of clinical trials continues to be debated, and unfortunately, the available results may not always be reliable. The same problem arises with regard to meta-analyses. How valid are the results of RCTs that they include? How far are their samples compatible? The often wide variation in these characteristics has spurred ongoing criticism of meta-analysis as a method.

If there are no clinical trials that directly compare several drugs, today the most common solution is to simply compare the effect sizes of different RCTs. However, this is incorrect, since this approach deprives RCTs of their
RESEARCH. ANALYSIS. EXPERTISE

The result of any RCT is always relative (versus some control — placebo, standard therapy, etc) and is composed of the specific effect (treatment effect) and non-specific effects (placebo effect, Hawthorn effect, etc). Even if we assume that the calculated difference in the effect size might correspond to that discovered in a direct comparative study, it is equally important to know whether this difference is statistically significant. The method described above cannot answer this question.

The method of adjusted indirect treatment comparison (ITC) uses a common control in order to obtain a scientifically sound estimate of the relative efficacy of two drugs that have not been directly compared in clinical trials [1]. The common control may be placebo or standard (basic) therapy. Fig. 1-2 illustrates the situation when there are studies comparing interventions A vs C and B vs C, while the researcher is interested in comparing A with B. It may be noted that A-C and B-C comparisons may use the results of either single RCTs or meta-analyses (that pool the results of high-quality clinical trials).

This is the most straightforward way of performing an indirect comparison, but this method is applicable to considerably more complex combinations of clinical trials [2].

The method of indirect comparison produces robust results, but only provided that the correct methodology is used [3].

As with meta-analysis, indirect comparison requires that the clinical trials used for the comparison should be equally valid and generalizable. The most difficult part of indirect comparison is precisely to decide whether these conditions are met.

Here are the main stages of an indirect comparison:

Stage I — searching for publications with pre-defined search parameters.

Stage II — compiling the set of studies for the subsequent analysis using inclusion/exclusion criteria.

Stage III — analyzing the heterogeneity of included studies/meta-analyses, considering the following:

a) whether the study samples match in terms of gender, age, severity and stage of the disease, etc (if they do not match perfectly, it must be decided whether the differences might affect the absolute or relative effect size),

b) whether the analyzed studies used the same dosage, administration method, etc,

c) whether the same model of meta-analysis was used (if two meta-analyses are compared), i.e. whether fixed or random effects models were used, etc.

So far there are no formal criteria of assessing the heterogeneity of studies, and this issue continues to be debated [4].

Stage IV — calculation of the relative effects $d_{AC}$ and $d_{BC}$ in direct studies A-C and B-C, respectively (point and interval estimates of the effect); normally the analyzed effects are odds ratios, relative risk, the difference in continuous effects magnitude, or hazard ratios (in survival analysis).

Stage V — calculation of the indirect relative effect $d_{AB} = d_{AC} - d_{BC}$ (point and interval estimates). It must be noted that this procedure does not forfeit the benefits of randomization, since the relative effects in direct comparisons are calculated before the synthesis of effects. Both probability and Bayesian approaches are possible.

Stage VI — sensitivity analysis of the results applied to studies that are included in the analysis but are methodologically less rigorous.

Stage VII — summary of the indirect comparison. It can be prepared in accordance with the guidelines of the British National Institute for Health and Clinical Excellence, “Guide to the methods of technology appraisal”, June 2008, sections 5.3.13—5.3.22, and with [2, 4].

Thus, even if there are no direct comparative studies of two drugs, the method of indirect comparison produces the necessary evidence with equally high or sometimes even superior validity [5]. Often a situation arises when both direct and indirect comparisons are employed simultaneously. This is referred to as mixed treatment comparison (MTC, Fig. 1-3). In this case the results of indirect comparison may be included in meta-analysis to check the robustness of its evidence, which makes it even more reliable.

AN ILLUSTRATION OF THE EFFECTIVENESS OF INDIRECT COMPARISONS

To illustrate the method of indirect comparison, we will use the example of the relatively new treatments for chronic hepatitis C — pegylated interferons (PegIF). At present there are two such drugs: PegIF-α2a (Pegasys®,
Inclusion Criteria in the Clinical Trials of Pegylated Interferons

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>M. P. Manns et al., 2001</th>
<th>M. W. Fried et al., 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral load</td>
<td>Hepatitis C RNA “+” in PCR array</td>
<td>Hepatitis C RNA &gt;2000 in PCR array</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Hepatitis C based on liver biopsy 6 months prior to study</td>
<td>Hepatitis C based on liver biopsy 1 year prior to study</td>
</tr>
<tr>
<td>ALT</td>
<td>Above the upper limit of normal</td>
<td>—</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&gt;12 g/dl for females and &gt;13 g/dl for males</td>
<td>—</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>&gt;1500 m³</td>
<td>—</td>
</tr>
<tr>
<td>Platelets</td>
<td>&gt;90 • 10³/μl</td>
<td>&gt;100 • 10³/μl</td>
</tr>
<tr>
<td>Plasma creatinine</td>
<td>No more than 1.5 of normal level</td>
<td>Normal</td>
</tr>
<tr>
<td>Plasma albumin and bilirubin</td>
<td>—</td>
<td>Normal</td>
</tr>
<tr>
<td>Additional criteria</td>
<td>No other liver diseases, no HIV, no concomitant and/or uncontrolled somatic and mental disorders</td>
<td>—</td>
</tr>
</tbody>
</table>

Hoffmann-La Roche) and PegIF-α2b (Pegintron®, Shering-Plough). Given that both the prevalence of this disease and the therapy cost are high, it is highly desirable to find out whether the two drugs are equivalent or whether one has a superior clinical efficacy. This issue has long been debated, with the main evidence provided by two RCTs performed by M.G. Rumi et al. and A. Ascione et al., which compared the efficacy of these two drugs [6, 7]. However, these studies have a number of limitations. For example, the duration of treatment varied depending on the viral genotype and was 48 weeks for genotypes 1 and 4, but only 24 weeks for genotypes 2 and 3; at the same time, the studies were designed to detect overall difference in the whole study population, and the instructions for use of both medications recommend the same duration of treatment, regardless of the viral genotype. This issue was finally solved by the larger and better designed IDEAL study, but the method of indirect comparison would have served equally well [8]. Let us demonstrate this.

We have discovered two published RCTs that compared PegIF-α2b (M.P. Manns et al.) and PegIF-α2a (M. W. Fried et al.) with the standard IF-α2b (Intron A®, Shering-Plough), which can thus be used as the common control in an indirect comparison [9, 10]. Both studies have an identical design of open RCTs. Judging by the dates of publication (2001 and 2002, respectively), it may be assumed that they were conducted around the same time, which is also important. The duration was 48 weeks of active treatment plus 24 weeks of observation. The treatment regimen was PegIF-α2b 1.5 g/kg s/c once/week + ribavirin 800 mg/day, or IF-α2b 3 ml units s/c 3 times per week + ribavirin 1000 mg/day for weight <75 kg or 1200 mg for weight >75 kg in the RCT conducted by M.P. Manns et al. In the RCT conducted by M.W. Fried et al., it was PegIF-α2a 180 g s/c once/week + ribavirin 1000 mg/day for weight <75 kg or 1200 mg for weight >75 kg, or IF-α2b 3 ml units s/c 3 times per week + ribavirin 1000 mg/day for weight <75 kg or 1200 mg for weight >75 kg. In both studies the main efficacy criterion was the rate of sustained virological response (SVR), defined as undetectable blood levels of hepatitis C virus RNA in the end of the observation period. Both studies had sufficient power to assess the efficacy based on this parameter. The data was analyzed by intention to treat. Thus, the results of both studies are equally reliable. The samples were also identical: both studies were performed in several centers located in several different countries. Only previously untreated adult patients were included. Additional inclusion criteria are given in the Table. Interestingly, the sample sizes were also quite similar: 511/505 patients in the experimental group and 453/444 patients in the control group in the RCTs by M. P. Manns et al. and M.W. Fried et al., respectively. A comparison of study groups confirmed their similarity.

Then we extracted from the publications data on the rates of SVR, calculated its relative risk (RR) and the corresponding 95% confidence intervals (CIs). In both cases the rate of SVR was higher in the PegIF group compared to the standard IF: in the study by M. P. Manns et al. RR = 1.15 (95% CI 1.02—1.30), and in the study by M.W. Fried et al. RR = 1.28 (95% CI 1.20—1.46). These estimates were used for indirect comparison of the two drugs, which showed that they do not differ in the rate of achieving SVR: RR = 1.11 (95% CI 0.95—1.30). The IDEAL study mentioned above led to a similar conclusion: RR = 1.03 (95% CI 0.92—1.14). Thus the point estimates of the effect are very similar in both direct and indirect comparisons. Furthermore, the lower boundaries of the confidence intervals are practically identical. The lower boundary in the IDEAL study may be due to its sample size, which was twice as large as in the studies used for our indirect comparison (approximately 2000 and 1000 patients, respectively). However, the point estimates in the direct and indirect comparisons fall into each other’s CIs, as they should according to the principles of mathematical statistics.

In conclusion, as long as appropriate methodology is used, the method of indirect comparison leads to reliable results which may be used both for decision-making in clinical practice and for the purposes of clinical and economic analysis.

REFERENCES


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Given the global shortage of resources in the healthcare system, one of the strategically important goals is to implement rationing of healthcare. One form of rationing is to finance only those medical technologies whose efficacy and safety have been established in high-quality clinical trials and whose use is economically justified.

Rationing considerations are particularly important for widespread diseases that are associated with significant individual, social and economic consequences. Chronic hepatitis C (CHC), the most common chronic liver disease in Europe and North America, is one of them. CHC leads to a more than 20-fold increase in the risk of hepatocellular carcinoma, and it is the prime culprit in the etiology of liver cirrhosis — the second most common cause of death from gastrointestinal diseases after cancer. According to the WHO, there are 170 million CHC patients worldwide today [1], and this number is expected to increase, primarily because of the greater use of invasive procedures and the growing number of patients with chronic conditions associated with a higher risk of being infected with hepatitis C virus: patients on lifelong immunosuppressive therapy, patients on hemodialysis, and HIV patients [2].

Russia began to register infections caused by hepatitis C virus as part of its national statistics in 1994, and between 1994 and 2001 the incidence of acute hepatitis C increased from 3.2 to 20.9 cases per 100,000 population. Its incidence began to decrease in 2002 and dropped to 2.84 per 100,000 in 2008. The same dynamics applies to viral "carriage", but with a more gradual decrease. On the contrary, the prevalence of CHC has been growing steadily: from a mere 0.8 cases per 100,000 population in 1994 it had doubled by 1995 and reached 39.1 per 100,000 by 2008 [3]. By decree 715 of the Russian government, issued on 01.12.2004, hepatitis C is included into the list of socially important diseases.

Pegylated interferons α-2a and α-2b (PegIF α-2a and PegIF α-2b) in combination with ribavirin are currently considered to be the most effective treatment for chronic hepatitis C (CHC). The results of the limited number of studies that compared the efficacy of these two types of interferon and the analytic reviews based on these studies remain controversial. Therefore we considered it appropriate to provide a critical review of the publications which compare the efficacy of these drugs in the treatment of CHC, using the methods of evidence-based medicine. Our analysis revealed that currently there is no solid evidence to claim the greater efficacy of either of the two drugs in the treatment of CHC.

KEYWORDS: chronic hepatitis C; treatment; pegylated interferon α-2a; pegylated interferon α-2b; efficacy; evidence-based medicine.
As the main inclusion criterion in our analysis, the declared goals of selected studies had to include a direct comparison of the efficacy of PegIF α-2a and PegIF α-2b. A total of 16 publications were selected for the analysis [4—19].

**Evaluation of selected publications. Concepts and instruments**

Experts had to answer the following questions:

- Does the actual methodology of the study correspond to that declared by the authors?
- Are the methods adequate for comparing the efficacy of drugs under study?
- What are the quantitative measures of the quality of identified controlled clinical trials (CCTs) and/or randomized clinical trials (RCTs)?

The current “gold standard” in the study of treatment efficacy is the RCT and meta-analysis of high-quality RCTs.

To assess the quality of selected publications quantitatively, we used the Jadad scale, which has been validated in many trials [23, 24]. Studies which scored 3 or more on the Jadad scale are considered to be valid [25] (and suitable for inclusion in meta-analysis) [26], therefore we used this threshold quality value in our study.

**RESULTS**

The main results of the selected studies and their methodological quality are reviewed in the table below.

A quantitative assessment of the quality of CCTs is presented in the figure, which shows that 6 studies (included into meta-analysis [4]) failed to reach the threshold quality level required for inclusion in the meta-analysis.

The main currently accepted intermediate (surrogate) criterion for the efficacy of antiviral therapy for CHC is the achievement of sustained virologic response (SVR), defined as undetectable levels of hepatitis C virus RNA in blood serum 24 weeks (6 months) after the end of antiviral treatment. This is the criterion that was chosen as the required treatment outcome in most of the reviewed publications.

We have collected all the currently available publications that directly compare the two types of PegIFs in the treatment of CHC.

The following considerations need to be taken into account when evaluating the methodological quality of the publications (see Table). Dedicated studies have demonstrated that clinical trials with inadequate blinding at randomization discovered a 41 % higher treatment effect [27]. There is also evidence that with incorrect or absent randomization the effect may be either overestimated by 150 % or underestimated by 90 % [28]. Besides, D. Moher et al. have demonstrated that the treatment effect discovered in a meta-analysis of RCTs that scored between 0 and 2 on the Jadad scale is 34 % higher compared to a similar meta-analysis of RCTs that scored 3 or more (relative risk 0.66; 95 % confidence interval 0.52 — 0.83). Thus, the lower the methodological quality, the greater the error in the estimated treatment effect [25].

The table shows that the available publications are not homogenous in terms of their methodological quality. Some were originally designed to study other outcomes than SVR, and/or their design was inadequate for the evaluation of treatment efficacy. Most of the studies are based on small samples that fail to represent the diversity in the general population adequately.

Apart from the shortcomings described in the table, all the studies have two more defects.

Firstly, efficacy was assessed solely based on the surrogate criterion — SVR. Clinical outcomes were not analyzed.

The second source of possible bias is the use of combination therapy with ribavirin, which is produced both by the manufacturer of PegIF α-2a and by the manufacturer of PegIF α-2b (Rebetol and Copegus, produced by Shering-Plough and Hoffman-LaRoche, respectively). Unfortunately, most studies fail to specify the manufacturer of the ribavirin used, and sometimes ribavirin from both manufacturers was used simultaneously [6, 13]. It remains unclear how far the two sources of ribavirin might differ in their efficacy, especially since the recommended dosage of ribavirin used in the studies depends on its manufacturer [4].

**DISCUSSION**

This review has uncovered a great number of interesting and methodologically important issues. It demonstrated that the declared study design, firstly, does not always correspond to the actual design, and secondly, there is no guarantee of methodological quality, which has to be carefully verified.

Based on formal criteria, 10 of the selected papers had a declared design adequate to the purposes of the study: one meta-analysis [4] and nine RCTs [5—9, 11, 12, 14, 15]. However, the “gold standard” used to evaluate treatment efficacy is not simply RCTs or meta-analyses but well-planned, large RCTs and meta-analyses of such studies. Only the IDEAL study [7] meets this criterion.

The meta-analysis [4], which officially occupies the top position in the hierarchy of medical evidence, merits a separate discussion. The authors consider that it has demonstrated the superiority of PegIF α-2a over PegIF α-2b in achieving SVR, as its title declares in a stately manner. However, it is primarily based on low-quality clinical trials, as confirmed by their scores on the Jadad scale (see Figure), some of which cannot even be regarded as RCTs, regardless of what their authors might claim [10—13].
### The Results and Main Methodological Characteristics of Selected Studies

<table>
<thead>
<tr>
<th>1st author/country</th>
<th>Design</th>
<th>Sample</th>
<th>Treatment allocation to groups</th>
<th>Facets contributing to group heterogeneity</th>
<th>Facets contributing to bias</th>
<th>Results (rate of sustained virologic response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascione et al./Italy</td>
<td>Prospective RCT</td>
<td>320 previously untreated patients; 2 equal-sized groups; 1 center</td>
<td>PegIF α-2a 180 μg once/week, PegIF α-2b 1.5 μg/kg once/week, plus ribavirin per body weight</td>
<td>Several viral genotypes (1, 2, 3, 4), variable treatment duration (genotypes 2 and 3 — 24 weeks, genotypes 1 and 4 — 48 weeks)</td>
<td>Single center study, no blinding</td>
<td>In groups overall: PegIF α-2a — 68.8%; PegIF α-2b — 54.4% (p = 0.008) Pooled for genotypes 1 and 4: PegIF α-2a — 54.8%; PegIF α-2b — 39.8% (p = 0.04) For genotype 2: PegIF α-2a — 91.8%; PegIF α-2b — 76.0% (p = 0.062) For genotype 3: PegIF α-2a — 77.8%; PegIF α-2b — 70.6% (p = 0.92) Pooled for genotypes 2 and 3: PegIF α-2a — 88.1%; PegIF α-2b — 74.6% (p = 0.046, but p = 0.21 when results from genotypes 2 and 3 are compared separately)</td>
</tr>
<tr>
<td>Rumi et al. (MIST)/Italy</td>
<td>RCT</td>
<td>431 previously untreated patients; 2 equal-sized groups; 1 center</td>
<td>PegIF α-2a 180 μg once/week, PegIF α-2b 1.5 μg/kg once/week, plus ribavirin per body weight</td>
<td>Several viral genotypes (1, 2, 3, 4), variable treatment duration (genotypes 2 and 3 — 24 weeks, genotypes 1 and 4 — 48 weeks)</td>
<td>Single center study, no blinding</td>
<td>In groups overall: PegIF α-2a — 66%; PegIF α-2b — 54% (p = 0.02) For genotype 1: PegIF α-2a — 48%; PegIF α-2b — 32% (p = 0.04) For genotype 2: PegIF α-2a — 96%; PegIF α-2b — 82% (p = 0.01) For genotype 3: PegIF α-2a — 65%; PegIF α-2b — 69% (p = 0.09) For genotype 4: PegIF α-2a — 44%; PegIF α-2b — 31% (p = 0.5)</td>
</tr>
<tr>
<td>McHutchinson et al. (IDEAL)/USA</td>
<td>RCT</td>
<td>3070 previously untreated patients; 3 equal-sized groups; 118 centers</td>
<td>PegIF α-2b 1.5 μg/kg once/week, PegIF α-2b 1 μg/kg once/week, PegIF α-2a 180 μg once/week, plus ribavirin per body weight</td>
<td>—</td>
<td>Only patients with genotype 1</td>
<td>PegIF α-2b 1.5 μg/kg — 39.8% PegIF α-2b 1 μg/kg — 38% PegIF α-2a 40.9% (1-3, p = 0.57; 1-2, p = 0.2)</td>
</tr>
<tr>
<td>Laguno et al./Spain</td>
<td>RCT</td>
<td>182 previously untreated patients; 2 equal-sized groups; 5 centers</td>
<td>PegIF α-2b 80-150 μg/kg once/week (dep. on body weight), PegIF α-2a 180 μg once/week, plus ribavirin per body weight</td>
<td>Several viral genotypes (1, 2, 3, 4)</td>
<td>No blinding, concomitant HIV infection</td>
<td>In groups overall: PegIF α-2b — 41.86%; PegIF α-2a — 45.83% (p = 0.654) Pooled for genotypes 1 and 4: PegIF α-2b — 27.66%; PegIF α-2a — 32.26% (p = 0.677) Pooled for genotypes 2 and 3: PegIF α-2b — 61.76%; PegIF α-2a — 70.97% (p = 0.6)</td>
</tr>
<tr>
<td>Scotto et al./Italy</td>
<td>RCT</td>
<td>143 patients resistant to standard IF; 2 equal-sized groups; 1 center</td>
<td>PegIF α-2a 180 μg once/week, PegIF α-2b 1.5 μg/kg once/week, plus ribavirin per body weight</td>
<td>Several viral genotypes (1, 2, 3, 4)</td>
<td>Single center study, randomization method not specified, no blinding, inclusion of patients resistant to previous therapy</td>
<td>In groups overall: PegIF α-2a — 19.7%; PegIF α-2b — 18.0% (NS)</td>
</tr>
<tr>
<td>1st author/country</td>
<td>Design</td>
<td>Sample</td>
<td>Treatment allocation to groups</td>
<td>Factors contributing to group heterogeneity</td>
<td>Factors contributing to bias</td>
<td>Results (rate of sustained virologic response)</td>
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<tr>
<td>Witthoeft et al. (PRACTICE)/Germany</td>
<td>Retrospective</td>
<td>3470 both previously treated and untreated patients; 2 unequal groups; 23 centers</td>
<td>PegIF α-2a, PegIF α-2b, plus ribavirin; different regimens used</td>
<td>Several viral genotypes (1, 2, 3, 4, 5, 6), various and individually determined dosages and duration of treatment, inclusion of both previously untreated patients and patients resistant to primary therapy</td>
<td>Design not suitable for comparison of efficacy, unequally sized treatment groups, non-randomized trial, no blinding</td>
<td>Groups defined by a number of criteria were compared. Comparison of groups defined by one set of criteria: overall PegIF α-2a — 59.9 %, PegIF α-2b — 55.9 % (p = 0.051); genotype 1: PegIF α-2a — 48.7 %, PegIF α-2b — 44.1 %; genotypes 2 and 3: PegIF α-2a — 78.7 %, PegIF α-2b — 76.0 % (NS). Comparison of groups defined by another set of criteria: overall PegIF α-2a — 59.1 %, PegIF α-2b — 54.4 % (p = 0.054); genotype 1: PegIF α-2a — 49.6 %, PegIF α-2b — 43.7 % (p = 0.047); genotypes 2 and 3: PegIF α-2a — 78.3 %, PegIF α-2b — 76.8 % (NS)</td>
</tr>
<tr>
<td>Craxi et al. (PROBE)/Italy</td>
<td>Prospective observational</td>
<td>1017 patients; 2 unequal groups; 167 centers</td>
<td>PegIF α-2a, PegIF α-2b, use of ribavirin therapy not indicated; different regimens used</td>
<td>Various dosages and duration of treatment determined individually by each center</td>
<td>Design not suitable for comparison of efficacy, inclusion of only genotype 1 patients, unequally sized treatment groups, non-randomized trial, no blinding</td>
<td>A different study goal, namely the identification of predictors of SVR. Overall: PegIF α-2a — 36 %, PegIF α-2b — 29 % (p = 0.02)</td>
</tr>
<tr>
<td>Backus et al. (US Veterans)/USA</td>
<td>Retrospective observational cohort</td>
<td>5944 previously treated or untreated patients; 121 centers</td>
<td>PegIF α-2a, PegIF α-2b, plus ribavirin; different regimens used</td>
<td>Several viral genotypes (1, 2, 3), inclusion of both previously treated patients and patients resistant to primary therapy, various dosages and duration of treatment</td>
<td>Design not suitable for comparison of efficacy, unequally sized treatment groups, narrow cohort (veterans), no randomization or blinding, pre-2003 treatment with PegIF α-2b was not included</td>
<td>The main study goal was to identify predictors of SVR. Overall: PegIF α-2a — 41 %, PegIF α-2b — 36 % (p &lt; 0.001)</td>
</tr>
<tr>
<td>Berak et al./Poland</td>
<td>CCT</td>
<td>237 patients; 1 center</td>
<td>PegIF α-2a, PegIF α-2b, plus ribavirin; dosages not indicated</td>
<td>Several viral genotypes (2 and 3 were excluded)</td>
<td>Single center study, no randomization, no blinding</td>
<td>Study purpose: to explore the rate of EVR; SVR was not measured</td>
</tr>
<tr>
<td>Bruno et al./Italy</td>
<td>RCT</td>
<td>22 patients; 2 equal-sized groups; 1 center</td>
<td>PegIF α-2a 180 μg once/week, PegIF α-2b 1 μg/kg once/week, plus ribavirin per body weight</td>
<td>Several viral genotypes (1, 2, 3)</td>
<td>Single center study, randomization method not specified, no blinding</td>
<td>Study purpose: to explore pharmacokinetics, pharmacodynamics, and EVR; SVR was not measured</td>
</tr>
</tbody>
</table>
### Table: Factors contributing to group heterogeneity and bias

<table>
<thead>
<tr>
<th>1st author/country</th>
<th>Design</th>
<th>Sample</th>
<th>Treatment allocation to groups</th>
<th>Factors contributing to group heterogeneity</th>
<th>Factors contributing to bias</th>
<th>Results (rate of sustained virologic response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Besceglie et al./USA</td>
<td>RCT</td>
<td>380 previously untreated patients; 2 equal-sized groups; 41 centers</td>
<td>PegIF α-2a 180 μg once/week, PegIF α-2b 1.5 μg/kg once/week, plus ribavirin per body weight</td>
<td>—</td>
<td>Only genotype 1 patients; randomization method not specified, no blinding</td>
<td>Study purpose: to evaluate the rate of EVR; SVR was not measured</td>
</tr>
<tr>
<td>Kolakowska et al./Poland</td>
<td>CCT</td>
<td>67 previously untreated patients; 2 equal-sized groups; 1 center</td>
<td>PegIF α-2a, PegIF α-2b (dosages not indicated), plus ribavirin per body weight</td>
<td>—</td>
<td>Single center, non-randomized study, only genotype 3 patients, no blinding</td>
<td>PegIF α-2a — 84 %, PegIF α-2b — 79 % (NS)</td>
</tr>
<tr>
<td>Silva et al./Argentina, Mexico, Germany</td>
<td>RCT in parallel groups</td>
<td>36 patients; 2 equal-sized groups; 3 centers</td>
<td>PegIF α-2b 1.5 μg/kg once/week, PegIF α-2a 180 μg once/week, plus ribavirin 13 mg/kg</td>
<td>—</td>
<td>Only genotype 1 patients, randomization method not specified, high dropout rate (24 %)</td>
<td>Study purpose: to explore pharmacokinetics, pharmacodynamics, and EVR; SVR was not measured</td>
</tr>
<tr>
<td>Yenice et al./Turkey</td>
<td>RCT</td>
<td>74 patients; 2 equal-sized groups; 1 center</td>
<td>PegIF α-2a 180 μg once/week, PegIF α-2b 1.5 μg/kg once/week, plus ribavirin per body weight</td>
<td>—</td>
<td>Single center study, only genotype 1 patients, randomization method not specified, no blinding</td>
<td>PegIF α-2a — 48.6 %, PegIF α-2b — 35.1 % (p = 0.239)</td>
</tr>
<tr>
<td>Awad et al.</td>
<td>MA</td>
<td>5008 patients</td>
<td>The studies included in MA varied with respect to viral genotypes, dosage regimens, and treatment duration</td>
<td>—</td>
<td>Low methodological quality of the majority of included studies</td>
<td>PegIF α-2a — 47 %, PegIF α-2b — 41 % (p = 0.004)</td>
</tr>
</tbody>
</table>

**Note:** RCT — Randomized Controlled Trial; CCT — Controlled Clinical Trial; SVR — Sustained Virologic Response; EVR — Early Virologic Response; NS — non-significant (no statistically significant difference).
These studies also differed in the duration of treatment. In addition, this meta-analysis included four publications that did not even look at how often SVR was achieved. The authors state that these studies were included only to evaluate the safety.

A further reason to doubt the methodological soundness of this meta-analysis is the fact that it was not found in Cochrane library, where it is registered as a protocol, but in a specialized periodical.

There is reason to believe that the authors of analytical reviews mentioned in this publication took advantage of the fact that many non-specialist readers were unable to follow all the subtleties and complexities of the analyzed studies, and thus the authors chose to emphasize only some “contextually advantageous” aspects of these studies. For instance, S. Zeuzem [20] reviews the results of several large studies [5—7, 17—19] without any regard for the methodological integrity of data collection. Reviewing the IDEAL study, the author emphasizes that the rate of end-of-treatment virologic response was higher with PegIF α-2a but fails to mention that this indicator is not a major predictor of treatment outcome and downplays the fact that the main efficacy criterion of antiviral therapy, SVR, showed no statistically significant difference between PegIF α-2a and PegIF α-2b.

S. Zeuzem also concludes that the studies by A. Ascione and M. Rumi, “loose change” in many reviews, have demonstrated the advantage of PegIF α-2a over PegIF α-2b in achieving SVR. What is not mentioned is that the duration of treatment depended on the viral genotype. Analyzing the results of these studies, the authors calculated the rate of SVR for treatment groups overall and noted the statistically significant advantage of using PegIF α-2a, but the question remains: why were all the genotypes pooled together? The same studies show the rates of SVR for each genotype separately, with completely different results (see table), but this fact is not mentioned in the conclusions.

Besides, the sample size in these studies is too small to be certain of the clinical significance of these results.

It sometimes comes to the ridiculous. A criticism of the IDEAL study cited by A. Craxi [21] is that the study was conducted only in the United States and included too many Afro-Americans (p. 134). Not a word about that fact that the other studies cited as counter-evidence to the IDEAL were conducted in countries with far less genetic diversity, drawing on tiny samples from a single medical center. Trying to prove the superiority of PegIF α-2a, the same article (p. 35) quotes a study of American veterans [18], in which the location in the USA is no longer a shortcoming, and neither are the specific age, race, etc. Not to mention that the design of this study, as well as of other studies included in this review (PROBE and PRACTICE) and quoted by A. Craxi, is not even suitable for the purpose of comparing drug efficacy.

**CONCLUSIONS**

1. All the currently available studies share a common drawback: they look at surrogate criteria (SVR) as their main outcomes.

2. Of all the reviewed studies that directly compared PegIF α-2a and PegIF α-2b, only the large RCT IDEAL can be considered valid, but its results hold only for genotype 1 of hepatitis C virus.

3. The systematic review, which would normally be counted among studies that hold the top position in the hierarchy of evidence, in this case cannot be considered valid, since it includes low-quality studies, many of which fail to satisfy the quantitative criteria of quality and thus should not be included in meta-analyses.

4. In our analysis we did not discover any evidence of greater efficacy of either of the two PegIF drugs.

5. Additional large and high-quality RCTs have to be performed in order to settle the question of the respective efficacy of the drugs under study.

A Quantitative Evaluation of the Validity of Selected Studies on the Jadad Scale
REFERENCES


3. Gosudarstvenny doklad o sanitarno-epidemicheskoi obstanovke v RF v 2008 g.


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Hepatocellular carcinoma (HCC) is one of the most common types of hepatic malignancies. Without early treatment it develops rapidly with poor survival prospects. The groups at high risk of HCC include patients suffering from hepatic cirrhosis and chronic infections caused by hepatitis B and C viruses, inherited liver disorders or prolonged exposure to aflatoxins. Since the early stages of HCC are asymptomatic, only a few patients are diagnosed with HCC early enough for a radical surgery (resection, liver transplantation, local destructive techniques). The efficacy of chemotherapy in primary liver cancer is limited, and it has little effect on the clinical outcome or the quality of life. The standard treatment approach in most countries is doxorubicin monotherapy, but occasionally epirubicin, mitoxantrone, cisplatin, vepezid and 5-fluorouracil are also used, though the actual efficacy remains below 20 % with the median life expectancy of 3—4 months. In this situation physicians are often tempted to use drugs off-label, i.e. outside the registered prescription range, in the hope for achieving at least minimal effect. An analysis of the range of drugs prescribed in 2006 to patients with primary liver cancer as part of the federal reimbursement program of supplementary drug supply (rus. DLO) revealed that a total of 7.23 mln rubles was spent on the treatment of 2110 participants in this program, while the majority of prescribed drugs, some quite expensive, had not been proved effective in the treatment of liver cancer [1]. Sorafenib, a new drug for targeted therapy, improves the time to progression and survival rate in HCC patients [2], but its availability in the common clinical practice remains very low. At present sorafenib remains the first and so far the only drug registered for the treatment of HCC in over 60 countries, including Russia.

The new standards of the HCC treatment require a clinical and economic evaluation, which necessitates an analysis of social and economic burden of HCC in Russia — the goal of this study. Study objectives included the following:

1) to analyze the epidemiology of HCC in the RF;
2) to analyze the provision of medical care to HCC patients in the RF with respect to the current standards and the common practice;
3) to evaluate the direct and indirect costs of HCC in the RF.

**METHODOLOGY**

This study used the “cost-of-illness” method, which is based on identification and assessment of the direct costs of medical care provision and the indirect costs due to loss of gross domestic product (GDP) and payments on sick leave.

The study included the following: a review of publications on the epidemiology and treatment of liver cancer; an analysis of government statistic data; an analysis of regulations concerning the provision of medical care to HCC patients in the RF; an expert evaluation of the volume of healthcare services provided to HCC patients; a cost-of-illness analysis. All the analyses were based on the statistics for 2008. The epidemiological analysis was based on official statistical sources (provided by the Russian Center for Information Technologies and Epidemiological Studies in Oncology, the Ministry of Health and Social

**KEYWORDS**: hepatocellular carcinoma; epidemiology of hepatocellular carcinoma; social and economic burden; cost of illness analysis; direct and indirect costs.
Development of the RF, and the Federal Service for State Statistics of the RF), scientific publications, the register of the N. N. Blohin Russian Oncological Research Center, and the Population Cancer Register of the Krasnodar region [3]. The economic burden was evaluated using the data on incidence and prevalence of HCC and the age distribution of patients.

Since in many cases objective data required for an evaluation of costs are missing, we made a number of assumptions, as described below.

Morbidity and death from cancer of the liver and intrahepatic bile ducts is registered in Russia as a single category, without distinguishing among various types of this disease, therefore we had to estimate the number of newly diagnosed HCC patients. The incidence of primary HCC per 100 000 population was estimated for the period of 1998—2008 using the statistics on primary cancer of the liver and intrahepatic bile ducts [4] and the published research on the share of HCC in the spectrum of liver cancers [5—7]. The absolute number of newly diagnosed HCC patients was estimated using the annual data on the population size provided by the Federal Service for State Statistics of the RF. To determine the number of HCC patients registered in oncological therapeutic and preventive centers in 2008 (which can be regarded as an indicator of prevalence), we extrapolated the data in the Population Cancer Register of the Krasnodar region to the whole of Russia (the calculations are based on 7-year survival rates). Thus, our estimates are based on the assumption that the survival rates and prevalence do not differ significantly between various regions. Our analysis of the distribution of HCC patients with regard to gender, age, disability category, comorbidity, and HCC stage is based on the database of the N. N. Blohin Russian Oncological Research Center as it was at the time of performing the study.

Provision of medical care to patients with malignant tumors in Russia falls within the framework of standard primary and specialized medical care, including a program for High-technology Medical Care (HMC). The management of oncological patients includes active treatment (surgery, radiation therapy, and drug therapy) and palliative treatment [7—15].

To analyze the common practice of HCC diagnostic and treatment, we performed a survey among the leading experts. 12 experts from the N. N. Blohin Russian Oncological Research Center, B. V. Petrovsky State Research Centre of Surgery, and regional oncological centers (the Altai oncological dispensary, Federal State Agency “Volga Region Medical Center” of the RF, the Rostov State Medical University Hospital) took part in the survey. The opinions of surveyed experts were used to study diagnostic criteria, procedures used to confirm the diagnosis, choice of treatment, and the magnitude and type of treatment depending on the stage of the disease.

As a result, disaggregated costs of the following procedures were considered for the estimation of direct costs of treating HCC patients:

1) medical examination to confirm the diagnosis and prepare the patient for referral to a medical center;
2) specialized medical services, including HMC, depending on the stage of the disease;
3) medical care in the course of outpatient monitoring, depending on the stage of the disease.

The costs of the initial medical examination, outpatient monitoring and hospitalization of patients at the terminal stage in specialized wards for palliative care were calculated using the prices specified by the system of mandatory medical insurance in Moscow in 2008. The costs of HMC (hospitalization for surgery and chemotherapy) were calculated in accordance with the charges for HMC stipulated by the decree regulating state provision of high-technology medical care financed from the federal budget in 2008 to citizens of the Russian Federation (order No 458n from August 27, 2008 of the Ministry of Health and Social Development of the RF). In accordance with this decree, the charges for the provision of medical care classified as “oncological” HMC (code 9, subdivisions 9.1, 9.3, 9.5, 9.8, depending on the type of services) to one patient should not exceed 109.8 thousand rubles (so called quota for HMC).

The costs of drug therapy in outpatient care for HCC patients was estimated through an analysis of reimbursed drug consumption in three areas: the Moscow region, Saint-Petersburg, and Nizhny Novgorod. The cost was estimated based on the number of HCC patients (classified using ICD-10) in the region, the number of prescriptions, and the price of each prescription. The costs of drug supply for chemotherapy and palliative therapy were calculated per patient. The data on drug consumption in these three regions were extrapolated for HCC patients in the whole of Russia. The estimation was based on the assumption that all patients had 100 % access to therapy, with the exception of medications for targeted therapy, since the latter are only available for outpatient treatment if there are dedicated oncological programs in the region, and these still remain uncommon.

There are no precise figures to estimate the duration of the temporary disability of HCC patients. Therefore we considered the cost of sick leave payments for patients of working age for the duration of their hospitalization, assuming that upon being discharged they would either return to work or be registered as permanently disabled. The social benefits in the case of temporary disability or injury cover the whole period of leave from work until the day the person goes back to work or becomes registered as

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1 In federal regions the provision of drugs to patients entitled to special allowances is subsidized from the local budget in accordance with decree No.890 of 30.07.1994 of the government of the RF and with the regional legislation on the provision of medicinal drugs.
disabled with limited capacity for work\(^2\), and the amount of corresponding payments is in proportion with the qualifying pensionable service. Sick leave payments are calculated on the basis of average earnings per day, the cost of treatment and the qualifying pensionable service. We used the expert survey to estimate the average length of hospitalization depending on the stage of disease, assuming that HCC patients have worked for 8 years or more and that the benefits amount to 100 % of the salary.

The loss of GDP incurred because of temporary disability was estimated using the data of the Federal Service for State Statistics of the RF on GDP and the size of economically active population in 2008. These numbers were used to calculate per capita GDP for one worker per day. The loss of GDP was calculated based on the average annual duration of treatment and the number of HCC patients of working age.\(^3\) The loss of GDP due to permanent disability was also taken into account in this study.

Based on the expert opinions, we assumed that 50 % of intermediate and 100 % of terminal HCC patients are disabled due to their illness.

RESULTS

There were 6473 registered patients with cancer of the liver and intrahepatic bile ducts in Russia in 2008\(^4\). Since the share of HCC in the spectrum of liver cancers is about 85 %, the estimated total number of newly diagnosed HCC patients was 5502, including 3109 men and 2393 women. The estimated “crude” and “standardized” incidence rate of HCC was 3.88 and 2.41 per 100,000 population for men and women, respectively. The number of HCC patients registered at medical centers for treatment and prevention of oncological diseases (HCC prevalence) was estimated at 8658. The age distribution of HCC patients was as follows: 15—29 years of age — 0.84 %, 30—59 — 32.39 %, 59 and older — 66.78 %. Thus 24.85 % of newly diagnosed patients were of working age. The rate of deaths to newly registered cases was 0.92, and there were 5.7 deaths per 100 000 population due to HCC in 2008 [4, 7, 16].

Primary liver cancer comprises 3—5 % of all malignant tumors in Russia. However, since the number of patients with chronic hepatitis B and C and liver cirrhosis has recently been on the rise in Russia, the prevalence of liver cancers may also be expected to grow [17, 18]. According to the register of the N. N. Blohin Russian Oncological Research Center, 21.9 % of HCC patients developed the malignancy while suffering from chronic hepatitis, which was hepatitis B in 25.3 % of cases and hepatitis C in 26.1 % of cases.

According to the opinion of surveyed experts, among HCC patients treated each year 9 % have localized stage of the disease, 61 % — intermediate stage, 30 % — terminal stage. The experts claim that 100 % of HCC patients at the localized and intermediate stages and 50 % of patients at the terminal stage receive high-technology medical care. Surgical intervention (resection of the liver) remains the only radical method of treating malignant hepatic tumors. Approximately 14.5 % of HCC patients at the localized and intermediate stages are hospitalized for surgical intervention. If liver resection cannot be performed, HCC patients are hospitalized for localized liver interventions (28.5 %) and/or chemotherapy, including intra-arterial chemotherapy (30 %). Symptomatic treatment is given in 90 % of the terminal cases.

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The survey of experts suggests that liver resection requires one hospitalization (one quota of HMC provision), but chemotherapy requires the average of nine quotas for each patient in this category per year. After the high-technology treatment the patient has to be followed up by

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\(^3\) Indirect costs were estimated using the method of friction cost, which assumes that the real loss of GDP occurs only within a short, so-called frictional period, after which the sick worker will be replaced (the method is described in the book ed. by P.A. Vorobiev, “Clinical and economic analysis”, Moscow 2008). The allowance for friction cost was assumed to be 10 %, i.e. the actual loss of GDP was considered to be 10 % of the cost calculated using the human capital method.
an oncologist with mandatory regular tests for tumor markers. Each of the regular examinations includes an ultrasound scan of the liver, α-fetoprotein test, hematology and blood biochemistry, and computer tomography as indicated. The number of visits to an oncologist that HCC patients perform depends on the stage of the disease, and the experts estimate about four visits per year for patients at the localized stage and seven visits at the intermediate stage. HCC patients at the terminal stage visit an oncologist every month.

The cost of medical examination to confirm the diagnosis and prepare the patients for treatment, was estimated based on the results of our expert survey, in 2008 stood at 64.53 mln rubles. The costs of treating HCC patients, depending on the stage of the disease, were as follows:

1) for HCC patients at the localized stage — 242.01 mln rubles, including 237.85 mln (98.28 %) spent on hospital care and 4.16 mln (1.72 %) spent on outpatient monitoring;

2) for HCC patients at the intermediate stage — 1718.05 mln rubles, including 1641.10 mln (95.52 %) spent on hospital care and 76.95 mln (4.48 %) spent on outpatient monitoring;

3) for HCC patients at the terminal stage — 184.34 mln rubles, including 119.47 mln (64.80 %) spent on hospital care and 64.88 mln (35.19 %) spent on outpatient monitoring.

The estimated cost of outpatient provision of medications to HCC patients was 310.88 mln rubles in 2008, including 27.98 mln rubles (9.0 %) for patients with localized HCC, 189.63 mln rubles (61.0 %) for patients with intermediate HCC, and 93.26 mln rubles (30.0 %) for patients with terminal HCC.

The total cost of treating HCC patients amounted to 2519.80 mln rubles, of which the direct medical costs were 2519.80 mln rubles (95.3 %) and the indirect costs were 124.22 mln rubles (4.7 %). It is worth noting that the overall cost of providing free healthcare to the citizens of the Russian Federation guaranteed by the state in 2008 amounted to 1185.1 billion rubles [19]. Thus, despite the small number of patients, HCC entails relatively large financial expenses (approximately 0.2 % of all resources available to the healthcare system), mainly because of the need to provide high-technology medical care.

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Chronic myeloid leukemia (CML) is a malignant tumor blood disorder characterized by pathologic growth of monoclonal lines of hematopoietic stem cells and making up 7–15% of all diagnosed forms of leukemia in adults [1]. For a long time the main drug therapy of CML was prescription of alpha-interferon (α-IF), hydroxyurea and busulfan, but the clinical efficacy of these methods was low. At the same time allogeneic bone marrow transplantation played a significant role in the treatment. Even now it is considered to be the only method that can cure CML, since transplant has an ability to eliminate completely a pool of stem cells that can serve as a source of disease recurrence. The results of analysis of more than three thousand patients who underwent bone marrow transplantation showed that two-year survival rate among them was 61% and recurrence rate — 22% [2]. However, one must consider all possible risks associated with conducting this surgery such as life-threatening infectious complications, graft-versus-host disease, secondary tumors, etc. Thus in the analysis mentioned above the mortality in the two years was 30%. Additionally one has to keep in mind the difficulty of finding a potential donor, the need for subsequent therapy, and significant financial expenses.

Fundamental change in the approaches for CML treatment and an even greater reduction of the role of bone marrow transplantation in particular is associated with development in the late 90s of the twentieth century of a new class of drugs for targeted therapy of this disease — tyrosine kinase inhibitors (TKIs), imatinib was the first of them. Large clinical trials IRIS showed that 1.5 years of imatinib therapy which was begun during the chronic phase of CML resulted with a statistically significant higher rate of complete cytogenetic response (CCyR) compared with standard therapy with α-IF in combination with cytarabine: 14.5 and 76.2% respectively (p < 0.001) [3]. After five years of imatinib therapy CCyR was observed in 87% of patients, and stable course of disease without transition to progression phase or blast crisis — in 93% of patients [4]. Five-year survival rate among those who received imatinib as initial therapy was 89%. Due to its high efficacy and good tolerability imatinib quickly became the drug of first-line treatment for CML, and its advent is rightly considered as a milestone in CML therapy and one of the most significant events in modern clinical medicine.

Unfortunately, despite a great stride forward in the struggle against CML, there are some patients (25% by some estimates) resistant to imatinib [5]. Increasing the dose of imatinib from the standard 400 to 800 mg per day does not increase the frequency of CCyR [6]. However, the recently developed second-generation TKIs — dasatinib (Sprycel®, Bristol Myers-Squibb) and nilotinib (Tasigna®, Novartis) enable to achieve the effect in patients who are resistant or intolerant to imatinib. For example, results of I-II phases of clinical trials of dasatinib demonstrated that...
after 8 months of treatment CCyR was observed in 39 % of patients with chronic phase CML resistant or intolerant to imatinib. One-year survival rate without disease progression was 92.4 % [7]. The results of a comparative study of dasatinib and high-dosage prescription regime of imatinib in patients in chronic phase with resistance to standard dosages of imatinib have also shown that after 15 months statistically significant higher rate of CCyR was observed in the dasatinib group: 40 and 16 % respectively (p = 0.004); survival in the absence of progression was also 86 % higher in the dasatinib group during this period [8]. After eight months of dasatinib treatment in the phase of progression or blast crisis CCyR was observed in 24 % and 27 % respectively [9, 10]. According to the results of clinical trials prescription of nilotinib has allowed to get CCyR in the following six months in 31 % of patients with chronic phase of CML resistant to imatinib, one-year survival rate in this case was 95 % [11]. When nilotinib was administered in the accelerated phase frequency of CCyR following one year of treatment was 16 % and overall survival rate — 79 % [12]. According to the studies efficacy of dasatinib and nilotinib in imatinib-resistant patients allowed to consider them as second-line drugs for CML therapy [13].

All TKIs are expensive drugs. From 2006 patients with CML in Russia have been receiving imatinib through a special federal program of “seven expensive nosologies”. However, the second generation TKIs are not covered by this program and not included in the list of vital and essential drugs and standards of CML treatment. As a result, patients with resistance or intolerance to imatinib have no effective treatment in most cases. The only possibility is the targeted purchase of these drugs for individual patients at the expense of the constituent entities of the Russian Federation, which is difficult to implement in the regions (especially subsidized) and should not be considered as a systematic and equitable approach to drug supply.

The necessity to address the problem of drug therapy for imatinib-intolerant or resistant patients with CML and the existence of two alternative second generation TKI drugs on the pharmaceutical market became reasons for conducting this study.

PURPOSE OF THE STUDY: to conduct pharmaco-economic analysis of dasatinib and nilotinib for the second-line therapy for chronic phase CML patients resistant to imatinib.

Research objectives:
- to perform examination of the Markov model developed by IMS Health for pharmacoeconomic analysis of alternative strategies for the 2d line treatment of patients with CML;
- to calculate direct medical costs for treating imatinib-resistant patients with dasatinib and nilotinib in the model;
- to calculate the number of life-years saved and quality-adjusted life-years (QALY) saved for each type of therapy in the model;
- to analyze cost-effectiveness and cost-utility of dasatinib and nilotinib therapy for patients in chronic phase CML.

Research hypothesis: dasatinib therapy is more effective and less expensive compared to nilotinib therapy in patients resistant to imatinib with chronic phase CML.

MATERIALS AND METHODS

The model developed in 2009 by IMS Health Company for pharmacoeconomic analysis of alternative strategies for second-line therapy in patients with CML was used to conduct the study. In the present paper, this model was used to compare dasatinib with nilotinib in chronic phase CML. The model was subjected to examination for its validity in terms of the used data on effectiveness of dasatinib and nilotinib, and compliance with the real clinical practice in the management of patients with chronic phase CML in Russia.

DESCRIPTION OF THE MODEL

The model predicted the long-term effectiveness and costs associated with dasatinib and nilotinib therapy, based on short-term data on the initial best response to treatment and disease progression obtained in clinical trials. Criteria for evaluating the effectiveness in the model were traditional for clinical research and CML treatment practice: complete hematologic response (CHR), partial cytogenetic response (PCyR), complete cytogenetic response (CCyR) (Table 1). The most clinical significant response was considered to be initial best response in the first cycle of therapy. For example, if both CHR and CCyR are observed in a patient, only CCyR is recorded for this patient as initial best response to treatment.

### Table 1. Criteria of CML Therapy Effectiveness*

<table>
<thead>
<tr>
<th>Definition</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete hematologic response (CHR)</td>
<td>Leukocytes &lt; 100000/μl; platelets &lt; 4500000/μl; basophils &lt; 5%; absence of granulocytes precursors; non-palpable spleen</td>
</tr>
<tr>
<td>Cytogenetic response:</td>
<td></td>
</tr>
<tr>
<td>complete (CCyR)</td>
<td>0 % Ph+</td>
</tr>
<tr>
<td>partial (PCyR)</td>
<td>1—35 % Ph+</td>
</tr>
<tr>
<td>minor</td>
<td>36—65 % Ph+</td>
</tr>
<tr>
<td>minimal</td>
<td>66—95 % Ph+</td>
</tr>
<tr>
<td>no</td>
<td>&gt;95 % Ph+</td>
</tr>
<tr>
<td>Molecular response:</td>
<td></td>
</tr>
<tr>
<td>complete (CMR)</td>
<td>Transcripts are not determined</td>
</tr>
<tr>
<td>major (MMR)</td>
<td>Proportion bcr-abl&gt; abl/m0,10 according to the established international scale</td>
</tr>
</tbody>
</table>

*According to European LeukemiaNet recommendations [14].
In the absence of direct comparative studies and meta-analyses of the second generation TKIs, the probabilities of achievement of the best response in the model were taken from the II and III phases of nilotinib and dasatinib open randomized trials completed by the time of the model development [11, 16, 17] (Table 2).

Dosage regimen of drugs in the model corresponded to the dosage regimen in the studies underlying the model, and in the prescribing information: dasatinib — 100 mg once daily, nilotinib — 400 mg twice daily.

Structure of the model is shown in Figure 1. After evaluation of the response to treatment the fate of a patient was simulated using Markov method. In each subsequent cycle of the model the patient’s condition may remain stable (disease remains in the same phase); move to a more severe phase (accelerated phase or blast crisis) or the patient may die.

The only difference in the Markov cycles between two types of therapy (dasatinib and nilotinib) laid in the frequency of achievement of different types of response to therapy. Further progression of the disease depended only on the type of patient response but not on the type of treatment received. Probability of disease progression was calculated based on the results of clinical trials of dasatinib [16].

The specific utility value in the model corresponded to each Markov state (i.e. each CML stage). The developers used the study as a source of information about the utility [18].

Results of the clinical effectiveness simulation are presented in the model as a number of quality-adjusted life-years (QALY) and life-years saved.

Sources of information used in the model for each data type are given in Table. 3.

The model allows calculating the costs of patient treatment for any time period ranging from one year to the entire patient life span (or until discontinuation of treatment due to disease progression or toxicity of the drug). In the basic analysis, we calculated the cost of treatment for the entire life expectancy of patients. The costs of drugs were calculated based on the prices at which they were bought at the auction in September 2010 (provided by the IRS “CursOR”). Price per pack of dasatinib (Sprycel®) 50 mg № 60 was 213 340.00 rubles, of nilotinib (Tasigna®) 200 mg № 112 — 244 263.00 rubles.
Characteristics of the patients included in the model were consistent with the patients who participated in the multicenter clinical trials of TKIs in CML treatment [15—17]. Patients from several countries, and also from Russia were included in the studies (Table 4). The analysis was carried out on adult patients with CML resistant or intolerant to prior imatinib treatment.

In the course of sensitivity analysis the following parameters varied: age of patients in each phase at the beginning of treatment, the prices of drugs and the levels of utility. Prices of drugs and the utility levels ranged within ±20%, the age — from 0 to 10%.

RESULTS AND DISCUSSION

Evaluation of the model

We have studied the structure of the model and the validity of the data that were laid in its foundation. The model is based on the efficiency criteria for the treatment of CML traditionally used in the research and practice. Assessment of hematological response is the earliest simplest and affordable way to monitor treatment process and drugs side effects, and serves as the first line diagnostic test. The goal of treatment is to achieve a complete hematological response. However, the “gold standard” for monitoring the treatment of CML is a cytogenetic study of a biopsy sample of bone marrow cells due to its availability, accuracy, and a significant difference in survival of patients with cytogenetic response and without it [6]. Achievement of CCyR is now the main aim of the CML therapy, which is reflected in the recommendations of European LeukemiaNet and National Comprehensive Cancer Network. CCyR is the most significant and independent predictor of the long-term survival of patients [13]. Cytogenetic tests are recommended early in the treatment and then every six months, until CCyR is achieved. Thus, the model is built on the adequate assumption that survival of patients with CML can be predicted on the basis of the initial best response.

Markov conditions in the model (chronic phase, accelerated phase and blast crisis) correspond to the modern notions about the course of CML. One can also state that the model is based on the adequate assumption that the only difference in the Markov cycles between two types of the therapy (dasatinib and nilotinib) is in the rate of achievement different types of response to therapy, and further progression of the disease depends only on the type of response, but not on the type of treatment received. This approach is appropriate, because long-term effect of the second generation TKIs treatment is currently unknown, and any assumptions regarding the differences in long-term effect will generate serious doubts and possible lack of objectivity.

The main difference in clinical effectiveness of alternative TKIs factored in into the model is a slight difference in the frequency of achievement of different types of response to treatment. These data represent an indirect comparison, since neither direct comparison studies of dasatinib and nilotinib, nor meta-analysis of these drugs have been carried out. Thus, in this case we have the assumption based on the currently available data.

The developers used a foreign study as a source of information on utility which may not be fully applicable to the Russian population [20]. However, the result of clinical efficacy simulation is represented not only in the form of quality-adjusted life-years (QALY), but also in the form of life-years saved, that allows to use the model for Russian conditions. It should be noted that in Russia there is no regulatory requirement to use QALY to assess the efficiency of medical technologies application (unlike, for example, in the UK), and life expectancy is often considered by experts to be more important than the number of quality-adjusted life years.

There is a consensus among experts that the data on clinical efficacy can be extrapolated from one population

### Table 3. Source of Data for the Model

<table>
<thead>
<tr>
<th>Type of data</th>
<th>Source of data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data on using resources (amount of medical care for patients with different phases of CML)</td>
<td>Survey of Russian specialists in the period August 31 — September 4, 2009. Tariffs of mandatory medical insurance program in Saint-Petersburg</td>
</tr>
<tr>
<td>Information about the rate of serious side effects (III or IV degrees)</td>
<td>Results of clinical trials [16, 17]</td>
</tr>
<tr>
<td>Data on costs of side effects treatment</td>
<td>Survey of Russian specialists in the period August 31 — September 4, 2009. Tariffs of mandatory medical insurance program in Saint-Petersburg</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Study of methods to evaluate the utility [20]</td>
</tr>
<tr>
<td>Costs for second generation TKIs</td>
<td>Data on procurement of drugs at auctions given for September 2010</td>
</tr>
</tbody>
</table>

### Table 4. Characteristics of CML Patients Participating in Clinical Trials of Second-Line Treatment with TKIs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median of age of patients, years</td>
<td>56</td>
</tr>
<tr>
<td>Proportion of males in the total sample, %</td>
<td>50</td>
</tr>
<tr>
<td>The number of months from the moment of CML diagnosis</td>
<td>55</td>
</tr>
</tbody>
</table>
of patients to another (if there is no reason to assume the contrary, for example, because of the ethnic differences). However, the amount of medical care and the cost of medical services and drugs should be consistent with the country for which pharmacoeconomic analysis is carried out. In this case, the developer of the model used local data on the resources used for medical care provided to patients (based on the expert interviews in the large constituent entity — Saint Petersburg), that makes the model suitable for the pharmacoeconomic analysis with regard to the Russian health care system.

Thus, the model developed by the IMS Health allows to describe adequately the course of the disease and to make necessary calculations for the “cost-effectiveness” and “cost-utility” analysis.

**Pharmacoeconomic analysis**

The cost of CML therapy for one patient throughout the lifespan for dasatinib and nilotinib is 17 705 976 and 21 139 901 rubles respectively. In the first case, the cost of the drug was equal to 17 100 314 rubles, and the costs associated with other elements of medical care and side effects were equal to 605 562 rubles. In the second case, these figures were 20 537 050 and 602 851 rubles respectively (Fig. 2).

The number of life-years and QALY saved was a bit higher for dasatinib compared to nilotinib: 7.02; 6.75 and 6.93; 5.65 respectively (Table 5). Thus, dasatinib is a preferred alternative: its use in comparison with nilotinib allows saving 3 434 025 rubles while life expectancy increases by 0.1 years (equivalent to 37 days which is a little over 1 month).

The simulation results for the different observation periods have shown that the cost difference in favor of

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total costs, rubles</td>
<td>17 705 876</td>
<td>21 139 901</td>
<td>– 3 434 025</td>
</tr>
<tr>
<td>Number of life- years saved</td>
<td>7.02</td>
<td>6.93</td>
<td>0.10</td>
</tr>
<tr>
<td>Number of quality- adjusted life- years (QALY)</td>
<td>5.75</td>
<td>5.65</td>
<td>0.10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of life- years saved</td>
<td>0.90</td>
<td>0.90</td>
<td>0.00</td>
</tr>
<tr>
<td>Number of quality- adjusted life- years (QALY)</td>
<td>0.74</td>
<td>0.74</td>
<td>0.00</td>
</tr>
<tr>
<td>Costs of the drug, rubles</td>
<td>2 301 070</td>
<td>2 814 169</td>
<td>–513 099</td>
</tr>
<tr>
<td>Other medical costs, rubles</td>
<td>78 287</td>
<td>78 824</td>
<td>–537</td>
</tr>
<tr>
<td>Total costs, rubles</td>
<td>2 379 357</td>
<td>2 892 993</td>
<td>–513 636</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dasatinib</th>
<th>Nilotinib</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of life- years saved</td>
<td>5.43</td>
<td>5.37</td>
<td>0.06</td>
</tr>
<tr>
<td>Number of quality- adjusted life- years (QALY)</td>
<td>4.42</td>
<td>4.36</td>
<td>0.06</td>
</tr>
<tr>
<td>Costs of the drug, rubles</td>
<td>13 111 921</td>
<td>15 777 175</td>
<td>–2 665 254</td>
</tr>
<tr>
<td>Other medical costs, rubles</td>
<td>472 087</td>
<td>472 060</td>
<td>27</td>
</tr>
<tr>
<td>Total costs, rubles</td>
<td>13 584 008</td>
<td>16 249 235</td>
<td>–2 665 227</td>
</tr>
</tbody>
</table>
dasatinib is already evident after one year of the therapy and increases with extension of the observation period (Table 6). There is no difference in effectiveness during the first year but by the tenth year dasatinib shows a slight advantage.

One-sided sensitivity analysis of the results of the model has demonstrated their low sensitivity to the drug price variations within 0 to 20%.

It should be noted that small differences in the clinical efficacy of the drugs identified in the model are currently based on the assumption, since no direct comparative studies of dasatinib and nilotinib were conducted. It is useful to accumulate and summarize data about practical effectiveness of the second generation TKIs that will allow making a more accurate conclusion on the clinical and economic aspects of their use.

CONCLUSION

The use of dasatinib compared to nilotinib is more cost-effective for second-line treatment of imatinib-resistant or intolerant patients with CML. At that the price of the second-generation TKI drugs is a key factor which determines the difference between them in terms of pharmacoeconomic analysis.

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Expert Evaluation

New Medicines. How Can Innovativeness Be Assessed?

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The modern system of regulation of medicines turnover includes two stages of expert examination. The first one, pre-registration examination, precedes the state registration of medicines and is oriented, mostly, to the assessment of their safety and clinical efficacy compared with placebo, other drug, sometimes not registered in the territory of the country; the second one is connected with the assessment of comparative efficacy of the drugs previously approved before its inclusion into limited and reimbursement lists [1].

For justice’s sake, it should be noted that the pharmaceutical industry plays a very important role in development of the drug evaluation system. This role is connected with formation of competitive environment and necessity of creation and presentation of conclusive arguments supporting efficacy and safety of drugs. This, in turn, dictates the need for creative approaches in organization and performance of clinical trials, interpretation of their results, increase of strength of evidence, carrying out studies for comparison with the real practice, as well as implementation of other economic and statistical instruments of analysis.

Thus, at examination of new drugs, initially including assessment of their efficacy and safety, administration convenience and cost of a pack, now consideration of additional parameters of its clinical efficacy and economic efficiency as well as socially significant parameters of the corresponding disease is stipulated. To the latter ones, prevalence and social and economic burden of the disease, results of cost-effectiveness analysis and budget impact analysis, changes of quality of life, evaluation of cost of additional therapeutic value of the drug, its effectiveness in real practice in different groups (segments) of patients can be attributed. Possibility of promotion and subsequent funding of new drugs because of regarding them as highly innovative technologies should be considered separately.

In its turn, the state implements additional regulatory barriers for control and restriction of drug supply expenses. These barriers may include implementation of health technologies assessment (HTA) and the DRG system (diagnosis-related groups) for in-patient care funding, development of approaches to price regulation for medicines, criteria for generic and therapeutic replacements [2]. Change of responsibility for drug supply financing, including drugs into “negative” lists or assignment of the “over-the-counter” status to them can also be considered as this kind of measure. Some countries have chosen the way of increasing the budget for drug supply using tax and excise rise, as well as increase of insurance contribution in the system of medical (including drug) insurance. Some countries, including the RF, take measures on restriction of promotion and advertising of medicinal products or implement legislative increase of tax burden on activity connected with it (France) [3].

Drug supply is the most science intensive and innovative area of development of new treatment technologies. Implementation in practice of innovative medical technologies and medicines leads to the change of approaches to monitoring and treatment of diseases, improves the quality of life, and at the same time, increases expenses of the health care system. At that, drug manufacturers often, but not always, use the term “innovative” as an instrument for promotion of the drug.

State regulatory organs appear to be pressed by the industry, professional communities, and associations of patients on inclusion of new technologies in the system of their reimbursement. However, considering permanently restricted budgets, it is rather difficult to make a reasonable choice in the favor of these or those technologies, and
sometimes it is practically impossible. As a result — decisions appear to be non-systemic, insufficiently clear and subjective.

It is necessary to admit that in the modern world there exists a definite level of dissatisfaction with regulatory organs caused by doubts in objectivity and transparency of decisions on financing and reimbursement of medical technologies. Apparently, these “claims” may be regarded fair only in the case when expert professional community manages to achieve consensus on main requirements to submission of necessary information on technologies from one hand, and — on criteria of decision-making, from the other hand. Disregard of these approaches, counteraction to their implementation in the real practice of making managerial decisions may be considered as a sufficient shortcoming and “narrowness” of mind of members of administrative staff in the health care system. At the same time, accusation of regulatory organs in making subjective decisions seems to be premature and quite unsupported, as there are no elaborated and validated technologies for their decision-making.

Today innovative technologies make serious contribution to the improvement of quality of medical care, and this circumstance determines the need for search of rational balance between availability and their acceptance, including financing of innovations themselves. That’s why, necessity of development of technologies for quantitative or score assessment of innovativeness of medicines with possibility of its further practical use becomes obvious. Stated plans of the Russian Government about state support of the innovative way of development of the pharmaceutical industry transfer discussion of the problem of determination of innovative medicines from the theoretical plane into the sphere of practical decisions.

Currently, innovations may be defined as created (implemented) new or advanced technologies, types of production or services, as well as organizational and technical decisions of manufacturing, administrative, commercial or another direction, facilitating promotion of technologies, products and services to the market. Innovations may be connected with the creation of a new product, decrease of its production expenses or increase of value (significance) of the already existing product. Innovativeness assessment in medicine cannot neglect its value and significance for the health care system and patients.

Innovative activity in the pharmaceutical industry may provide production of a new substance, revelation of a new indications or a new way of administration for the already existing product. All three types of innovations may provide significant value of the drug for a patient. Mainly, development of innovations today is focused on synthesis of new active substances, but wider approaches should be taken in account.

Currently, several concepts of innovations in pharmaceutical industry are being discussed. The technological concept is connected with the change in technology of drugs development and production, for example, creation of an isomer or a metabolite of some already used medicine, as well as application of biotechnologies in production and development of new systems of the active substance delivery. The commercial concept suggests a new approach to the organization of manufacturing process, its logistics and positioning providing increase of commercial attractiveness for a company-manufacturer. Appearance and registration of a new form of the drug, a new indication for its use and a new treatment method using a specific drug can be attributed to these approaches. “Customer’s” interest to the technology innovativeness determines the therapeutical concept connected with the development of a new treatment method, change of care tactics providing additional therapeutic effect, i.e. real advantages for a patient — due to more efficacy, safety and convenience of administration.

From the common sense, the degree of innovativeness should be influenced by such factors as the degree of novelty of the drug compared with the existing medicinal practice, the degree of influence on duration and quality of life of patients, safety profile, convenience of administration of the drug and etc.

In the world practice, approaches to the assessment of medicines’ innovativeness are different and before now have been poorly agreed.

There are approaches determining innovativeness at the stage of pre-registration examination, for example, for identifying the drugs that should get priority market authorization (USA). Other countries carry out innovativeness assessment for making decisions on reimbursement and inclusion of drugs into limited lists (France, Italy, Sweden).

Food and Drug Administration, FDA, assesses such characteristics as composition, molecule novelty and therapeutical significance of the drug in market authorization process [4]. FDA specifies the following groups of medicines:

- new molecular formula or chemical compound not registered and not used before in the USA territory;
- chemical derivative of an existing and earlier approved drug;
- new medicinal form of an earlier registered drug;
- combination of two and more active substances of earlier registered drugs;
- reproduced drugs (generics);
- new indications for registered drugs (change of the drug status — prescription/over-the-counter);
- medicines that are presented in turnover but not approved by FDA.

The Association of German Innovative Manufacturer suggests classification of innovations on
similar criteria depending on presence of specific parameters, such as [5]:

- new active substances for the treatment of diseases, for which no effective therapy existed before (for example, the vaccine against herpes, therapy of thrombocytopenic purpura, age-dependent macular degeneration of the retina);
- new principle of action in the treatment of the disease if no effective enough therapy was known (infliximab, adalimumab in the treatment of juvenile rheumatoid arthritis);
- new medicinal forms providing useful properties of already known active substances: higher bioavailability, less adverse events or more convenient dosing regimen [more advanced forms of delivery of inhalation glucocorticoids (IGCS) for the treatment of bronchial asthma, Zetamax for the treatment of community-acquired pneumonia];
- new technologies decreasing risks caused by an active substance (gene-engineered blood-clotting X-factor at hemophilia); new indications for known drugs (monoclonal antibodies for the treatment of other malignant tumors);
- combination of several earlier known and used substances (IGCS and beta-agonists, drugs for plasma lipid level decrease and calcium antagonists — the concept of “poly-tablet” or “multipill”).

Innovative activity can not only influence the manufacturing process, but lead to creation of a new product, change its qualities from the viewpoint of its value. In practice, it is very difficult to differ the product innovativeness from innovativeness of the manufacturing process. At the same time, an innovative product requires innovative manufacturing, i.e. an innovative process. Some innovations may directly influence creation of new drugs, while other appear in the result of fundamental research, just initiate or stimulate development of new innovative decisions and do not allow rapid return of investments.

Today it is possible to single out the following prioritized directions in development of innovative medicinal technologies:

- synthesis of new chemical products;
- synthesis of pharmacologically active metabolites or their isomers (as an example of successful realization of this strategy, it is possible to refer, specifically, to the antibacterial drug levofloxacin — L-isomer of ofloxacin, that relatively recently has appeared in the market; antisercretory drug esomeprazole, which is an S-isomer of omeprazole; anticonvulsant oxcarbazepine);
- development of new medicinal forms with improved pharmacokinetic properties that ensure maintenance of constant concentration of an active substance in blood and help to decrease multiplicity of MP administration;
- new methods of drugs delivery — inhalation, nasal, transdermal;
- biotechnological and bioengineer technologies that are ones of the most dynamically developing modern scientific directions;
- development of multi-component drugs, so-called multipills, combined from several drug with proved efficacy and safety (for example, the combination of amlopidine and atorvastatin — drug Caduet manufactured by Pfizer; combination of atorvastatin and torcetrapib increasing high density lipoprotein

### Table 1. Assessment Criteria for Innovative Projects in the Area “Pharmaceuticals”

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
<th>Scores of assessment system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innovative orientation</td>
<td>Characteristics of innovations</td>
<td>Drugs</td>
</tr>
<tr>
<td>Patentability of intellectual property</td>
<td>Novelty level and promising prospects of innovative Russian medical products</td>
<td>1 — reproduction of advanced processes of development used in the world (absence of patent prospects at lack of risks of patent disputes); 3 — patent value in the RF, convincing evidences of competitive ability compared with analogues; 7 — existence of world-class patents (not only countries from the former USSR), convincing evidences of competitive ability compared with analogues</td>
</tr>
<tr>
<td>Completeness and quality of preclinical studies</td>
<td>Assessment of preclinical studies</td>
<td>3 — study drug metabolism and safety are investigated; 5 — mechanism of action of the study drug is investigated on clinical condition /diseases models; 7 — therapeutical index (ratio of mean lethal dose LD50 to mean effective dose ED50 determined based on clinical condition /diseases models of the study drug is higher than a comparator with the level of clinical efficacy probabilistic force not less than “B” in the treatment of specific disease or clinical condition</td>
</tr>
</tbody>
</table>
level in blood plasma, currently being studied in the III phase of clinical trials; the combination of new hypolipidemic agent blocking cholesterol absorption in the gastrointestinal tract, ezetimib and simvastatin — Vytorin (the drug is produced by Merck/Schering-Plough, it helps to decrease significantly low density lipoprotein and triglyceride levels in blood plasma) and etc.

At present, in the RF, development of domestic pharmaceutical industry is taking place programs of replacement of imported product are launched. That’s why development of criteria determining innovativeness of drugs for statement of priorities and formulation of policy of state support of the pharmaceutical branch are discussed increasingly more actively. The task force “Medical techniques and pharmaceutics” at the Commission on modernization and technological development of Russian economy under the President of the Russian Federation in 2010 formulated certain approaches to innovativeness assessment at realization of projects aimed at replacement of imported products. Criteria of score assessment of innovative projects in the area “Pharmaceuticals” are presented in table 1.

As it can be seen from table 1, at assessment of project innovativeness in the pharmaceutical industry, the following main parameters of medicines’ innovativeness are taken in account: new manufacturing technology, way of delivery, formula, influence on a new “target”, new mechanism of action of drugs. However, patients’ and doctors’ points of view, the opinion of the Ministry of Health and Social development of the RF — the main payer for medicines are not taken into account and are not sufficiently discussed. Actions organized with participation of the pharmaceutical industry, representatives of the Ministry of Industry and Trade of the RF and the Ministry of Education and Science of the RF do not have the objective to discuss issues of value and innovativeness of new medicines from the position of patients and health care organisations.

Each factor presented in the figure allows the drug being regarded as innovative with all subsequent preferences for inclusion into limited lists, treatment standards, programs with state financing. However, particularly therapeutical innovativeness, i.e. added therapeutic effect of any new drug determines reasonability of its development and the following funding. All factors of development, production, distribution, character of excipients and combinations are meaningful only from the position of this specific additional value of the product for the final consumer, i.e. for a patient. Other parameters, not supported in terms of clinical advantages of the drug, do not have the right to additional or supplementary financing and most often are of speculative character.

Positions of the Ministry of Industry and Trade of the RF and the Ministry of Education and Science of the RF on the question may be different due to diverse interests of these offices and the Ministry of Health and Social development of the RF.

Thus, a number of innovations can really be considered as undoubtedly promising and necessary for development of both pharmaceutical science and the whole branch.
However, their financing should not be based on additional expenditure of always restricted and insufficient budget of the health care system, as it will lead to decrease of coverage and intensity of medical care without any guarantee of its quality increase. Therapeutic advantages of medical technologies determine their innovativeness for a patient. At the same time, despite different points of view, the common way of innovativeness assessment is consideration of the added therapeutic effect of a new product compared with the existing variants of treatment.

Nevertheless, certain difficulties with formulation of the concept of therapeutic innovativeness exist:
- added therapeutic effect of the product may depend on medical practice and clinical culture in the health care system;
- added therapeutic effect may be assessed either by comparing the degree of a patient’s condition improvement, number of added years of life, or from the position of safety and decrease of adverse events of the drug.

Let’s try to formulate main questions, we have to answer to determine novelty, value and significance of innovation for its final consumer:
- Does the technology increase survival and decrease expenses for treatment?
- How does the technology influence expenses of the health care system as a whole?
- Does the technology facilitate patients returning to the normal life and restoration of their work capacity?
- Does this intervention have advantages on the considered parameters compared with existing and used alternatives?

The superior independent advisory organ in the sphere of health care in France — Haute autorite de sante (HAS) — ranges main criteria of drugs innovativeness according to the classification on ASMR scale characterizing a new drug by their additional therapeutic effect compared with the existing practice of treating patients with a particular disease [6].

Innovativeness score ranges from 1 to 5 points:
I. Maximal degree: “Maximal therapeutic progress”.
II. Significant degree: “Essential improvement”.
III. Moderate degree: “Moderate improvement”.
IV. Insignificant degree: “Insignificant improvement”.
V. “No improvements”.

The Sweden system suggested by the HTA agency “Dental and Pharmaceutical Benefits Agency” TLA assesses parameter of economic efficiency stimulating innovations from the point of view of social expectations [7].

Decision-making is based on three principles:
- value for a patient;
- need and social justice;
- cost-effectiveness.

The Italian medical agency L’Agenzia Italiana del Farmaco (AIFA) at decision-making on drugs reimbursement carries out innovativeness assessment based on the disease severity and prevalence, availability of existing treatment methods and the degree of their therapeutic effect [8]. The elaborated system reflects therapeutical innovativeness quantitatively based on interlinking and integration of different categories of innovativeness (Fig. 2).

Characteristic features and therapeutic advantages of drugs based on the results of clinical trials allow FDA

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**Fig. 2.** Approaches to Classification of Therapeutical Innovativeness of Drugs Approved in Italy: A — drugs for the treatment of serious life-threatening diseases requiring hospitalization and leading to complete disability (Parkinson’s disease, oncology); B — drugs decreasing or excluding the risk of development of serious diseases (AH, obesity); C — drugs for the therapy of mild, «non-serious» diseases (cold, allergic rhinitis)
to single out three groups of drugs: “O”, “P” and “S”. However, it is necessary to note that this classification is used only for determination of a drug registration procedure for its further use in the USA territory. The group “O” (“orphan drug”) includes drugs for the treatment of orphan diseases receiving a separate registration status. The group “P” (“priority review drug”) contains drugs possessing significant therapeutic advantages compared with the existing drugs. Inclusion of the drug in this group is determined by existence of advantages at consideration of an application for market authorization. To the group “S” (“standard review drug”), drugs with efficacy similar with preparations available at that moment are referred. Drugs from this group are subjected to the standard evaluation procedure. Not all new molecular compounds are necessarily classified by FDA as drugs for the group “P”, and, on the contrary, — not all drugs from the group “P” are well-known. It may be connected with modification of previously known drugs, stipulated by new indications, as well as lack of additional advantages of the new drug.

Today, it is possible to note three main approaches to determination of therapeutical innovativeness and its influence on the price of the drug and its reimbursement degree (Fig. 3). The first approach is determined by free pricing, subsequent assessment of treatment expenses and outcomes, as well as assessment of the number of patients and need for the drug. The second approach is based on the assessment of therapeutical efficacy of the drug, i.e. its value, and taking this into account, gradation of its innovativeness level, determination of its price and reimbursement level are carried out. The third approach is based on the assessment of innovative properties of the drug determining its price and reimbursement level.

Proceeding from the main principles of drug provision and clinical pharmacology, it is possible to specify rather big number of parameters to this or that extent influencing the value of innovation (Table 2).

As follows from the table, the list of parameters determining the value of new technologies includes properties of the drug itself, such as the molecule novelty and production of the disease, clinical and economic efficacy and etc.

At the same time, factors determined by the disease itself, such as prevalence, life threat, disability risk and others, can be allocated among these parameters. Each of them from the common sense can influence innovative attractiveness of the drug. However, it is important to find out, which particular parameter from the list determines the total technology value, i.e. its innovativeness.

Thus, today it is necessary to single out and assess a relative weighted significance of main properties of drugs determining their innovative value for a patient and for the whole health care system.

This will make possible consolidation of experts’ and professional communities’ opinions, as well as patients’

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**Fig. 3. Modern Approaches to Medicines’ Therapeutic Innovativeness Assessment:**

<table>
<thead>
<tr>
<th>Approach A</th>
<th>Approach B</th>
<th>Approach C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free pricing</td>
<td>Based on classification depending on the product</td>
<td>Based on individual characteristics of the drug</td>
</tr>
<tr>
<td>Ex-post analysis assessment of expenses and treatment outcomes</td>
<td>The assessment is directed to:</td>
<td>The analysis is based on the following:</td>
</tr>
<tr>
<td></td>
<td>✓ Analysis of the degree of clinical effect improvement</td>
<td>✓ Assessment of the product properties from the point of view of innovativeness</td>
</tr>
<tr>
<td></td>
<td>✓ Ranging of the improvement degree according to the innovativeness level and based on the latter characteristic-determination of the character of reimbursement and price</td>
<td>✓ Character of reimbursement and price are determined by these properties of the drug</td>
</tr>
<tr>
<td></td>
<td>Determination of need</td>
<td>Determination of reimbursement and P&amp;R status</td>
</tr>
</tbody>
</table>

Approach A:
- Free pricing
- Ex-post analysis assessment of expenses and treatment outcomes
- Determination of need

Approach B:
- Based on classification depending on the product
- Ex-ante analysis incremental analysis of innovations

Approach C:
- Based on individual characteristics of the drug
- Determination of reimbursement and P&R status
points of view, for answering the question — what should be considered as innovation? For the medicines’ innovativeness analysis it is necessary to create the unified system of their assessment and classification of therapeutical value for making decisions on their further financing and reimbursement. It dictates a need for development of a “scale” for ranging the total innovativeness of drugs incorporated in the transparent system of assessment, along with the other variables of their analysis, such as efficacy, change of quality of life, economic acceptability, consideration of the disease severity and etc.

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<table>
<thead>
<tr>
<th>Parameters of the drug</th>
<th>Innovativeness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Influence on disability</td>
</tr>
<tr>
<td>Safety</td>
<td>Influence on quality of life</td>
</tr>
<tr>
<td>Administration convenience</td>
<td>Influence on life duration</td>
</tr>
<tr>
<td>Administration regimen</td>
<td>New active substance</td>
</tr>
<tr>
<td>Existence/absence of pharmaceutical therapy of the disease</td>
<td>New principle of action</td>
</tr>
<tr>
<td>Whether the drug is life-saving</td>
<td>Use of new production technology</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>New medicinal form</td>
</tr>
<tr>
<td>Disease cost</td>
<td>Use for new indications</td>
</tr>
<tr>
<td>Disease epidemiology</td>
<td>New combination of drugs</td>
</tr>
</tbody>
</table>
Methodology

Methodological Issues of Cost-of-Illness Analysis

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Cost-of-illness analysis is a method for evaluating the total cost of a disease given the actual state of current medical practice, regardless of the applied or desired methods of diagnosis, treatment and prevention. There are various ways to evaluate the direct and indirect costs of diseases, each has its advantages and disadvantages. We discuss the pros and cons of microcosting as a method for estimating direct costs compared with the method based on charges. Different methods of estimating costs produce incommensurable results, thus lowering the practical significance of such studies. There is a need for standardized methodology that will increase the significance of cost-of-illness analysis for the determination of healthcare policy.

KEYWORDS: cost-of-illness analysis, pharmacoeconomic analysis, direct costs, indirect costs, microcosting, human capital method, friction costs method, absenteeism, presenteeism.

Cost-of-illness studies aim to evaluate the economic burden of a particular disease or health condition through identification, measurement and evaluation of its direct and indirect costs [1]. This method reflects the existing practice, regardless of the applied or desired methods of diagnosis, treatment and prevention.

Cost-of-illness studies are not considered to be a part of pharmacoeconomic analysis by foreign experts, since its goal does not include the assessment of the impact that particular medical technologies might have. The cost-of-illness is not mentioned in the tour-de-force monograph [2] that describes the methods of economic evaluation in healthcare. Russian experts count cost-of-illness analysis among the supplementary methods of economic evaluation [3], thus emphasizing its importance for Russian healthcare. However, the practical significance of cost-of-illness analysis for healthcare policies is still debated in the international medical periodicals. Some experts are even concerned that the estimated costs might confuse decision makers, since the identification of those areas where the greatest expenditure occurs does not mean that these resources are spent ineffectively. Inefficiency only becomes a concern if there are alternative ways of allocating resources, as when there are other technologies that could be more beneficial in terms of public health. However, the evaluation of alternative solutions is precisely the domain of full-scale pharmacoeconomic studies, which rely on cost-effectiveness, cost-utility and cost-benefit analyses [4, 5].

Even so, it is certainly necessary to have some cost-of-illness data in order to conduct a classical pharmacoeconomic study. For instance, pharmacoeconomic analysis that justifies the introduction of a new, more expensive technology is commonly based on the assumption that its use will reduce the risk of, or delay the onset of, serious health conditions (such as heart attack, stroke, diabetes, etc). This assumption cannot be comprehensively tested without an assessment of the cost of such medical conditions. Cost-of-illness evaluations performed in comparative pharmacoeconomic studies can subsequently lay the foundation for a database proving the clinical efficacy and economic acceptability of a novel technology as it is included in limited lists and as financial decisions are made.

Furthermore, cost-of-illness studies of particular conditions will promote the recognition of their social significance and allow for greater objectivity in setting the priorities and allocating resources in the healthcare system, for example by identifying the areas in which clinical and economic evaluation of alternative diagnostic, therapeutic and preventive procedures is of particular importance.

The modern system of evaluating medicinal drugs and medical technologies for their inclusion in reimbursement and financing lists is crucially dependant on an assessment of the social significance of the condition which is targeted by the technology, since such decisions are driven by considerations of planning and allocating financial resources. From this perspective, the social significance of an illness depends on its epidemiology, diagnostics, recommended and actual treatment methods, and its social and economic burden (the cost of illness). In other words, the economic burden of illness, or the cost of illness, consists of a number of parameters that need to be considered when decisions regarding reimbursement and financing of medical technologies are made.

Apart from the important aspects of cost-of-illness studies discussed above, they produce additional insights
into optimal management of the disease itself. For instance, they generate disaggregated data on individual patients and the cost of illness management (including treatment), identify possible “scenarios” of managing patients, and define groups or categories of patients that demand different approaches and accordingly entail different treatment costs.

Such studies make it possible to analyze the structure of expenditures for a particular disease in order to suggest ways in which these resources could be reallocated within this disease, and to compare it with the costs of other health conditions.

A detailed study of a disease that attracts little attention from state authorities and assessment of its impact in terms of economic and social burden has the potential to form the basis on which one can argue that its social significance status needs to be upgraded and “lobby” for more financial resources for its diagnostics and treatment.

From a different perspective, such studies have produced a body of data of considerable significance for strategic planning of drug and medical technology promotion (market access), which is widely used by pharmaceutical companies.

Studies of the economic burden of diseases are supported by the WHO and the World Bank, and this fact is indirect proof that cost-of-illness data are of importance to policy-making in the healthcare. However, their studies use a different approach: the cost of a particular illness for the society is expressed in the number of disability-adjusted life-years lost, rather than in terms of monetary costs [6].

Two techniques of performing cost-of-illness analysis that differ in the method of evaluating morbidity have been published:

1) incidence-based;
2) prevalence-based [7, 8].

In the first approach, anticipated life-long expenditures are calculated for the cohort of patients who became ill in a given year. In the second approach, the expenditures for all patients suffering from the disease at a particular time point (usually a year) are calculated. This method consumes fewer resources, since it requires considerably less data compared to the first approach. From the practical point of view, the two methods are complementary. The analysis of prevalence identifies the areas of greatest expenditures, in which it may be expedient to introduce reasonable restrictions or reallocate the resources. On the contrary, a clinical and economic analysis of prevention techniques requires data on primary morbidity, i.e. the anticipated life-long expenditures for patients suffering from a specific disease.

Ideally, a cost-of-illness analysis should be performed from the societal perspective and consider all the costs of a particular disease: direct, indirect, and the so-called intangible costs (Fig. 1).

![Cost-of-Illness Analysis](image)

**Fig. 1.** The Types of Costs Considered in a Cost-of-Illness Analysis
Direct costs measure the expenditures with regard to the alternative value of spent resources, or the "opportunity cost", i.e. the sum that could be spent on something else if this disease did not exist. Direct costs include medical costs (the expenditures of the healthcare system for the provision of medical care) and nonmedical costs (expenditures in other sectors, such as social benefits and personal costs for the patient — transportation to the place where medical care is provided, lifestyle changes due to illness, etc).

Indirect costs measure the value of goods and services that would have not been produced because of the disease: the social losses in productivity due to temporary or permanent disability and premature death. Finally, intangible costs refer to the suffering of the patient due to illness (e.g. pain or loss of ability to move), which is obviously present but hard to express in monetary terms.

The evaluation of direct costs of a disease is the common task of both cost-of-illness analysis and classical methods of economic evaluation: cost-effectiveness, cost-utility and cost-benefit analyses. Cost-of-illness analysis of direct costs employs two approaches: top-down and bottom-up. The top-down approach classifies the known expenditures in the health sector according to groups of diseases or single diseases. For instance, if we are interested in the cost of hospitalizations for acute myocardial infarction, we multiply the total cost of hospitalizations by the percentage of hospitalizations due to myocardial infarction. Similarly, the cost of doctor visits, medications etc can also be calculated.

The bottom-up approach starts with an assessment of the amount of medical care provided to patients with a particular disease and its monetary value, i.e. a bottom-up calculation of the cost of hospitalizations for myocardial infarction would multiply the number of patient-days for myocardial infarction by the cost of one patient-day of hospitalization; the cost of doctor visits would be calculated as the product of the number of visits and the cost of one visit, etc.

As this description shows, the two approaches require different types of data, thus the choice of the method may depend on what information is available. The top-down approach was used in the classical research carried out in the USA by D. Rice (1966) and B. S. Cooper & D. Rice (1972) — two studies which are usually cited as the first full-scale assessment of the cost of illness and remain the methodological cornerstone of all contemporary studies with similar goals [9, 10]. The authors presented the distribution of direct costs among the major categories of diseases, using the data of the Department of Social Insurance on various healthcare expenditures (hospitalization, doctor visits, etc), the data of National Center for Healthcare Statistics on the number of patient-days of hospitalization for various diagnoses, a number of other open-access sources (Table 1). The top-down approach is still used in a number of cost-of-illness studies, but the bottom-up method is becoming increasingly common, perhaps because data on the allocation of budgetary resources into different categories of medical care and diagnosis are not always available. Thus, so far it would be impossible to use top-down methods in the RF, since the necessary statistics are not available.

Theoretically, bottom-up assessment of direct medical costs appears fairly straightforward: all that is needed is an estimate of the number of patients with a particular illness, the extent of medical care they receive, and its monetary cost. But in practice, bottom-up assessment of direct medical costs in the RF faces many difficulties. First of all, there is usually insufficient data on disease prevalence and the management of patients in real-life clinical practice. State statistical sources do not register or analyze the prevalence of many diseases and the data on the extent of medical care provided to patients with specific diseases (even summarized as the number of visits or patient-days) is also often missing. To obtain the data needed to perform the calculations, researchers have to rely on isolated studies or expert evaluations.

Moreover, some peculiarities of the system through which the healthcare is financed also spawn multiple methodological problems. For example, the prices of medical services show considerable variation across medical organizations and federal regions, and the current control of reimbursement and multi-channel financing of medical organizations is inadequate. As a result, different studies rely on various approaches to the estimating medical costs, so that the results of such studies are often incomparable. Some studies perform the calculations using prices in commercial medical care, some rely on the tariffs of mandatory medical insurance (MMI), while some prefer the financial standards of the Program of the state guarantees of free medical care rendering for citizens of RF. Besides, the researchers are forced to make numerous assumptions. Thus, the costs estimated from the MMI tariffs are sometimes adjusted using a coefficient equal to the share of MMI in the total healthcare expenditures [11]. All of these problems are equally relevant both to pharmacoeconomic studies, and to cost-of-illness analyses. The effect that the choice of method has on the offered estimates of direct medical costs is particularly clearly seen in the case of pharmacoeconomic studies. Different methods of estimating direct costs may...
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total</th>
<th>Hospitalizations</th>
<th>Doctor visits</th>
<th>Dental care</th>
<th>Other professional care</th>
<th>Medications</th>
<th>Glasses and other rehabilitation devices</th>
<th>Nursing home care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>75281</td>
<td>34219</td>
<td>16916</td>
<td>5581</td>
<td>1717</td>
<td>8628</td>
<td>1896</td>
<td>6274</td>
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<td>Infective and parasitic diseases</td>
<td>1412</td>
<td>660</td>
<td>333</td>
<td>5</td>
<td>192</td>
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<td>Neoplasms</td>
<td>3872</td>
<td>2957</td>
<td>528</td>
<td>-</td>
<td>47</td>
<td>186</td>
<td>-</td>
<td>154</td>
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<tr>
<td>Endocrine, nutritional, and metabolic disorders</td>
<td>3436</td>
<td>920</td>
<td>1294</td>
<td>-</td>
<td>25</td>
<td>869</td>
<td>-</td>
<td>328</td>
</tr>
<tr>
<td>Diseases of the blood and blood-forming organs</td>
<td>491</td>
<td>228</td>
<td>151</td>
<td>-</td>
<td>4</td>
<td>77</td>
<td>-</td>
<td>31</td>
</tr>
<tr>
<td>Mental disorders</td>
<td>6985</td>
<td>5261</td>
<td>685</td>
<td>-</td>
<td>9</td>
<td>434</td>
<td>-</td>
<td>596</td>
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<td>Diseases of the nervous system and sense organs</td>
<td>5947</td>
<td>1033</td>
<td>1294</td>
<td>-</td>
<td>655</td>
<td>594</td>
<td>1896</td>
<td>475</td>
</tr>
<tr>
<td>Diseases of the circulatory system</td>
<td>10919</td>
<td>5271</td>
<td>1676</td>
<td>-</td>
<td>86</td>
<td>1305</td>
<td>-</td>
<td>2581</td>
</tr>
<tr>
<td>Diseases of the respiratory system</td>
<td>5981</td>
<td>2473</td>
<td>1851</td>
<td>-</td>
<td>30</td>
<td>1460</td>
<td>-</td>
<td>117</td>
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<tr>
<td>Diseases of the digestive system</td>
<td>11100</td>
<td>3996</td>
<td>880</td>
<td>5581</td>
<td>43</td>
<td>444</td>
<td>-</td>
<td>156</td>
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<tr>
<td>Diseases of the genitourinary system</td>
<td>4471</td>
<td>2699</td>
<td>1089</td>
<td>-</td>
<td>34</td>
<td>571</td>
<td>-</td>
<td>78</td>
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<tr>
<td>Complications of pregnancy, childbirth, and the puerperum</td>
<td>2607</td>
<td>2881</td>
<td>151</td>
<td>-</td>
<td>39</td>
<td>86</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diseases of the skin and subcutaneous tissue</td>
<td>1525</td>
<td>488</td>
<td>656</td>
<td>-</td>
<td>6</td>
<td>354</td>
<td>-</td>
<td>21</td>
</tr>
<tr>
<td>Diseases of the musculoskeletal system and connective tissue</td>
<td>3636</td>
<td>1661</td>
<td>770</td>
<td>-</td>
<td>368</td>
<td>425</td>
<td>-</td>
<td>412</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>381</td>
<td>313</td>
<td>44</td>
<td>-</td>
<td>3</td>
<td>8</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>Accidents, poisonings, and violence</td>
<td>5121</td>
<td>3134</td>
<td>1222</td>
<td>-</td>
<td>88</td>
<td>852</td>
<td>-</td>
<td>375</td>
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<tr>
<td>Other</td>
<td>7398</td>
<td>794</td>
<td>4292</td>
<td>-</td>
<td>825</td>
<td>1271</td>
<td>-</td>
<td>716</td>
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</table>
even lead to diametrically opposed conclusions regarding the economic acceptability of medical technologies. For instance, in a pharmacoeconomic study that compared two treatments of patients with critical limb ischemia, alprostadil (vasaprostan) *versus* traditional treatment, the cost-effectiveness ratio of alprostadil was lower compared to the traditional practice for the one method of estimation and higher for the other methods (Fig. 2). The incremental cost-effectiveness ratio differed by a factor of 2, varying for different estimation methods from 14 to 29 thousand rubles per one additional case of preventing limb amputation in patients with critical limb ischemia treated with alprostadil compared to the traditional treatment. Obviously, as long as different methods for estimating direct costs are used, the results of cost-of-illness analysis will be useless because they cannot be compared and generalized.

In our view, each of the various methods for estimating direct costs has its advantages and disadvantages. The MMI tariffs so far reflect only a part of the expenditures of medical organizations, though a gradual transition to a comprehensive tariff is being planned. Besides, the tariffs are evidently lower than the needs — the price of the daily dose of some medications is dozens of times greater than the reimbursement for one patient-day at hospital (while the expenditures for medications during hospitalizations are supposed to be covered by the MMI). The same applies to the standards of financial security in the Program of the state guarantees, which are also artificially low, and this is often offered as a good reason to use the commercial medical care prices to estimate direct costs. Physicians, in particular, insist on using this approach, since from their (justified) point of view, no new technology will ever look economically acceptable as long as the calculations are based on the current financial standards.

However, if the analysis is performed from the perspective of the state or healthcare system, the commercial medical care prices are not suitable. Let us imagine that in future such calculations will be used to justify the inclusion of a new drug in the program for the provision of essential medicines. The expenditures for the new medication are calculated from the perspective of the state (the medication costs will be reimbursed from the budget), but the potential benefit from fewer complications is calculated from the perspective of the patient, who pays from personal means for medical services at private organizations. We think that these calculations will be rather unconvincing to healthcare officials, who are well aware that the treatment of complications will be financed from the budget according to current tariffs.

It would be an exaggeration to claim that foreign economists have no experience of calculating direct medical costs. Publications discussing the methodology of cost-of-illness analysis often note that direct costs are estimated based not on the actual cost of medical services, and certainly not on the opportunity cost, but rather on the charges in the healthcare system, since only this information is available. Some specialists regard this aspect of the analysis as a serious methodological drawback: in fact, the charges does not always correspond to the cost of resources expended, since the healthcare system never functions strictly according to the market laws. Direct costs calculated from the standard charges do not adequately reflect the alternative costs, therefore foreign experts regard the method of microcosting as the “gold standard”. This method is based on careful identification of all the resources expended in the course of providing medical care (working time of staff and equipment, material resources etc necessary for performance of the service), and it is certainly considerably more precise compared to the methods that look at the current reimbursement standards, sometimes with very considerable differences in the estimates. For instance, A. Heeley et al. (2002, Ireland) estimated the cost of managing hospitalized patients with HIV, acute myocardial infarction (AMI) and heart failure using microcosting and compared the results with those based on reimbursement standards: the difference amounted to between 9 and 60 % (Table 2). The authors recommend microcosting for all cases when new expensive technology is employed in providing medical care: in this situation the existing reimbursement standards lag behind real-life expenditures [13].

At the same time, microcosting is an extremely labor-intensive method, and despite its advantages, it is thus
necessary to consider the ratio of anticipated gains and time invested. While theoretically this method is superior to all others, in practice it is justified to use microcosting only if the study aims to compare the cost structures in different organizations, e.g. when comparing the costs of patient management on the general medical floor versus specialized units, in central versus local hospitals, etc.

Furthermore, it must be noted that microcosting provides precise data only for the organizations that were investigated, and extrapolating to other organizations or especially to the whole country is necessarily an assumption that is imprecise in proportion to the possible variation in patient treatment and prices of medical services. It is clearly impossible to use microcosting to estimate the cost of patient management in the RF within a reasonable timeframe, not even for a single disease in a representative sample of medical organizations. Accordingly, at present the only realistic way to estimate the cost of illness from the societal perspective is still based on the current financial standards in the healthcare system. In addition, in order to improve the methodology, it would be useful to conduct studies that compare the results of estimating direct medical costs using different methods.

The estimation of indirect costs is an even more problematic part of cost-of-illness analysis. Foreign publications discuss two principle methods of estimating indirect costs: human capital and friction costs. Both methods suffer from serious shortcomings [1, 7, 8].

The human capital method estimates the lost earnings over the period of absence from work due to illness (the average salary for a given age is multiplied by the probability of reaching that age), taking into account the whole duration of disability over the whole anticipated period of working life and assuming that the earnings are equal to the market value of labor. A modification of this method also takes into account housework (mostly for housewives) by including the average earnings of a domestic assistant (assuming that the value of the work performed by a housewife is equal to the salary of a domestic assistant, even though housewives are not salaried employees).

The main criticism of this approach is that it overestimates the costs [14]. Some economists claim that in situations when unemployment is a greater problem than lack of workers, costs for society are limited to the period when the employer is looking for an adequate substitute for the absent worker. This period is called “friction period”, and the method that considers only the costs for this period is known as the friction costs method. If the disability is temporary, it is even easier for the employer to redistribute the tasks among other workers, so that the productivity may only decrease slightly, if at all.

Thus, the friction costs method does not consider the losses over the entire period of disability, but only until the employer replaces the sick worker and trains the new worker to achieve the same level of productivity as the previous worker had before sick leave. This method also has certain drawbacks. First of all, it is hard to know the duration of the friction period. Besides, according to some specialists, the concept of easily replacing one worker with another without any loss of productivity or social damage contradicts the principles of social healthcare, which state that human life has an intrinsic value [15].

The differences between these two methods of estimating indirect costs are quite significant, and again they are better illustrated by pharmacoeconomic

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<th>Table 2. The Cost of Patient Management [13]</th>
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<td>Disease</td>
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<td>---------------------------------------------</td>
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<tr>
<td>Percutaneous revascularization in AMI</td>
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<tr>
<td>AMI with complications</td>
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<tr>
<td>AMI without complications</td>
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<tr>
<td>AMI resulting in death</td>
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<tr>
<td>Heart failure</td>
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<tr>
<td>HIV + serious comorbidity</td>
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<td>HIV without serious comorbidities</td>
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Note: AMI — Acute Myocardial Infarction; DRG — Diagnosis-Related Group

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<th>Table 3. Incremental Cost-Effectiveness Ratios of Combination Therapy for Rheumatoid Arthritis [16]</th>
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<td>Perspective Assumed in the Study</td>
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<tr>
<td>The healthcare system</td>
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<tr>
<td>Society (estimation of indirect costs using the human capital method)</td>
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<tr>
<td>Society (estimation of indirect costs using the friction costs method)</td>
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studies. For example, W.R. van der Hout estimated the total costs of four treatments of rheumatoid arthritis in the Netherlands. If indirect costs were estimated using the human capital method, combination therapy with infliximab was economically acceptable, but with the friction costs method, infliximab showed unacceptably high expenditures per quality-adjusted life year (Table 3; W.B. van der Hout, 2010, the Netherlands) [16].

In the Soviet economic analysis of the healthcare system the cost of absence from work was estimated based on the share of Gross Domestic Product (GDP) produced by one worker per calendar period, rather than the salary [17]. Essentially this is a modification of the human capital method, with all its drawbacks. Moreover, GDP is an aggregate economic indicator that expresses the market value of all goods and services produced in all economic sectors of a country, including healthcare. Therefore it appears that loss of GDP is not equivalent to loss of labor productivity: a sick person continues to take part in the production of GDP, e.g. when he pays for medical care and other services or acquire goods.

There is also another, fairly recent approach to estimating lost productivity: in some cases a worker may be absent without an official sick leave or continue to work while sick, with a lower productivity. These two situations are known as absenteeism and presenteeism, respectively. The rate of unofficial absences from work and the extent of losses in productivity due to illness are determined by means of surveys, following which it is possible to use the methods of human capital or friction costs to estimate the economic costs. Thus, the issue of choosing between these two methods is equally relevant to this aspect of analysis, just as in the case of traditional calculations that consider only documented absence from work.

Thus, at present the methodology of cost-of-illness analysis is far from perfect. Both in Russia and abroad, experts have recommended different methods for estimating direct and indirect costs, and as a result, the estimates are often incommensurable. Each method has its advantages and disadvantages (Table 4). However, healthcare officials need data on the cost of diseases

<table>
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<th>Table 4. The Principle Methods of Cost-of-Illness Analysis</th>
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<td><strong>Method</strong></td>
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<td>Top-down approach</td>
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<td>Bottom-up approach</td>
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<tr>
<td>Microcosting</td>
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<tr>
<td>Estimation using the established standards for reimbursement of charges</td>
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<tr>
<td>Estimation using the prices of medical services in the commercial sector</td>
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<tr>
<td><strong>Estimation of indirect costs</strong></td>
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<tr>
<td>Human capital method, estimation of damage to the society based on lost personal income</td>
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<tr>
<td>Human capital method, estimation of damage to the society based on lost GDP</td>
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<td>Friction costs method</td>
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in order to allocate resources rationally. A unified coordinated methodology of cost-of-illness analysis must be developed in the RF, so that the costs of major diseases to the society can be estimated.

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Clinical And Economical Expertise in Preparing Drug Lists

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The historical aspects of preparing drug lists at the different levels of healthcare system are described. The disadvantages of the current practice for drugs assessment are discussed, and approaches to the system improvement are proposed. The meeting of experts in the field of clinical studies and economic evaluation took place in 2010 at the Research Center for Clinical and Economic Evaluation and Pharmacoeconomics. The experts created the Order of Clinical and Economical Expertise of Drugs in the process of preparing reimbursement drug lists. This document includes clinical and economic expertise rules and requirements for submission and assessment of data and is proposed for drug lists made at all levels of health care system.

KEYWORDS: drug list, clinical and economical expertise.
By now, the formulary drug lists developed locally or in health care organizations do not have any clearly determined common principles, including criteria for drug selection and evaluation, procedures for formulary committees, or algorithms of decision making. Different regions and health care organizations have different criteria for drug selection and evaluation, while formulary committees do not monitor the effectiveness of the implementation of drug lists, no ABC/VEN-analysis of drug consumption is held, and documented evaluation of data on clinical and economical effectiveness of drugs is often declarative [1, 8].

Today, criteria for evaluation of clinical and economical characteristics of drugs are undetermined, and the system of drug lists development and decision-making is unclear. This prompted the leading experts from various academic schools, engaged in clinical and economic analysis and corresponding expertise for many years, to join efforts in order to develop coordinated recommendations for clinical and economical expertise in the process of drug lists development.

Thereby, in the beginning of 2010 the Research Center for Clinical and Economic Evaluation and Pharmacoeconomics at the Russian State Medical University organized two workshops. The first one was devoted to the aspects of clinical expertise, while the second discussed economic evaluation of drugs during the development of reimbursement lists.

The workshop on clinical expertise was attended by 27 experts from Moscow, St. Petersburg, Volgograd, etc., representatives of various research institutions and pharmaceutical companies, and independent experts, engaged in the activities concerning evidence-based medicine, clinical studies and aspects of drugs selection for normative documents.

The workshop dedicated to the economic evaluation was attended by 23 experts from Moscow, St. Petersburg, Volgograd, etc., who represented various academic schools and had experience in clinical and economic analysis including economic evaluation of drugs during development of drug lists.

As a result of these workshops, the draft “Order on Clinical and Economical Expertise of Drugs in the Process of Development of Reimbursement Drug Lists. Decision-Making Criteria” was prepared. The full text of the draft Order will be presented in a separate publication. In the given paper, we briefly outlined the main points of this document.

The purpose of its development was to determine the requirements for reporting clinical efficacy, safety and economic acceptability of drugs, and procedures for clinical and economical expertise in the process of drug lists preparing. The draft Order includes 10 sections, terminology index, and 7 annexes.

According to the draft Order, procedure of drug evaluation by the expert body should include three levels: clinical expertise, economic expertise and making final decision on drug inclusion (exclusion, rejection) based on clinical and economical expertise.

The draft Order describes requirements for submitting data on clinical efficacy and safety, analysis of the common practice of disease management, and economic acceptability of the drug.

According to the draft Order, information about drug efficacy and safety should be based on the results of randomized controlled studies and meta-analysis. The applicant must determine the level of evidence of each submitted clinical trial using the determined scale.

Data on the common practice of the disease treatment should be based on patient registries and/or analysis of in-patient case records (in case of hospital use of drug), or out-patient medical records (in case of outpatient use of drug), and/or survey of competent experts.

The information on the drug economic acceptability/cost-effectiveness should be based on the results of domestic pharmacoeconomic studies. The main types of pharmacoeconomic analysis are: cost-effectiveness, cost-utility, cost-benefit, or, if compared drugs are of equal effectiveness, cost minimization. Cost-of-illness and budget impact analysis can be used as supplementary methods. The draft Order thoroughly describes quality requirements for clinical and economical expertise, selection of comparators, criteria for evaluation of efficacy (outcomes), and costs.

Also, this document determines the order of clinical and economical evaluation of drug in details. According to the document, a clinical expertise covers evaluation of clinical studies, analysis of the common practice of disease management, expertise of bioequivalence and therapeutic equivalence studies. During the evaluation of clinical studies, experts should follow the scale of “Levels of evidence” when considering the quality of each single clinical trial, and the scale of “Grades of recommendations” when assessing the whole body of evidence from different clinical studies. These scales are described in the annexes to the Order.

Economic expertise includes evaluation of the adequacy of selected type of economic evaluation; assessment of clinical data and criteria for effectiveness, underlying the pharmacoeconomical study; perspective of the study; selection of comparator(s); presentation of study results, etc.

The draft Order includes acceptance criteria for recommendations on drug inclusion (exclusion, rejection) according to the results of clinical and economical expertise. Annexes contain forms of preliminary conclusions of clinical and economical expertise of applications.

Thus, the draft Order clearly determines requirements for the quality of submitted clinical studies and economic
evaluation, as well as corresponding acceptance criteria. In addition, the given document describes the criteria for making decisions on drug inclusion/non-inclusion into drug lists, whereas expert opinions must be submitted in accordance with the approved forms.

The main points of the draft Order should form the basis for developing proposals on amendments and supplements into the running order of the Minzdravotsotsrazvitiya of Russia on the development of VEDL lists, as well as making recommendations for the development of drug lists in the regions and medical organizations.

Acknowledgments


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The Work of the Formulary Committee of the Ministry of Health of the Moscow Region on the Preparing of the Regional Reimbursement Drug List

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The article describes the work of the Formulary Committee of the Ministry of Health of the Moscow Region. The approved version of the dossier (application form) for the inclusion of drugs into the Regional Reimbursement List consists of over 30 items relating to the clinical efficacy and cost — effectiveness of the medications, cost of its use for 1 year, current practice of treatment in the region, treatment regimen, dosage, indications for inclusion, advantages of the new drug over those already on the List, etc. A dedicated automated system called “Regional reimbursement” with its own Internet site has been created to assist in completing and submitting the dossier for a new drug. This system includes an electronic application form and an electronic database that allows users to enter, edit, refresh, store and retrieve information on the new drugs submitted to the Formulary Committee for an expert review, and on the drugs already included in the List.

KEYWORDS: Formulary Committee; drug lists; application for inclusion of drugs in the Regional Reimbursement List.

The system of providing patients with medications has seen sweeping changes worldwide over the last few years. For many years the main attention was paid to clinical research aimed at providing high level of evidence. Many experts and public research centres insisted that only such evidence could be used as the basis of policy-making. It was the system of expert evaluation of the efficacy and safety of medicinal drugs that formed the cornerstone of pre-registration assessment (expert evaluation before market authorization). Later, as the system of approving new drugs evolved, the need for a further stage of drug evaluation arose. At this stage it has to be decided whether to include the drug into the limited (reimbursement) lists, which would guarantee their sales and provide considerable advantages to their manufacturers.

At the same time, the procedures currently adopted by regulatory authorities and agencies in charge of evaluation of medical technologies make it evident that the data obtained in randomized clinical trials and meta-analyses is not sufficient for making an informed decision to include or exclude a particular drug from the limited reimbursement lists [1].

The rational selection and prescription of medicinal drugs have been discussed in Russia for several decades. Over the years a great number of documents have been produced and revised at every level of the healthcare system in order to regulate the selection of drugs for inclusion into limited lists and the work of authorities in charge of the evaluation of drugs and medical technologies [2].

At present there is no consolidated evidence on the nature and results of the activities of formulary committees in different subjects of the Federation. As far as regional formulary committees are concerned, all that can be said is that they have been created in the majority of regions and their functions, structure and membership have been determined. However, there are no unified guidelines to regulate their activities, no single procedure for preparing and reviewing the lists, no standard criteria of drug selection, no accepted format for the expert conclusions, etc. [2, 3].

The approaches to preparing limited lists, making them mandatory, have been repeatedly discussed in the Russian Federation over the last few years. In view of the experience of other countries, the inclusion/exclusion criteria were justifiably based on the expert evaluation of the clinical efficacy and safety and economic acceptability of new technologies, including medicinal drugs. At the same time, the required evidence on the use of new drugs, their expert evaluation remained abstract, out of touch with the real-life conditions of providing and financing medical care, therefore the resulting decisions could not be applied to the actual practice. However, the changes that have recently taken place in the system of drug supply have made it possible to adopt a more
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responsible attitude to the role of expert evaluation that preceded the inclusion of a new drug into the regional limited lists.

The life cycle of a new drug includes several stages: development and manufacturing, clinical studies and registration/market authorization, acquisition paid for by the patients, analysis of efficacy and inclusion into limited lists leading to reimbursement of its cost and financial support by various parties, such as the state or insurance companies (Fig. 1).

There are two stages involving expert evaluation in this cycle of medical technologies, including medicinal drugs: 1) prior to registration and 2) prior to inclusion into limited lists or reimbursement lists. It is worth noting the main difference between these two evaluations, which have completely different functional roles. The pre-registration evaluation is above all concerned with the safety of the new drug and its clinical efficacy compared usually with placebo or other drugs, which are often irrelevant to this particular country or region. The second stage of drug evaluation, as has already been noted, is concerned with the preparing of limited lists, which are not abstractions in terms of the life cycle of the drug but have quite concrete content which determines the financial outlay required to provide the region with medications. Because of this circumstance, it becomes necessary both to perform a clinical evaluation of the treatment of a particular disease in real-life conditions compared to the already reimbursed (acquired) alternatives, and to analyze the economic acceptability of the new drug in the current economic situation. Thus a complex analysis is required before the policy of preparing lists can be determined. Obviously, the results of pre-registration evaluation are a necessary component, but they are often not sufficient for the second stage of the drug evaluation.

Accordingly, a standard format of the dossier (application) for new drugs to be submitted to the authorities in charge of drug lists development for the constituent entities of Russian Federation has been developed by the Research Center for Clinical and Economic Evaluation and Pharmacoeconomics, N. I. Pirogov Russian State Medical University in collaboration with the Formulary Committee of the Ministry of Health of the Moscow Region.

The new dossier for the inclusion of new drugs into the Moscow Region reimbursement list has over 30 items relating both to the clinical efficacy and economic efficiency of the drug, and to its use in a particular region.

The system for inclusion of new medicinal drugs into the Moscow Region reimbursement list has a liberal slant: applications for inclusion/exclusion of drugs and medical products may be submitted by members of the Formulary Committee, leading experts from the Ministry of Health of the Moscow Region, independent experts, public organizations, and drug manufacturers. Once submitted, the applications must be processed within one month by the secretary and senior experts, who prepare a preliminary report. The preliminary report together with the submitted application are forwarded to the members of the Formulary Committee within two weeks. The applications are processed in the order of their submission and official registration. The chair of the Formulary Committee can decide to expedite the process of reviewing an application [4].

Dossiers are currently completed only for new drugs suggested for inclusion in the List, but new procedures are being developed so that applications will be accepted for all the drugs on the List and an electronic database covering all the drugs on the List will become available. A dedicated automated system called “Regional reimbursement” with its own Internet site has been created to assist in completing and submitting the dossier for a new drug. This system includes an electronic application form and an electronic database that allows users to enter, edit, refresh, store and retrieve information on new drugs submitted to the Formulary Committee for an expert review. This program allows the employees of the Ministry of Health of the Moscow Region and external experts, such as members of the Formulary Committee with access to the restricted information on this site, to process and analyze online the data contained in dossiers.

The first items of the dossier are a fairly traditional “passport” description of the drug: international nonproprietary name, trade name, manufacturer and applicant submitting the dossier (Fig. 2).

In accordance with the goal of establishing a civil society in Russia, any subject in the life cycle of medicinal drugs can submit the dossier: a leading expert, a professional association, a medical organization, a manufacturer, a research center, etc. The widespread perception of corruption in the procedure of lists development and the
The system of submitting dossiers by the manufacturers appears to be grossly exaggerated. In this case the anti-corruption aspect of inclusion in the list does not depend on who will submit the dossier and who will defend it, but rather on the professional evaluation of drugs in the process of preparing the actual List. And this is the stage that we consider crucial in the organization of the whole process.

The daily dose, dosing regimen and formulation are also specified in the dossier.

The next item concerns the status of the drug as original or reproduced (generic), since this determines the way pre-registration evaluation is performed. However, given the current regulations, the registration process for generic drugs has not been sufficiently well-described. Even so, at the regional level an evaluation of pharmaceutical, biological and therapeutic equivalence may be of additional value in the decision-making process.

After that the dossier asks to specify code of the disease the drug is for, according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10). This is an important point: in contrast to the pre-registration evaluation, the evaluation for inclusion into limited lists requires a clear description of the indications for which the drug is included in the List, i.e. the situations in which the cost of the drug will be reimbursed. Listing all the indications for which the drug is registered and used will in this case simply “distract” the regulatory authorities from a realistic assessment of the future expenses related to the therapy with this drug.

The specification of the pharmacotherapeutic group of the drug and its code according to the Anatomical Therapeutic Chemical (ATC) classification are also relevant to the future development of the lists and inclusion/exclusion of new drugs. Thus, being able to perform analyses for particular pharmacotherapeutic groups and ATC categories in the process of lists development means that it is possible to check which drugs from a given group have already been added to the list, how well they meet the standards of medical care, and whether new drugs need to be included.

The modern systems of drug supply in other countries increasingly emphasize that patients should be divided into groups that differ in the clinical efficacy of various medications or have different value (significance) for the administration of medicinal drugs. These differences between groups (or segments) are based on medical criteria and may not correspond to the current disease classifications or other clinical recommendations. In addition to the severity and type of disease, such criteria may include the functional activity, comorbidity, the number and severity of complications, biomarker tests, and other factors relevant to the choice of therapy or predictive of its effectiveness. Classifying patients into such groups lays the foundation for more focused policies.
of reimbursing patients for their medications, limiting unjustified prescriptions and ineffective use of financial resources by the purchaser. If these regulations are made explicit, the need to prescribe a medication to one group of patients and to limit or avoid its prescription to another group may become more transparent. The transparency of such decisions constitutes a certain “social contract” between the state and society that guarantees that the provision of medications to patients will better correspond to the principles of social justice, compared to delegating full responsibility for the choice to the physician alone.

In accordance with this principle, the dossier developed in the Moscow Region determines high-priority patient groups for each disease, in which the drug can demonstrate its maximal efficacy, on the one hand, and limits the number of patients to whom the drug will be prescribed, reducing expenses for the always restricted budget, on the other hand.

After that the dossier asks for evidence of clinical efficacy and economic acceptability of the drug from the perspective of evidence-based medicine and the basic principles of pharmacoeconomic analysis [5].

Describing the clinical efficacy, the party submitting the application should briefly summarize the results of clinical trials (design, number of patients included in the study, efficacy and safety criteria, results, conclusions) and specify the strength of evidence for the efficacy of the drug provided by each study, using the scale “Levels of evidence” attached to the application form. The stated levels may be reconsidered in the process of expert evaluation of the submitted dossier.

The evidence of clinical efficacy submitted with the dossier must demonstrate that the drug meets the needs of the healthcare system, i.e. it must include endpoints relating to the actual treatment outcomes rather than surrogate endpoints. This will ensure that the arguments for the use of the drug are more accessible to decision-makers and clarify the practical applicability of these arguments. In addition to the efficacy compared to placebo and abstract active comparators, the dossier draws particular attention to the superiority of the new medication in comparison with those technologies and drugs that are already included in the List and used in the common clinical practice in the same region for the treatment of the same disease. This is another difference that distinguishes the evaluation prior to inclusion in drug lists from the pre-registration evaluation.

The results of pharmacoeconomic studies are to be presented in the application under one of the five types of economic evaluation: 1 — cost-of-illness; 2 — cost-effectiveness; 3 — cost minimization; 4 — cost-utility; 5 — cost-benefit.

An additional interesting aspect of completing the dossier for inclusion of a new drug into the Regional Reimbursement List concerns the issue of regulating the cost of procurement of medicinal drugs in the Moscow Region. For instance, the dossier includes a question in which the applicant specifies the cost of including the drug in the List, which is calculated according to a formula that takes into account the number of patients entitled to reimbursement in the Moscow Region, the daily cost of treatment with the drug, the duration of treatment, and the proportion of patients that require treatment. Furthermore, the formula takes into account the costs that may potentially be avoided if the alternative drugs already on the List are excluded (or their use is limited).

Of particular importance are those parts of the dossier that estimate the number of patients in the region to whom the drug is indicated. It must be noted that it used to be impossible to estimate these numbers accurately, but since 2005, when the Program for the Supplementary Drug Supply (rus. DLO) was launched, patients entitled to reimbursement have received their medications by prescription and the details have been registered in the appropriate databases. At present such databases exist in almost all the constituent entities of the Russian Federation, and therefore experts may submit a query and gain access to information concerning the number of patients with particular ICD-10 codes and their treatment, i.e. which drugs the patients receive and what is the cost of a particular disease for the budget. The results of such “pharmacoepidemiological” studies are of great interest and ought to be used for the preparing of drug lists. This is the reason why the dossier must include information regarding the number of people who suffer from a given illness and the total expenses or cost of treating such patients.

Including this information in the dossiers for new drugs may considerably facilitate any future analyses and assist in developing straightforward rules of differential prescription of drugs to subgroups of patients representing various segments of the disease.

Moreover, one item in the dossier invites the applicant to offer their own suggestions for controlling the adequacy of drug prescription and to state whether they think it is necessary to arrange educational programs for physicians because of the “novelty” of the drug and the difficulties related to its use.

The new system of submitting a dossier before a drug is included into the limited list will ensure that the decisions to include new medical technologies and medicinal drugs, in the system of state reimbursement will be made after careful assessment and based on the solid evidence. A simultaneous
evaluation of the anticipated expenses for the new medication and the financial resources in a particular region lays the foundation for a more constructive dialog between manufacturers, medical experts and the state. If the new system is built in accordance with the suggested principles, the debates raging around the inclusion/exclusion of new technologies will shift from the virtual sphere to concrete solutions. The modern “win-win” concept is transformed into “win-win-win”, with the winners being all the subjects who take part in the process. The manufacturer will have a body of evidence for the inclusion of the new technology, experts and physicians will have the opportunity to provide their patients with the latest achievements of modern medicine, and the state will have a thorough understanding of how the treatment of a particular disease is managed, including its costs, the common practice, and the optimization opportunities for those patients and in those segments where the new technology can produce the maximal effect.

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Over the past several decades, demographers have repeatedly described the ageing of populations in industrialised countries, resulting from increasing longevity and falling fertility rates experienced over the past century [1]. While the efforts of humankind to increase life expectancy and avert famine as predicted by earlier demographers should be applauded, ageing populations pose numerous challenges for all of us — most notable of which is the shrinking numbers of working aged people expected to pay for social programmes. As populations age and increasingly place demands on government-funded social programmes, few easy policy options are available and often include cuts to public spending, increasing taxes to pay for increasing demand and in some instances both [2—4]. In many European countries, old-age dependency ratios are expected to reach 50 per cent by 2050, whereby two working aged people will be supporting one person over the age of 65 compared with the current ratio of four working aged people to one retired person [2].

As the number of working aged people starts to decline, macroeconomic theory suggests growth will start to decline. Increases in physical capital (for example infrastructure, technology) and productivity can partially mitigate the effects of ageing populations [5]. However, to maintain living standards the rate of productivity increase will need to be greater than the effects of ageing. This increasingly looks unlikely, considering that productivity growth has been declining in many parts of Europe over the past two decades [6, 7]. Labour market reform that encourages people to work longer and delay retirement has also been put forward as one potential option to minimise the impact of ageing on public finances. However, as illustrated by Manton et al, increasing the age of retirement is only feasible provided people are healthy enough to remain working [8].

The demographer Phillip Longman, writing on the subject, suggests that ‘With a shrinking labor supply, Europe’s future economic growth will therefore depend entirely on getting more out of each remaining worker (many of them unskilled, recently arrived immigrants), even as it has to tax them at higher and higher rates to pay for old-age pensions and health care’ [9].

In this article, we consider the health investment framework and how health status influences economic outcomes. We consider this relationship in the context of ageing populations, as well as options available for assessing the return on investment from health programmes. We also consider who benefits from societal health gains — in particular, considering the government perspective and the influence of investing in health on future government tax receipts. We will illustrate this point using a previously developed model for infertility and consider its broader application to inform health care priority-setting.

HEALTH AS AN INVESTMENT

Few people question the positive correlation between health and economic growth that serves as one of the cornerstones of development economics, although the direction of the relationship is often debated. The traditional belief has been that wealthier nations have more command over health care resources and as a sequence were healthier.

However, this view has gradually changed and health as an important economic determinant has become
special

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recognized [10]. Perhaps one of the best-known examples is the relationship between life expectancy and economic growth [11, 12]. However, the relationship is more than simply keeping people alive for longer, but also recognises that economic growth is driven by the healthy that are able to supply labour to the market [13—15]. Therefore, the manner in which health influences labour force participation, labour productivity and creativity, and the absolute number of hours on the job can influence economic outcomes that should be considered when evaluating medical programmes and setting priorities. The necessity to understand this relationship is heightened by the declining numbers of working aged people in many industrialised countries and the desire to maintain current living standards.

The principles of health and wealth have long been championed by organisations such as the WHO. More recently, these ideas have caught on in Europe, as outlined in an independent report to the European Commission published in 2005, in which it was noted that ‘policy-makers who are interested in improving economic outcomes (for example on the labour market or for the entire economy) would have good reasons to consider investment in health as one of their options by which to meet their economic objectives’ [16]. The authors of the report acknowledge that the subject is often overlooked in wealthier nations, and highlighted the importance of investing in health to achieve economic growth in the context of ageing populations. The relationship between health and economic outcomes is based on human capital theory and that individuals invest in themselves to improve their economic condition [17]. Human capital takes many shapes but is often thought of in terms of knowledge, skills and experiences, but also includes investments in health. Much of the early human capital work was conducted by Becker to explain monetary returns from educational ideas of human capital where he defined health both as consumption good and as a capital good [19]. According to Grossman, health as a consumption good makes people feel better, and as a capital good health can enhance an individual’s earning capacity. An appreciation of the relationship between health and economic outcomes can also be gained by exploring the drivers of macroeconomic growth, often defined in terms of gross domestic product (GDP). Numerous models have been developed to describe economic growth, however one of the better-known models was developed by Robert Solow in which he defined the key determinants of economic growth in terms of technological progress (A), capital (K) and labour supply (L) [20]. According to the model developed by Solow, for which he was later awarded the Nobel Prize, economic growth can occur if either A, K or L or increases.

Although the Solow growth model does not specifically address human and health capital, we know that health can directly or indirectly impact each of the inputs known to influence economic growth [21]. For example, health influences the supply of labour in terms of both quantity and quality (L). Health also influences educational attainment and creativity, which undoubtedly influences technological progress (A) [22]. Furthermore, the relationship between improved health and longevity is believed to increase the personal savings rate as people expect to live longer [10]. Consequently, an increased savings rate makes more money available for investing in physical capital (K), which in turn influences economic growth.

HEALTH INVESTMENT VERSUS HEALTH EFFICIENCY

If investing in health is good for the economy, it is worth considering the methodological framework for assessing this relationship. Furthermore, it is important to contrast a health investment framework with the more commonly known cost-effectiveness analysis (CEA) used by many Health Technology Assessment (HTA) agencies that influence product reimbursement and funding decisions [23]. Broadly speaking, the health investment framework seeks to understand how disease and available health technologies impact economic parameters such as labour force participation, productivity, wages or macroeconomic growth. Within this classification we also include cost–benefit analysis as a health investment framework in cases where benefits are defined using labour wage rates. The methodologies and perspectives applied to assess health investments can vary, and in the majority of cases the value of an intervention or disease burden is often defined solely in economic terms. In the health economics literature, these costs are often referred to as indirect costs. Unlike HTA agencies that emphasise CEA, there are no prescriptive guidelines that define a methodological approach with health investment. For an overview of the different methodological approaches, interested readers are referred to the report prepared for the Commission by Suhrcke et al. [16]. For many health researchers, defining health benefits exclusively in economic terms has serious limitation because it fails to account for the intangible value that people assign to good health [24]. Additionally, valuing health benefits in economic terms also raises concerns because it might favour those employed compared to those not working (for example housewives, retired persons, unemployed) [25]. In seeking to dismiss the sole valuation of health benefits based on lost earnings, Mishan argued that such an approach could only be rationalised if programme value was defined based on contribution to gross national product [26]. Because of the limitations of valuing health in monetary terms, many argued that an optimal method for valuing health benefits.
should be based on welfare economics. Therefore, it was argued that values assigned to health should be based on societal valuations and what people would be willing to sacrifice to obtain particular health benefits. Because of the perceived weaknesses of valuing health benefits defined purely in economic terms, the approach quickly went out of fashion, although valuing health benefits in economic terms is still recognised as being substantial and an important element for valuing health improvements. However, it is worth noting that few economic studies include indirect costs and there is often confusion among analysts about when and how to include these costs in studies [27]. The ensuing years saw increased interest and use of the quality-adjusted life year (QALY) that captures both morbidity and mortality in a single metric. Because the morbidity component of the QALY was valued using societal preferences for different health conditions — often using multi-attribute utility measures — it was considered to be a more appropriate measure for valuing health conditions. Furthermore, because it reflected patient utility related to different conditions, it was deemed an appropriate measure for informing resource allocation decisions in an effort to maximise social utility.

Over the past two decades the QALY has become the most widely used measurement of health status and has been endorsed by numerous HTA agencies such as the National Institute for Health and Clinical Excellence in the United Kingdom [28, 29]. Although the QALY does reflect societal values for health conditions, it can not be translated into economic outcomes that inform health investment questions like those raised in the previous section. To complicate matters, several government agencies responsible for evaluating technologies fail to consider the societal costs in their decision-making by excluding indirect costs [28, 29]. As a result, questions regarding the economic consequences of many technologies that could inform the health investment debate remain unanswered.

This brief description of methodologies for valuing health benefits underscores the challenges in adopting a health investment framework for valuing medical technologies. The early rejection of human capital methods for valuing health status changes by many health economists has led to the almost universal acceptance of the QALY for valuing health and allocating resources. The need for a formal health investment framework is further underscored by the fact that many HTA agencies and researchers either are not concerned with or fail to estimate the broader economic consequences (that is, indirect costs) of morbidity and mortality changes. Consequently, questions with regard to the wider economic benefits to society of new health technologies can often remain unknown.

Despite concerns over valuing health in economic terms, there are strong suggestions that maintaining living standards and economic outcomes are important — especially in light of ageing populations and concerns over sustainability of public finances — and health may undisputedly contribute. While maintaining living standards is only one factor important to society, there is much that can be learned about how health impacts the economy using human capital approaches to value health. While Mishan was correct that a comprehensive measure to value health is appropriate, this does not seem to justify the abandonment of valuing health in economic terms that has occurred in many settings. In fact, the choice of methodologies does not have to be mutually exclusive. Rather both approaches — health investment and QALY — should be used to inform resource allocation decisions. Furthermore, if recent interest in health and the economy continues to grow, this may revive interest in human capital approaches for valuing health.

**BE neficiaries from Investments in Health**

If health has economic value, it is worth considering who benefits from improved population health. At the individual level, it is clear that the individual experiencing a health improvement is the beneficiary regardless of whether measured in terms of reduced pain, increased quality of life or economics. When health improvements occur at the aggregate level, things are much different with a wider range of beneficiaries across society. This takes into consideration both aggregate measures of health but also the externality of poor health that can have consequences even for healthy individuals, especially in relation to communicable diseases. On the whole, it is clear that as population health improves then society as a whole will benefit from health status improvements and accrue economic benefits.

Moreover, if health has an economic value then this value will surely be taxed. This point seeks to acknowledge that governments also benefit from economic growth regardless of the causes. As economies expand, whether brought about through natural growth, economic stimulus or improved population health, all things being equal, governments can benefit from increased tax revenue resulting from economic expansion. This seemingly benign point is important, particularly in light of concerns over tax-funded social programmes and a shrinking tax base, and at a practical level could potentially be used to influence government resource allocation decisions in health care, much in the same way that governments invest in technology and education.

Popular belief often suggests that governments can increase tax revenue by increasing rates of taxation. However, this is not necessarily supported by the empirical evidence whereby growth is seen to be a more effective tool. Studies have shown that increasing tax rates can have limited impact on tax revenue, as higher rates of taxation increase incentives for misreporting and
increases demand for leisure time. This point is illustrated from an analysis in the United States, which shows that changes to the highest marginal tax rate between 91 per cent and 35 per cent over 40 years did not significantly impact government tax revenue as a per cent of GDP [30]. Supply-side economists make the case for lowering taxes to stimulate economic growth as a more efficient means for governments to increase tax revenues [31]. The relationship between economic growth and increasing tax revenues has also been noted in Congressional reports [32].

Applying the growth and tax perspective to health highlights that governments, especially those with tax-funded health systems, might be better positioned to influence tax receipts based on how resources are allocated within the health service. There is nothing sinister about the relationship, and it simply acknowledges that a component of the economic growth attributed to health gains described earlier will be collected in the form of taxes as economies expand [8, 16, 30]. The relationship between poor health and reduced government tax receipts is equally applicable as recently acknowledged in a report from the WHO on the economic consequences of disease and injury [33]. Moreover, investing in health programmes that enable people to work longer into retirement, avoid short- and long-term sick leave or avoid illness altogether will increase productivity and stimulate economic outcomes for individuals, but can also benefit government both in terms of increased tax receipts and reduced demand on publicly funded programmes.

THE TAX VALUE OF A LIFE

With the above government tax perspective in mind, the authors of this article previously evaluated the tax value of life in an assessment of fertility treatments. The Lifetime Net Tax (LNT) model that we developed treats medical costs required to conceive a single child using in vitro fertilisation (IVF) as an investment with future economic consequences. Within the LNT model we assessed age-related financial transfers between government and an individual to derive average lifetime net tax revenue.

On average, an individual receives an education, medical care, allowances and a pension from government. In exchange, the government is entitled to lifetime tax receipts once the child enters the workforce [34, 35]. The model estimates average discounted net tax revenue from gross taxes paid minus age-related government expenditure every year over the life course assessed in the LNT model.

Using a tax-based modelling approach, we found that there is a strong economic case for health services to publicly subsidise IVF treatments. Our analysis demonstrates that based on an initial investment of £13,000 in the United Kingdom to produce one IVF child, the present discounted value of the investment in future net tax revenue was approximately £109,000, representing an eightfold return on investment [34]. To put these figures into perspective, there were over 11,000 children born from assisted reproduction in 2005 in the United Kingdom [36]. Furthermore, because the model emphasises the government perspective, it significantly underestimates the true economic value of an individual to society that results from a lifetime of demanding goods and supplying labour.

The LNT approach described above is not an economic evaluation similar to those typically used by HTA agencies. Because it emphasises tax benefits attributed to improved health status or reduced mortality, it places no value on health; consequently, it undervalues the benefits of improved health status from the societal perspective. The approach solely focuses on individuals as economic entities and how health status changes can influence the manner in which future economic activities take place. In this respect, the health investment model addresses a fundamentally different question and considers the costs and consequences of changes in population health on government accounts. This approach may be useful for evaluating other technologies because it addresses medical intervention costs in relation to increased productivity and sustainability of public finances (that is, tax revenue) in the same analysis.

The LNT is useful for evaluating fertility treatments because this ultimately leads to an increase in the supply of labour. However, for the methodology to be relevant to health care, decision-makers it needs to be applicable to a broader range of medical interventions. Although it is true that fertility treatments do influence the supply of labour, representing 6 per cent of national births in some countries [37], the same could be said for any medical intervention that saves lives or enables people to work longer. In economic terms, investing health care resources to create a life, using IVF, or investing resources to save a life is analysed using the same methodological framework for valuing human life, using labour wage rates. Whether you save a life or create a life by investing health care resources, the end result is the same because there is one additional person alive who would not have been alive if decisive medical care to save or to create life had not been taken. When changes in work capacity or, in the case of fertility treatments, the supply of future labour are viewed in the context of the Solow growth model described earlier, it is possible to see how investments into the health service can influence macroeconomic growth. Consequently, how we prioritise patient groups and allocate health care resources can directly influence economic outcomes.

RESOURCE ALLOCATION AND RETURNS ON INVESTING IN HEALTH

Because human capital and, in the IVF example, human life have exchangeable economic value, the LNT approach to value health illustrates several points regarding resource allocation decisions and health care
priority-setting. Firstly, programmes like IVF are often perceived by health services as a low health-care priority requiring costly interventions. In our analysis, we have shown that costs are actually an ‘investment’ when a broader range of costs and benefits are considered and the time period of the analysis is extended. Secondly, our analysis explicitly builds an economic case for public subsidy of fertility treatments. However, infertility is considered a low health-care priority within many health services and, consequently, often attracts limited funds. Ironically many of the same countries that have concerns over ageing populations fail to fund these treatments that could partially mitigate the effects of an ageing society. Nevertheless, this illustrates the challenges of integrating an economic growth framework into priority setting and resource allocation decisions normally influenced by burden of disease, capacity to benefit and equity concerns [38].

Our previous findings, although in some respects intuitive, can be used to contrast differences between where health-care resources are commonly spent and where tax revenues are generated. To illustrate this, we reproduce a figure from our previous work (Figure). The trace in Figure 1 illustrates the lifetime cash flow between an individual and their government. In the early stages of life, an individual is a net recipient of government transfers, also viewed as human capital investments. After entering the workforce, financial transfers flow in favour of government, as workers start to pay taxes (for example income taxes, consumption taxes, property taxes and levies). Finally, when individuals exit the workforce, they transition to a stage of reduced tax contributions while increasing demand on public services (for example health care, pension and social services). In terms of health-care spending, studies often report that health-care consumption and costs are often concentrated in the elderly and younger children [39, 40]. Because the need is higher in these groups, and in older persons in particular, current spending simply reflects demand. However, when age-related spending is viewed in the context of the LNT model in Figure 1, these two groups represent extreme ends of the economic life cycle with entirely different returns on investment from health expenditure. This simply reflects differences in future economic capacity between different age groups. Perhaps the more important question to ask is whether current spending on one age cohort is done to the detriment of another age cohort. Furthermore, is it possible to achieve the same level of health gain, while also influencing future tax revenues in a positive direction.

Priority setting and resource allocation decisions are influenced by a range of factors that include medical need, defined in various different ways, equity and increasing QALYs. If health services seek to influence economic outcomes, then it is conceivable that remaining economic capacity might need to be considered in priority setting in the future.

![Figure](image-url)

**Figure.** Lifetime fiscal balance sheet between an individual and US government over projected lifetime based on US government financial transfers and project average earnings and longevity.

**Source:** Reproduced from Connolly et al (2008) [35].
In this respect, the LNT approach that we have described can help to answer questions about how investing in programmes influences economic outcomes. Although the model we have developed was used to assess fertility treatments, it can easily be adapted to evaluate almost any intervention. In particular, those with an acute intervention cost, and clearly definable outcome, for example vaccination programmes that save lives or surgical interventions that influence future work capacity. However, it needs to be emphasised that this approach should never be used in isolation to influence resource allocation decisions. Rather, it should be used in conjunction with existing criteria for priority setting. Perhaps, it is most useful for pointing out some fairly glaring facts about where resources are allocated or are not being allocated as in the IVF case.

The major weakness in applying the LNT in decision-making is that one might always favour the young and working over the old and non-working. The allocation of resources based purely on remaining economic capacity is no doubt deplorable for many to contemplate. In fact, precedence already exists for priority setting that favours the young. Previous public assessments have shown that in the allocation of life-saving treatments the public often favour allocating resources to the young compared with the old [41, 42]. The rationale for why public opinion should favour the young over the old is often not explicit but is thought to be on moral grounds and remaining life. While claims over resources for the young are often made on moral grounds, the LNT provides an economic rationale for allocating resources in this manner.

**CONCLUSIONS**

For many readers, allocating resources on the basis of economic benefits or future revenue for government is a ghastly prospect on which to base disease prioritisation and treatment decisions. On the other hand, we know that sustainability of public finances, economic growth and maintaining living standards are also important to society. The options for maintaining all of these parameters will be challenging, as the number of working aged people decreases at the same time that demands on public pensions, health and social services are increasing. For many nations, difficult decisions have to be made to maintain economic growth, delivering generous health and social programmes, while balancing how much they intend to tax future generations.

In reality, every element of the ageing population problem and all of the possible solutions should not be seen in isolation from one another. If nations can use their health services to improve economic sustainability in the face of ageing populations, then it might be in their interests to do so, particularly if the economic rewards of growth are shared among all members of society. This suggests there might be a need to take resources away from some health programmes and allocate it to programmes that offer better economic prospects. But, if all members can share from the economic benefits then it is still possible to maximise societal welfare in doing so. Conversely, ignoring opportunities for achieving growth using the health service seems equally objectionable.

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The Concept of establishing a pharmaceutical cluster in Saint-Petersburg has been created in order to define the main directions for the development of pharmaceutical industry and to create the Saint-Petersburg pharmaceutical cluster in accordance with the Strategy for the Development of Pharmaceutical Industry in the Russian Federation for the period up to 2020, ratified by order N 965 from 23.10.2009 of the Ministry of Industry and Trade of the RF [1]. The central idea behind this Concept is based on the potential that Saint-Petersburg has for the development, manufacture and incorporation into medical practice of innovative drugs and reproduced pharmaceuticals (generics) in accordance with the main objective of the Strategy. The availability of material and technological resources, highly qualified personnel and scientific capital will ensure that the main objectives of the Concept are met within a time frame that is acceptable with regard to the implementation of the Strategy and the objective development of the pharmaceutical market assuming a reasonable level of budgetary investment [2].

The main objective of the Concept is to define a single consistent stance toward the creation of the Saint-Petersburg pharmaceutical cluster on the part of profile government authorities, cluster participants and potential investors, including Russian and foreign pharmaceutical companies.

The Concept must be implemented through measures that aim to prepare suitable areas for future development of the industrial segment of the cluster, ensure contracts with future investors, and enlarge the scope of the cluster through creation of new innovative organizations that will develop chemical substances and drugs and provide technological expertise for their manufacturing. The global problems at the level of the RF, which must be solved in the course of implementing the Concept to ensure the development of pharmaceutical industry in Saint-Petersburg, are the following:

- the technological lag at every stage of the life cycle of drugs, from scientific research to implementation into medical practice;
- the lack of emphasis on the use of innovative products (it results in the fact that government supply orders for drugs entail considerable expenses towards the procurement of products that entered the circulation after the expiry of exclusive patent rights for the original pharmaceuticals (generics) and pharmaceutical companies have limited development opportunities as a result of low added value of traditional generics);
- the lack of coordination in the development of pharmaceutical products, their marketing and implementation into clinical practice (this factor considerably increases the risk of investment in scientific research both by the state and by private investors).

One of the major objectives of developing pharmaceutical industry in Saint-Petersburg is to solve these problems on the basis of cooperation between the state and the private sector, even though the current legal structure for the performance of joint development projects partially financed from the national budget has important shortcomings. However, the realization of this objective and optimization of the organizational and legal frameworks for cooperation between the state and the private sector will streamline the process of incorporating new products into medical practice and minimize the risks associated with financing the modernization of material, technological and industrial resources of research centers and existing pharmaceutical companies through private and public investment.
CLUSTERING POLICY

Clustering policy in the development of pharmaceutical industry requires a close coordination of the goals and objectives of cluster participants to achieve a cumulative effect in the promotion of its products on the market in the RF and abroad. As a compensation for its efforts in developing and maintaining the cluster, Saint-Petersburg will attract the leading companies and experts of the pharmaceutical industry, benefit from tax revenues into its budget and gradually increase its investment attractiveness for innovative pharmaceutical companies.

The definition of a cluster

According to the definition in the Strategy, a cluster is a group of geographically localized and interconnected innovative companies: drug developers and manufacturers; suppliers of equipment, substances or specialized services; elements of infrastructure, such as research institutes, universities, industrial parks, business incubators and other mutually supportive organizations that enhance the competitiveness of individual companies and the cluster as a whole [1, 2]. The defining feature of effective clusters is the release of innovative products (see Figure).

Cluster development may present a number of advantages:
- it ensures organizational control at every stage of cluster development;
- it paces up the implementation of investment projects and reduces the initial costs for cluster participants;
- it lowers the investment risks for cluster participants;
- it improves the efficiency of resource allocation from the budget of Saint-Petersburg for the purpose of encouraging joint ventures;
- it leads to rotation of highly qualified personnel and enables a systemic approach to training, retraining and attracting personnel;
- it scales up the production and background scientific research in pharmaceutical companies; improves the investment desirability of Saint-Petersburg and increases tax revenues for the budget.

The greatest obstacle on the path of any projects of creating innovative products is the lack of mechanisms through which these products can be incorporated into practice. The market share of an innovative product will remain small until the state has provided it with effective consumer demand. As a result, the existing Russian innovations will remain the exception rather than the rule. To create demand for innovative products, their effectiveness should be promptly evaluated, following which they should be immediately included in the appropriate treatment guidelines. Putting the Russian legislation in line with international standards, as the Strategy proclaims, will considerably increase the share of innovative products and ensure national medicinal safety.

In order to develop and incorporate innovative pharmaceuticals, it is necessary to: involve federal and regional research organizations in projects of drug development and preclinical studies; involve federal and regional clinical centers in conducting clinical trials and researching the use of new drugs; create expert groups involving Russian and foreign specialists to ensure that the new standards of treatment with innovative pharmaceuticals are promptly developed and introduced; control the application of treatment guidelines in medical practice; create a public authority in charge of the manufacture and circulation of drugs.

The most important purpose for establishing the cluster and its greatest competitive feature is the creation of an expert research center in one of the higher educational institutions in Saint-Petersburg. If this objective is met, this will lead to the creation of a competitive system of expert evaluation, which will considerably speed up the registration of drugs, reduce its cost, and streamline the incorporation of the products created in the cluster into medical practice.

Any attempts to create innovative products and localize pharmaceutical industry cannot hope to come to fruition in accordance with the goals of the Strategy without a thorough revision of the procedure for the introduction of new pharmaceuticals and of the existing treatment guidelines. The great number of research centers, the well-developed preclinical and clinical base, the highest concentration of specialized medical institutes make Saint-Petersburg the ideal place for the creation of innovative pharmaceuticals, their manufacturing and incorporation into clinical practice.

With the above in mind, it seems appropriate to create an innovative cluster in Saint-Petersburg with a large share of research centers, universities and medical institutes for the purpose of creation of new products and their incorporation into medical practice. The actual industrial facilities will represent an important, but certainly not the only segment of the cluster. The output of such a cluster has export potential and long-term prospects, which will guarantee reinvestment in development. Considering the practical impossibility of having centers for fundamental and applied research, industrial facilities and suppliers all in the same area, the definition of an innovative cluster assumes that the participants will be located in Saint-Petersburg, making an allowance for the existing scientific and medical infrastructure.

To meet the objectives of the Concept, it is reasonable to limit the definition of the cluster at its formation stage to those segments that already exist and are necessary for its further development. Such existing prospective segments of the cluster include above all scientific
and medical organizations in Saint-Petersburg. Such organizations exist in all the segments essential to the development of the cluster, such as: development of innovative pharmaceuticals, creation and reproduction of pharmaceutical substances and drugs, the well-established preclinical research facilities with existing foreign partnerships, the well-established clinical research facilities in all branches of modern medicine, facilities for the training of highly qualified personnel, including experts in pharmaceutical industrial technology, the great numbers of medical representatives working for pharmaceutical companies, trained to modern standards in marketing and promotion of pharmaceutical products. Capitalizing on this existing groundwork can save years of efforts and budgetary expense, and it provides a unique opportunity to implement in Saint-Petersburg the aspects of the Strategy relating to the production of pharmaceuticals with the maximum share of added value.

The following elements are necessary to ensure the development of the cluster: availability of scientific findings and research compatible with the existing scientific and technological potential of Saint-Petersburg, with respect to the existing organizational structure and standards of GLP (Good Laboratory Practice); availability of modern, GMP-compliant (Good Manufacturing Practice) pharmaceutical industrial facilities for contractual production of pharmaceutical products by cluster participants and for the attraction of large foreign pharmaceutical companies.

Foreign companies must be attracted in order to ensure the transfer of technology and experts in other areas apart from pharmaceutical production. The implementation of the Strategy would be considerably slowed down by the lack of actual investment by the state because of the high risks of actual investment by the state because of the high risks of actual investment by the state because of the high risks. To compensate for state expenses, it may be suitable to attract adequately large investments in this sector by foreign companies that may be interested in acquiring the status of a local producer to preserve their shares of the Russian pharmaceutical market. Thus the leading international pharmaceutical companies will be able to reduce the share of their internal R&D costs by using outside expert groups more effectively for the development of innovative pharmaceutical products (the so-called outsourcing).

Industrial parks and business incubators can be set up in Saint-Petersburg universities after the creation of an organizational and legal framework that will ensure that the economic interests of educational institutions and expert groups are compatible.

**Thus,** for the purposes of the Concept a cluster is defined as the potential and prospective segments, which include the existing research centers forming the core of the cluster’s innovative research, the clinical research facilities for the evaluation and introduction of innovative products, and investment projects for the establishment of contractual and internal industrial production with a capacity large enough to meet the internal needs of the cluster and attract large foreign pharmaceutical companies.

**State participation and cluster financing**

The main purpose for the creation of this cluster is to coordinate the goals of individual participants in order to improve the efficiency of their sales on the Russian pharmaceutical market and abroad. One of the key elements of the cluster is provision of incentives for the promotion of approved drugs whose application has been tested and tallies with the goals of the Strategy.

A subsidiary purpose for the creation of a high-tech cluster is to develop fundamental and applied scientific research at no extra cost to the federal and regional budgets by means of conducting research and investing a share of the profits in modernizing the material and technological resources in research centers. This approach further justifies the participation of the state in cluster management, since investment in material and technological resources in the context of concrete research projects is much more effective than direct budgetary investment to support the functioning of research centers. The same approach is justified with regard to providing highly qualified workers who take part in concrete research projects with salaries in accordance with the individual qualification of each worker, as opposed to estimated budgetary funding of research centers without regard for the individual contribution of each worker.

Additional factors that justify state participation in the creation and maintenance of high-tech clusters include the following: the large scale and social significance of state contracts for the supply of pharmaceutical products, which necessarily requires an agreement between the client and supplier of strategically important goods; the need to ensure national safety and guarantee that there is no dependence on external factors in the case of economic or political changes on the global market.

The measures directed towards cluster development are financed through budgetary and non-budgetary investments. Budgetary expenses include investments from the budget of Saint-Petersburg in the engineering infrastructure in the cluster, investments from the federal budget in scientific research, experimental construction and capital investments in state enterprises (state-owned organizations, universities). Non-budgetary expenses include above all investments in the construction of pharmaceutical objects and performance of research projects. Some projects and objects in the cluster may be jointly financed within the organizational and legal
framework for cooperation between the state and private businesses.

To the extent that particular participants in the cluster (large industrial companies) achieve a sufficiently large scale, certain projects may be financed with the support of such participants. This applies particularly to supporting the establishment of small and medium-sized organizations engaged in projects of strategic value for the industrial companies and the cluster as a whole.

At the initial stage financial support from the budget will be particularly essential to the development of the cluster. Later on its economic viability will become evident to the participants, and simultaneously the role of the state will decrease.

**Advantages of cluster development for promotion of pharmaceutical products**

At the moment all the pharmaceutical producers distribute their products through a virtually uncontrolled network of retail and wholesale trade in pharmaceuticals. The existing licensing norms in retail and wholesale pharmaceutical trade offer no opportunity to control the number of market participants, despite the surplus of retail drug stores in the developed subjects of the RF and the lack of access to the products on the part of most middle-range and small wholesale traders. Because the number of licenses is unlimited, a chain of middlemen is created, with a corresponding increase in the cost of drugs due to the limited availability of the products and to the economic interest of all market participants, with the exception of the manufacturer, in raising the average cost of the item.

Thus, the constant and uncontrolled growth of the prices of pharmaceuticals, as well as the shift towards the more expensive end of the range of available goods, is taking place because the number of participants in the distribution network is unlimited.

The added value of pharmaceuticals is largely created in the trade domain, which dictates the conditions of access to the market. Therefore, the joint pressure from the distribution network is greater and more effective compared to the uncoordinated policies of pharmaceutical producers. In addition, the distribution network cannot invest a share of the added value into further development of pharmaceutical production, and the manufacturer benefits more from investing in promotion of existing products rather than in innovation and development. The actors that profit from this system are foreign pharmaceutical producers, whose share in the sales of their own products on the Russian market is fairly low, while for Russian industries the extra expenses incurred in promotion leave insufficient amounts of capital not only to foster further growth, but even to ensure quality control. It is particularly important to take into account the obligatory shift to GMP standards in implementing the policy of imported products replacement in state supply orders, otherwise it will be impossible to guarantee that the Russian pharmaceutical products paid for from the budget will be of sufficiently high quality.

Unless the existing imbalance is redressed, other measures will only have a temporary effect and all market participants will violate national regulations regarding the prices of pharmaceuticals.

In this regard, the major advantage of clustering approach to development of pharmaceutical industry is the joint position that cluster participants assume when they sell their products through state supply orders, which can compensate for the pressure from the distribution network. Apart from the quantitative increase of the share of products sold under state supply orders, cluster participants will have an opportunity to keep most of the added value for investment in material and technological resources and in the creation of new pharmaceutical products. Keeping a greater share of the added value will allow the existing traditional Russian industries to modernize the production in accordance with modern standards and to control the quality of substances and the technological process of producing medicinal drugs.

The material and technological resources of those research centers that are essential for the cluster will be modernized, partly through their engagement in projects of large Russian and foreign pharmaceutical companies. Engaging in R&D projects in the cluster will attract highly qualified personnel both to research centers and to cluster participants.

**The main measures for the implementation of the Concept**

*Objectives and target indicators of the Concept.*

For the Concept to be implemented, the following major objectives have to be met: provision of a sufficiently large (30 % or more) coverage for the list of vital drugs; support of pharmaceutical companies and promotion of cooperation among all cluster segments, e.g. research, development of new technologies, manufacture of substances, manufacture of drugs, promotion of drugs on the market; creation and support of research centers in the universities of Saint-Petersburg, performance of scientific research, e.g. in order to improve the material and technological resources in research centers and to attract highly qualified workers in the course of carrying out concrete research projects; creation of infrastructure for the introduction of innovative drugs into the medical practice in Saint-Petersburg that should go hand in hand with the implementation of appropriate treatment standards
in order to increase the share of innovative products in Russian healthcare; establishment of specialized training courses and attraction of highly qualified personnel; creation of organizational and legal frameworks to ensure private investment.

The following target indicators can be used to monitor the implementation of the Concept: the annual output of pharmaceuticals in Saint-Petersburg, including those on the Vital and Essential Drugs List; the number of duly registered and marketed innovative pharmaceuticals and generics included in the Vital and Essential Drugs List; the number of newly established research centers for conducting clinical trials and introducing pharmaceuticals into medical practice; the number of finished and ongoing research projects relating to the development and manufacture of drugs; the level of private investment in the creation and development of pharmaceutical industrial objects and organizations; the number of new jobs in pharmaceutical production; the number of internationally high-ranking specialists involved in the creation and development of new technologies and in researching pharmaceuticals.

**Creation of industrial facilities.** The cluster cannot function without a sufficient number of industrial objects capable of housing the internal or contractual production. The number of substances and/or drugs that an industrial organization possesses is often insufficient to fully and effectively engage their industrial capacities with regard to the number of products and batch sizes. A pharmaceutical company in possession of its own research department and an active marketing policy can hope to effectively engage its industrial capacity after 3 to 5 years on the market. During this period it is desirable to invite pharmaceutical market participants and organize contractual production.

The availability of industrial objects with surplus productive capacities or the creation of modern pharmaceutical industries to accommodate the production in the cluster or to attract foreign pharmaceutical companies constitute one of the key objectives of the cluster formation. The realization of this objective requires some engineering works for the preparation of areas suitable for housing the industrial objects. Budgetary investments in transport facilities, energy, heating, supply of gas, water and drainage constitute the necessary preparation for establishing the industrial sector of the cluster at the level of infrastructure. To minimize the expenses related to engineering works and optimize the use of land with respect to established sanitary zones, the industrial objects can be deployed in compact areas. If such areas are given the status of special economic zones, this can provide an additional lure for prospective investors and cluster participants.

**Thus,** budgetary investments in engineering works in preparation of the most promising areas together with additional tax and custom incentives for cluster participants represent the key prerequisites to developing the cluster within a reasonable timeframe.

In addition, the existing industrial capacity of Saint-Petersburg has to be taken into account. Though there should be a single standard of quality of produced goods and common goals for cluster participants, the industries currently established in Saint-Petersburg must be given additional opportunities and privileges to facilitate the distribution of their products and to make sure that they have adequate resources to further scale up the production.

Given the timeframes for engineering works in preparation of industrial areas and for the acquisition of the status of a special economic zone, private investors may want to consider acquiring already established industrial objects that are not properly used and refurbishing them for the purposes of cluster development. In this case the investors may reduce the delay and cost associated with the preparation of new areas but still be able to benefit from the privileges offered to cluster participants.

**Cluster segment integration.** At present pharmaceutical market participants have their own policies regarding the creation and promotion of their products. This leads to increased delays and costs associated with launching new drugs. In accordance with the main purpose for the creation of this cluster, the efforts of its participants must be coordinated to promote a more efficient distribution of its products compared to individual activities.

The geographical localization of cluster segments, including research centers, preclinical and clinical research facilities, modern industrial objects and expert organizations, is valuable in itself, since it reduces the costs in terms of time, logistics and communication. To participate in the cluster, all parties must agree to coordinate their efforts in order to promote the products of the cluster (improve the sales compared to independent efforts). Considering the competitive relations between pharmaceutical market participants, an additional effort is required to ensure effective allocation of finances during the production of import-replacement drugs.

As of today, no clear definitions exist of such terms as “local producer” or “local products”. A number of manufacturers of one and the same drug under various trade names are forced to share the market, which reduces their potential profits. The promotion of pharmaceutical products is further complicated by the federal law that requires that state supply orders must specify international non-patented names of drugs in the competition documents.
Thus, the cluster objectives can be achieved if its participants act in a coordinated and consistent fashion. At the initial stage the coordination may be achieved through the efforts of the executive branch of public authorities in Saint-Petersburg with due regard for the legally guaranteed protection of market competition.

In future more effective mechanisms to ensure coordination between the participants will have to be established. The main challenge will be to identify flexible organizational and legal frameworks that will both guarantee continued independence of participants in making decisions to preserve their competitiveness and provide binding norms of coordinated development (especially concerning creation of new technologies needed to replace imported products in the state supply chain).

One challenge facing this integration is related to the poor prospects of direct state investment in high-tech industries because of high risks and the impossibility of effective monitoring on the part of the state. Independent investors demand encouragement and incentives to localize production in the cluster, but at later stages the mutual dependence of cluster participants will decline and competitive relations will begin to dominate.

The integration of cluster segments would clearly be a positive development for Saint-Petersburg. The main advantages of such integration are the following: more orders for innovative pharmaceuticals and methods of producing generics in research centers and expert groups, resulting in a higher demand for specialists and scientists and modernization of material and technological resources in research centers; a growing demand for preclinical and clinical trials; an opportunity for the industrial segment of cluster participants to replace contractual production with production of their own pharmaceutical products (for innovative companies) or to acquire licenses for production and transfer of technologies (for contractual industries).

The process of establishing the cluster and the feasibility of its integration will further depend on the stance that public authorities in Saint-Petersburg assume towards the following key issues: the primary investor in the growth of Russian pharmaceutical industry (state, private investment, foreign investment, joint ventures); the contribution of Saint-Petersburg to the development of the cluster (engineering works in preparation of the area, organization and management); guarantees and incentives for the prospective cluster participants at the initial stage (investment decisions, cost reduction at the construction stage thanks to the availability of pre-installed infrastructure and expedited coordination of project documentation); incentives to cluster participants due to their integration (expedited development and marketing of pharmaceutical products, privileged access to state supply orders); export incentives for pharmaceutical products in case of joint ventures with R&D departments of large foreign companies.

Anticipated prospects of cluster development and its future directions. The Concept cannot be implemented without a concerted effort on the part of the state to boost pharmaceutical production, develop technological resources and create innovative pharmaceuticals and generics to replace the imported products. The major challenges relate to the difficulties inherent in scientific research and creation of technological capacities for the production of drugs, low efficacy of direct budgetary investment and inability of the state to ensure effective control, apart from placing a state supply order for a limited number of particularly important pharmaceuticals.

Unless changes are made in the laws regulating state supply orders, the prospective investors will be facing similar challenges due to high investment risks, complexity of the scientific process with a paucity of highly qualified professionals and managers, and the risks of selling high-tech specialized products. However, given the constantly growing healthcare costs, market participants and prospective investors cannot fail to appreciate the great economic potential of this sector. Many of the necessary decisions, e.g. the requirement to adhere to the standards of GMP or the creation of a state authority in charge of controlling the quality of pharmaceutical products, belong to the competence of federal state authorities. As long as these issues are not solved, investment in modern technological solutions on the part of conscientious market participants will suffer from unfair competition with companies that fail to meet the modern standards and thus can market their products at a lower cost. It is particularly important for Saint-Petersburg to have a number of well-developed, modern pharmaceutical companies of various profiles. Tax revenues, improved training standards in the participating universities, improved material and technological resources in research centers at no extra financial or organizational cost, greater prestige of Saint-Petersburg and involvement of experts in the sector, promotion of international scientific cooperation — these are only some of the benefits that can be expected to accrue with the development of the cluster. The cultural and social advantages of Saint-Petersburg (in contrast to remote areas and small cities, which cannot offer an acceptable quality of life) also constitute an important factor in attracting experts and highly qualified personnel.

Cluster management and cooperation of its participants have to provide a single standard approach and requirements to the quality of products and provide cluster participants with incentives and information. The selection of participants should be based on the significance and quantity of their output, the scale of
investment in pharmaceutical objects and the prospects for development with regard to conducting scientific research. The authority that manages the cluster must be responsible for informing the participants in good time about the promising directions of cluster development, e.g. about effective ways to incorporate their products into medical practice and about the potential and technological resources of research and educational centers in Saint-Petersburg for the purpose of engaging in joint ventures. So as to protect the interests of participants and adhere to the stipulated guarantees, the authority in charge of managing the cluster must maintain a single consistent policy in entering contractual agreements and engaging in joint ventures in the development, production and sale of pharmaceutical products.

The evaluation of the efficacy of Concept implementation and any changes in cluster management structure must be based on the target indicators both as stated in the Concept and as reformulated in future, taking into account the interim results of cluster development. One possible approach to cluster management is to create a Coordination Committee, which will include representatives of cluster participants, profile state authorities, including federal authorities as far as federal target programs are concerned, representatives of scientific and educational centers, and individual experts immediately involved in managing the cluster. The functions of the Coordination Committee will include determination of target indicators of cluster development, evaluation of interim results with respect to target indicators, and determination of whether particular pharmaceutical companies meet the requirements for participation in the cluster. In addition, the Coordination Committee may decide to implement measures in order to support cluster participants, carry out investment or research projects, etc. Apart from the Coordination Committee, it may be beneficial to consider creating a coordination body that will act continuously and thus will be in charge of the immediate administration of the cluster.

However, any management model must take into consideration the interests of actual cluster participants, their independence and competition.

The stages of cluster development. The initial stage (up to 2015) of cluster development includes the preparation of areas for the placement of prospective pharmaceutical industrial objects and investment in projects relating to creation of industrial objects and research centers in the existing scientific centers in Saint-Petersburg. Such measures will eliminate the technological and industrial lag in the pharmaceutical industry and partly replace imported products in the state supply orders. This objective calls for incorporation of the products of the cluster into medical practice so as to replace imported products and meet the need for pharmaceuticals in accordance with the list of strategically important, essential and vital pharmaceuticals. The manufacture of synthetic and biotechnological substances must be developed in parallel with the manufacture of medicinal drugs. Other important factors include the following: effective cooperation between scientific and medical centers and pharmaceutical companies to ensure the innovative character of cluster development; training and involvement of highly qualified personnel; establishment of frameworks for public-private partnerships for joint ventures, e.g. as part of federal target programs.

At the second stage (up to 2020) it will be necessary to increase the number of small and middle-range innovative enterprises and promote further growth of research centers in the major universities in Saint-Petersburg. This will allow for effective monitoring of developmental trends in the global pharmaceutical industry in order to ensure that the produced goods have export potential and to achieve better integration into international research projects. Growing exports of the products of the cluster will provide additional financial resources for fundamental and applied research, which are currently inaccessible to the local pharmaceutical companies because of financial difficulties they experience when selling their products on the Russian market.

Thus, the creation of this cluster is based on economic and political considerations and agrees with the potential of Saint-Petersburg and its strategic interests.

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Pharmacogenetics studies the role of genetic factors, such as “variations” in particular genes, in shaping the pharmacological response of the human body to medications [1]. In other words, pharmacogenetics is concerned with the effect of changes in specific genes on the efficacy and safety of medicinal drugs. For the most part these genetic factors (essentially, individual genetic features of the patient) depend on polymorphic loci in the genes that encode proteins involved in pharmacokinetics and pharmacodynamics of drugs. Changes in these loci may make the gene “dysfunctional”, so that no protein will be synthesized, or the protein may display an abnormally low or high level of activity, or the synthesis of normal protein may be enhanced or inhibited. Such modifications in polymorphic genetic loci are usually referred to as “polymorphisms” or “alleles”. Polymorphism in genes that code for proteins involved in pharmacokinetics or pharmacodynamics may lead to variations in the pharmacological response to a particular drug. The first group of so-called “pharmacokinetic polymorphisms” includes the genes that code for enzymes involved in biotransformation and transporter proteins involved in drug absorption, distribution and elimination.

The role of genes that control synthesis and activity of the enzymes responsible for biotransformation of drugs, such as cytochrome P-450 isoforms (CYP2D6, CYP2C9, CYP2C19) and enzymes of the second stage of biotransformation (N-acetyltransferase), is currently under investigation. There has also been some recent interest in the effect of polymorphism in the genes coding for transporter proteins on the pharmacokinetics of medicinal drugs. The second group of so-called “pharmacodynamic polymorphisms” includes genes that encode the “target molecules” of drugs or proteins that are functionally linked to the “target molecules” (receptors, enzymes, ion channels) and genes whose products are involved in pathogenetic processes (coagulation factors, apolipoproteins, etc).

Pharmacogenetic (PG) testing is a method of identifying specific polymorphic genes that affect pharmacological response. PG tests are based on polymerase chain reaction performed after obtaining a DNA sample from the patient. The source of DNA (that is, genetic material) may be blood or a buccal epithelial scrape. The collection of these biological samples requires no special preliminary procedures. The outcome of a PG test is the patient’s genotype for a particular polymorphic gene. For the most part the results are interpreted by a clinical pharmacologist, who provides recommendations concerning the choice of drug and its dosage for this particular patient. If a PG test is performed, it becomes possible to predict in advance the pharmacological response to a specific drug and thus to choose the individually appropriate drug, its dose, and sometimes the entire treatment strategy. In future, with the introduction of the chip technology, it will be possible to determine not only single polymorphisms of particular genes, but the whole (or almost the whole) spectrum of genetic variations that could affect the pharmacological response, and this is the goal of pharmacogenomics. It will then become possible to prepare something like a genetic passport for each patient. In this regard, pharmacogenetics and in future pharmacogenomics may be considered as promising directions for the development of personalized medicine [1].

According to the English version of the free online encyclopedia Wikipedia, personalized medicine is the...
method of using genomic and molecular technologies to improve the healthcare system, facilitate the creation and use of medicinal products (above all, drugs), and to identify individual susceptibility to diseases [2]. This definition can be adopted specifically for the use of medicinal drugs, as follows: personalized medicine is the principle of selecting the appropriate drug and its dose depending on the results of individual genomic and molecular tests (techniques) and especially genotyping, i.e. PG testing. Apart from PG testing, the toolkit of personalized medicine includes biomarkers¹ and pharmacotranscriptome tests².

Though some methods of personalizing the prescription of drugs have been studied for a long time, it would be wrong to say that they are effective and fully incorporated into clinical practice. At the beginning of the 21st century “trial and error” (for instance, in the treatment of hypertension) and “the rule of thumb” (based on personal “experience”) remain the most common methods of selecting the appropriate drug and its dosage. Of course, there are constantly updated treatment guidelines, international and country-specific regulations developed from the position of evidence-based medicine (which is based on randomized clinical trials (RCT)) to regulate the use of medicinal drugs in the treatment of various diseases. However, the results of a RCT only partially apply to any particular patient, since they present the “average” outcome describing a hypothetical “average” patient (according to the inclusion/exclusion criteria). But there are almost no such “average” patients in the real world. In this situation all that a physician can do is prescribe the “average” dose and hope that the drug will be as effective and safe for this particular patient as it was in the RCT. Because of this, some foreign experts have begun to refer to evidence-based medicine (EBM) as “hope-based medicine” (HBM) [3]. Thus, the method of choosing the individually appropriate treatment has still not been established, and this choice is not based on the objective individual characteristics of the patient. Accordingly, there is no doubt that the implementation in medical practice of the principles of personalized medicine, as they are currently understood, is an important task that will lead to the transition from empirical to personalized pharmacotherapy, providing maximally effective, safe, and, it may be pointed out, cost-effective treatment [4].

So far, widespread practical application of PG testing as a type of medical technology and the most promising tool of personalized medicine remains limited due to a number of problems that have not been conclusively solved:

1. Limited access to PG testing for physicians and patients because of its high cost and other reasons. This is a common opinion among physicians and healthcare officials. Even though PG testing is available in a number of commercial laboratories and research centers, not only in Moscow and Saint-Petersburg but even in a number of regions, these tests are almost never performed in medical institutions. However, all that is needed is the equipment for performing polymerase chain reaction (“PCR-arrays”), therefore the technical difficulties of performing PG testing in the clinical practice can be solved, especially since the creation of pharmacogenetic laboratories is stipulated in order No.494 of the Ministry of Health from October 22, 2003 “On improving the work of clinical pharmacologists”, which is still not complied with [5]. It is also important to emphasize that these tests have to be performed as quickly as possible (within 1-2 days), since the physician has to decide which drug to use rather promptly: the outcome of many diseases is improved by early treatment. This introduces another problem, since at present in many cases it is technically impossible to perform the test rapidly enough.

2. The lack of clear algorithms of choosing the appropriate drug or dosage depending on the results of PG testing. It is not always clear to the physician how to manage the patient after obtaining a particular result in a PG test. For instance, if a pregnant woman shows genotype TT on the polymorphic marker C3435T of ABCB1 gene (also known as MDR1, the gene encoding P-glycoprotein, a drug transporter) and this woman receives any medication (including drugs “allowed” during pregnancy), the child has a risk of congenital defects of the face and jaws (harelip or cleft palate) that is 4 times higher compared to women who also received medications but had genotype CT or CC [6]. Now, what should be done with pregnant women who have genotype TT? Should they be given no medications whatsoever? What if these are indicated? So far there are only a few algorithms of choosing the appropriate medication and its dosage for particular results of PG tests – the tools of personalized medicine. It would be useful if these algorithms could also consider other individual factors (age, gender, liver or kidney disease, ethnic origin, concomitant use of other drugs, smoking status, etc), thus providing a multi-factor model.

3. The lack of RCT-proven advantages of relying on PG testing for the choice of drug and its dosage compared to the “traditional” (“trial-and-error”) method. The obvious conclusions that can be drawn from the results of retrospective studies that employed PG testing do not mean that this method is superior to the “standard”, “traditional” methods of selecting the appropriate medication and its dosage. As a positive example, we can cite the RCT which demonstrated that the incidence of neutropenia was 4 times

¹ Biomarkers are substances (including proteins) that are somehow involved in pharmacokinetics or pharmacodynamics of medicinal drugs or in the pathogenesis of the disease for which the drug is indicated.

² Pharmacotranscriptome tests are used to assess the expression (“activity”) of genes that encode proteins involved in pharmacokinetics or pharmacodynamics of medicinal drugs by means of measuring the concentration of the corresponding m-RNA.
The “toolkit” of personalized medicine recommended for use in clinical practice

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<td>Patients with colorectal cancer who have to receive irinotecan</td>
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lower when the dose of the cytostatic drug irinotecan was selected individually based on the activity of CYP3A4 (assessed by the clearance of midozalam) compared to patients whose dose of irinotecan was chosen using the “traditional” method [7]. There are only a few of such studies, but it is impossible to implement PG testing as a type of medical technology without performing similar research. In addition, it would be desirable to prove the economic advantages of personalized selection of the appropriate medication and its dose compared to the “traditional” approach.

It is worth noting that at present the use of PG testing in Russia is not regulated; it is not included in the standard manuals and treatment guidelines. Some drug labels mention PG testing, but only as recommendations for the physician that are not binding.

The problems discussed above have only been solved for a handful of PG tests (see the Table). There have been some efforts to incorporate these tests into clinical practice. In our own experience, the type of PG testing most in demand in internal medicine is the test used to determine the individual dose of warfarin (the test for polymorphisms in CYP2C9 and VKORC1 genes) [8]. This PG test is commercially available in 15 laboratories in Moscow, Saint-Petersburg and other Russian cities, and its price varies from 850 to 12 000 rubles [9]. These prices are clearly artificially high, partly because the demand still remains low, therefore they can be expected to drop once the performance of this test becomes “routinized”.

In our practice we use the Gage algorithm to determine the dosage of warfarin depending on the results of PG testing, since this algorithm has proved to be the most applicable to Russian patients (we have tested five of the published algorithms). The Gage algorithm is a mathematical formula that takes into account both the genotypes identified with PG testing and other individual characteristics (age, gender, comorbidities, ethnic origin, concomitant use of amiodarone, statins or antifungal medications, and smoking status). To choose the individually appropriate dose of warfarin using this algorithm, any physician may access Internet page
MEDICAL TECHNOLOGIES ASSESSMENT AND CHOICE 

POLICY AND MANAGEMENT IN HEALTHCARE

www.warfarindosing.org, enter the patient’s details including the results of PG testing, and receive the recommended dose for initial and maintenance therapy with warfarin. According to our data, the risk of bleeding is 4.5 lower if this algorithm is used for personalized warfarin dosing compared to the “traditional” method [10].

However, the economic consequences of this type of PG testing are less clear. Thus, one of the studies evaluated the economic advantages of PG-assisted warfarin dosing over the traditional approach using “cost-effectiveness (utility)” analysis of cost per 1 quality-adjusted life year (QALY) [11]. With one PG test costing 400 USD and taking 5 days to perform, its cost per 1 QALY was 170,000 USD, which is unacceptably expensive. In the authors’ opinion, the cost of PG testing can remain under 50,000 USD per QALY only for 10 % of patients at high risk of bleeding when treated with warfarin. They think that the cost of QALY with PG testing for warfarin dosing can be lower than this sum only under the following conditions:

PG testing has to prevent over 32 % of major bleeding episodes;
PG testing has to be completed within maximum 24 hours;
the cost of a PG test has to be less than 200 USD [11].

To summarize, a number of problems prevent PG testing from being widely used and applied to all patients. However, it can benefit certain “difficult” patients, and it ought to be used in clinical practice today:

- when long-term treatment causes a broad spectrum of serious adverse drug reactions (ADRs), including drugs with a narrow therapeutic range, especially in patients at high risk of ADRs;
- when there is family history of serious ADRs;
- when the drug is known to be effective only in some groups of patients, especially for expensive drugs.

Thus, there is no doubt that PG testing as a practical medical technology holds great promise for improving the quality of pharmacotherapy and can already be used today for certain “difficult” categories of patients. However, a number of problems discussed above still have to be solved before it becomes generally applicable. Most likely it will prove expedient to introduce PG testing separately in the following fields: cardiology (anticoagulation and antiaggregation therapy), oncology (therapy with “target” and some other antitumor agents), psychiatry (therapy with antidepressants and neuroleptics), and phthisiatry. These are the medical fields where the medications may be “difficult” in terms of the individual variability of their efficacy or safety and where effective and economically acceptable PG tests are already available.

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Risk-sharing contracts or agreements are rather common in international and European practice. They normally guarantee that the manufacturer will be fully or partially reimbursed for the cost of medications if certain conditions are met, e.g., if target levels of efficacy are reached. Such agreements are made between the manufacturer of a medicinal drug and the reimbursement organization. Why is it that risk-sharing agreements are increasingly common in European countries, with their well-developed system of health technology assessment, standardized treatment strategies, comprehensive control of prices, and regulation of the access to reimbursement? What is their purpose? When are such agreements applicable? Who do they benefit — the regulatory authorities or the manufacturers? May similar agreements be introduced into the Russian healthcare practice?

To answer these questions, we need to consider healthcare regulation in its interaction with the process of developing innovative medical products.

The healthcare system is supposed to provide citizens — consumers of medical services — with equal access to the most effective medical technologies and products, ensuring financial stability as a guarantee of such equal access. Accordingly, the healthcare system should reimburse the costs of those technologies or products whose clinical effectiveness and economic efficiency has been convincingly proved. To ensure financial stability of the system, mechanisms of controlling the costs are used (pricing regulations, lists, etc.), while epidemiological data and clinical guidelines are used to estimate the anticipated consumption of medications. Thus, the “profile” of a medicinal drug that definitely needs to be included in the reimbursement system by the healthcare authorities is as follows:

— it has been extensively studied in clinical trials and is indicated to large groups of patients;
— it is indicated for a socially important disease or health condition;
— there is evidence of its economic superiority over alternative treatments;
— its impact on the budget is predictable (there is epidemiological data, dosage and price are known).

The manufacturers of innovative medical technologies or drugs also have these criteria in mind when developing a new medication. However, there are other factors that cannot be ignored:

1. Development of innovations requires immense investments without any guarantees that the end product will meet the desired criteria.
2. Investment in the creation of innovative medical products and technologies normally takes into account the global demand on the market of most countries. At the same time, the criteria used to determine the product’s value are country-specific, and therefore the same medication may receive very different ratings when its innovativeness and effectiveness for the healthcare are evaluated in different countries (Fig. 1). The differences are not even due to variations in genotype that might affect the efficacy of a drug, or in the familiarity with a particular drug in different countries: even the results of an international, multi-center clinical trial may be interpreted in various ways, depending on the priorities of the healthcare system or the particular features of country-specific treatment standards. In this case the manufacturer risks seeing its product excluded from the reimbursement system or included at the price of an alternative product.
3. Not all serious and socially important diseases are particularly widespread. The development of medications for the treatment of so-called orphan diseases does not presuppose large-scale clinical trials, since the number of such patients is limited. An economic evaluation of the
treatment of rare diseases in the context of the healthcare system as a whole is also irrelevant, and for the same reason: it concerns an improvement in the condition of a relatively small number of patients. In such cases the regulatory authorities have to make their decisions based on little clinical evidence and include in the reimbursement lists drugs that do not significantly affect the overall effectiveness of the healthcare system but are nevertheless rather expensive (as a result of considerable investment in their development and the limited number of patients).

4. Relying on the evidence of international multi-center clinical trials and the drug labels, which are based on this evidence, it is not always possible to decide which categories (subgroups) of patients show optimal response to a particular treatment and which groups are less susceptible. Besides, it may turn out that certain groups of patients require a higher dose or a longer duration of treatment to achieve the desired clinical effect. If the indications for use are broadly defined, regulatory authorities interpret this as inability to determine the number of patients who will receive this medication and/or its actual dosage, assuming that this data can only be obtained empirically, after the medication enters clinical practice. In some other cases, the evidence that the medication is safe may be considered inadequate. In all the situations described above, regulatory authorities in charge of including a new drug in the reimbursement system may submit a query for additional information, and if such data are at present not available, the decision may be negative.

The factor that all these situations have in common is the risk for the reimbursing party. In most cases this is financial risk associated with poor clinical and/or economic expediency or unpredictable costs. In some cases clinical risk may also be an important factor, as when there is insufficient evidence to prove the safety of a medication. On the other hand, the state or an insurance company may decide that the new medication can potentially be highly beneficial, providing that its effect claimed by the developer (manufacturer) is indeed achieved. In this case reimbursement may be offered conditional on minimizing the risk. In this situation the priority for the developer (manufacturer) is to ensure that patients have access to the new treatment and that clinical evidence is thus accumulated. Such evidence will prove the efficacy of the drug to the healthcare authorities, and as a result, the drug may be included in reimbursement lists and clinical guidelines. Apart from this, in some cases risk-sharing agreements may give the manufacturer a real opportunity to keep reimbursement prices high (naturally, on the condition that the economic effectiveness of the new medication is proved) (Fig. 2).

**Fig. 1. Health Technology Assessment: Different Perceptions of the Product’s Value [1].**

**Notes:**
- SMC — Scottish Medicines Consortium
- HAS — la Haute Autorité de Sante
- TLV — Dental and Pharmaceutical Benefits Agency
- PBAC — Pharmaceutical Benefits Advisory Committee
- NICE — National Institute for Health and Clinical Excellence
- CDR — Common Drug Review

**Fig. 2. Risk-Sharing Agreement**

**WHICH CREATIVE MODELS FOR PROVIDING PATIENTS WITH AN ACCESS TO INNOVATIONS EXIST AND ARE ACTUALLY USED?**

**Price-sales agreements**

If there are no detailed data on the prevalence of a particular indication and thus its anticipated cost for the budget, the state may reach an agreement with the manufacturer of an innovative medicinal drug stipulating that its price has to be gradually lowered as certain “threshold” numbers of prescriptions or applications to the Auction Committee are reached. This allows the state to decrease the risk of exceeding the expenditures for a particular drug anticipated in the budget, while providing the patients with an access to the medical product or technology.
The same approach may be regarded as part of the program for the transfer of technologies of drug development and manufacture to Russia. Such projects require considerable investments by the company producing the drug, therefore an agreement stipulating fixed supply conditions for a particular period of time (long-term contracts) would significantly reduce the risk for the company and increase the investment appeal of the project.

The following elements are necessary for this approach to be implemented:
- a prototype or “blueprint” for contracts applicable in the existing legal framework and coordinated with all regulatory authorities (the Ministry of Health and Social Development, the Federal Antimonopoly Service, the Ministry of Industry and Trade);
- a detailed, well-researched business model.

**Proof of the practical value of the medical product or technology (prescription with collection of clinical evidence)**

This model is relevant when the claimed value of the drug or its method of application (dosage, number of patients, safety, etc) is questioned. The drug is included in the reimbursement system at a high price based on the evidence for its clinical and economic superiority submitted by the manufacturer. At the same time, a clinical and economic study is initiated, its results are analyzed, and the properties claimed by the manufacturer are compared to the evidence from clinical practice. When a conclusion is reached, the following scenarios are possible:
- the innovative status and high price of the new medication are confirmed;
- the “added value” of the new medication is considered insufficient, and its price has to be reduced to match the alternative treatment;
- the actual consumption of the medication (dosage, regimen, patient groups) and thus its impact on the budget are considerably higher than anticipated, therefore the price has to be reduced.

Thus the main condition for reaching a risk-sharing agreement in this model is the need to clearly define and agree on the following criteria:
- indications for the medication;
- its efficacy criteria;
- the number of patients enrolled in the program;
- the time frame for the completion of the project;
- the criteria of permanently including the medication in the reimbursement system;
- the level at which monitoring and clinical and economic analysis will be performed;
- the cost of study;
- data analysis.

One of the key issues is to decide who will be in charge of expert evaluation, once the data has been collected. An independent expert authority with the necessary expertise must be involved.

**Guarantee of the expected effect**

As the common model in marketing goes, “...or you’ll get your money back”. The producer shoulders the entire risk of lower-than-expected efficacy of the new drug in some patient groups, since the healthcare system reimburses the costs only if the drug is clinically effective. The implementation of this model depends on clearly defined criteria of what constitutes a lack of clinical success, and it is easier to implement than the model with collection of additional clinical evidence. However, its precondition is a centralized patient database and clinical monitoring of these patients.

**Cost sharing**

This model is applied if it is uncertain whether the real value of the medication will correspond to that claimed, e.g. when there is limited clinical evidence. The treatment course is partly financed by the manufacturer (the medication is provided free of charge by its manufacturer). As with the model of clinical evaluation, the agreement stipulates its period of validity, the expected results, and the criteria for a comprehensive incorporation of the medication in the reimbursement system.

**Patient stratification**

It is used when heterogeneity of patient groups (genetic features, various stages of the disease or various scenarios of its progression, etc) entails a risk of less favorable cost-effectiveness ratio, which can occur if the drug is often prescribed to patients who poorly respond to this treatment. The manufacturer may suggest that the patients should be stratified to specify the subgroup most likely to achieve a good clinical effect and/or ask for reimbursement of expenses for additional diagnostic tests (which can be rather expensive). For example, various histological types of sarcoma are associated with different responses to treatment and require different strategies, therefore a precise subtyping with subsequent therapy specific to each subtype significantly improves the effectiveness of each therapeutic approach (Fig. 3). Stratification of patients with such conditions as schizophrenia or alcohol abuse allows researchers to select, out of a large number of patients, subgroups amenable to compensation and re-socialization with the help of medical technologies and innovative medications and to reduce the risk of expensive and ineffective treatment of those subgroups that do not respond to this treatment. The implementation of this model may require considerable investment into the development of stratification methods and optimal treatment strategies.
IS THERE DEMAND FOR SUCH AGREEMENTS IN THE RUSSIAN HEALTHCARE SYSTEM?

The answer is: “Definitely”. The criteria of inclusion into the List of Vital and Essential Drugs in general overlap with the criteria discussed above, which are used for expert evaluation of medical technologies, and therefore, some aspects of the medicinal drug supply do not meet these criteria (e.g. rare diseases). In the absence of a centralized database of all patients and all major diagnoses, it is not possible to predict the numbers of patients and prescriptions for all diseases. The Russian clinical practice is rather different from that found in most other countries. These considerations further hamper the access of innovative medications to the reimbursement system of the RF. Given this situation, the manufacturers of innovative drugs can suggest various models for risk sharing which will allow patients to have access to innovative medicines. In addition, this will produce valuable data on clinical outcomes when medications are used in the context of the Russian healthcare system. As a result, innovative diagnostic and treatment methods will be implemented in clinical practice.

Today, the Russian healthcare system is facing important tasks: to improve the effectiveness of Russian healthcare, to extend the average life expectancy quickly and significantly, to 75 years of age. Clearly, these tasks cannot be solved without innovative drugs and medical technologies. We suggest that both federal and regional healthcare authorities should encourage the initiatives on the part of manufacturers of innovative drugs to reach “price-sales” and risk-sharing agreements and support the creation of appropriate effective models. Such projects call for the development and implementation of:

— a legal framework (prototype contracts meeting the legal requirements in the RF and coordinated with the federal regulatory authorities, such as the Ministry of Health and Social Development, the Federal Antimonopoly Service, the Ministry of Justice);
— a database and/or registry of patients;
— models for sharing the costs of clinical and economic studies;
— methods of monitoring and evaluating the efficacy of medical technologies and drugs in the actual clinical practice.

If the state, business, academia and medical world joined their efforts, more patients would have an opportunity to receive a timely and effective treatment.

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How to Change Medical Practice: Guidelines of the UK National Institute for Health and Clinical Excellence

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The article describes the guidelines of the National Institute for Health and Clinical Excellence (NICE, UK) for changing the current medical practice. Specific methods for identifying and overcoming the obstacles on the way to change are suggested. The guideline also reviews the existing evidence for the efficacy of various methods of implementing innovations.

KEYWORDS: change management; change in medical practice; National Institute for Health and Clinical Excellence (NICE).

The greater popularity of evidence-based medicine, development of evidence-based clinical guidelines and health technology assessment (HTA) reports are important steps towards improving the quality of medical care. But the implementation of manuals and guidelines, even those based on the best scientific evidence, remains a difficult problem, since resistance to innovations is part of human nature, the healthcare systems are incapable of promptly incorporating innovations that require structural and financial changes, and in addition the medical community is fairly conservative. The efficacy of different methods of implementing innovations has been compared in a number of scientific studies, and there are even systematic reviews that summarize the results of such research [1]. Unfortunately, clinical practice is slow to change, and there is still little evidence that convincingly demonstrates the possibility of implementing innovations in a highly productive manner. Because of this, the organizations in charge of preparing treatment guidelines and HTA have been increasingly concerned about the best way of implementing scientific guidelines in medical practice.

Thanks to its transparency and detailed operational procedures, the National Institute for Health and Clinical Excellence (NICE) in the UK is probably one of the most world-famous and widely discussed centers for the HTA. The NICE has been producing treatment guidelines and preparing HTA reports since 1999. Some of its guidelines contradict the traditional treatment methods and require changes in the work of physicians, therefore the NICE has been investigating techniques that would assist healthcare professionals and managers in implementing innovations. There is a dedicated “NICE implementation programme”, which includes consultation services to specialists who wish to rearrange their practice in line with the NICE guidelines, evaluation of the economic advantages of following the guidelines, and the creation and promotion of educational materials and manuals for the solution of particular problems.

One of the guidelines published by the NICE concerns the ways of changing the current medical practice [2]. It introduces healthcare professionals to the main techniques of change management. In accordance with its principles, the NICE has based this guideline on scientific evidence, as far as such evidence is available; the efficacy of the proposed approaches has been studied and backed up by objective evidence (the full version of the systematic review of the efficacy of various methods of changing medical practice can be found at the NICE homepage). We have deemed it expedient to describe the main recommendations developed by the NICE, since the implementation of innovations is an important issue for the Russian health care system, and the most effective techniques of change management may allow the desired results to be achieved more promptly.

The NICE guideline begins by reminding the reader that any change is inherently difficult. In the healthcare system there is the additional problem of coordinating the efforts of many participants, a large number of medical organizations, physicians, and patients. An appreciation of the magnitude of the task is meant to prepare the medical professional, so that they will approach the task

1 Richard Hooker (1554—1600) was an English priest and theologian, one of the founders of Anglican theological tradition. This phrase of him is given in a NICE guideline discussed in the article.

2 http://www.nice.org.uk/media/AF1/42/HowToGuideKingsFundLiteratureReview.pdf
of changing the medical practice in a thoughtful manner, carefully planning the implementation of innovations and not admitting defeat too easily. “Changing practices takes a long time,” as the authors of the guidelines point out. A thorough implementation of one treatment guideline takes at least three years. Gradual change has to be envisioned: even small steps in the direction of the final goal are important (this principle is known in management as “the gradual change strategy”, and in everyday life it is expressed by the saying “steady does it”).

The guidelines suggest three stages of changing the medical practice:

1. Understanding the barriers (obstacles on the way to change).
2. Identifying the barriers.
3. Overcoming the barriers.

The first section of the manual described such barriers that prevent change from occurring, hinder innovations and create resistance on the part of medical workers. It emphasizes that recognizing the obstacles to change is the first step in implementing any innovations.

The first barrier is the lack of knowledge. Physicians are often not aware of the existence of new evidence-based guidelines, or they may be aware of their existence but ignorant of the specific recommendations. As a result of being poorly informed, physicians may feel that these guidelines undermine their autonomy or do not apply to the patients they are treating.

The lack of motivation is the next barrier that affects practically everything a person does. Motivation may be controlled with rewards and punishments, but internal motivation is also important. Personal goals, intentions, priorities, obligations affect the extent to which a person is ready for change. The medical profession presumes willingness to perfect one’s skills and knowledge in order to provide medical care in accordance with the highest standards, and this willingness may be further strengthened with the help of the methods described below.

Acceptance and beliefs may also become barriers to change. It is important that people understand what personal costs and benefits the change will entail. The opinions of others are also important: some professionals find it hard to implement guidelines that contradict the opinion of a respected colleague or the suggestions of a well-known professional association. Physicians may simply refuse to believe that the guidelines are based on solid evidence or that they will improve the effectiveness of medical care. Finally, doubts about one’s own ability to carry out the changes may also hamper the implementation of innovations.

In order to implement something, it is not enough to know what needs to be done — one has to know exactly how to do it. The lack of skills is another barrier mentioned by the NICE. Healthcare workers may not know enough about how the change can be performed, and they may need to receive special training, which in turn takes time.

Some features of the current practice, such as the lack of resources or traditional approaches to providing medical care, may present formidable obstacles. The implementation of new guidelines often requires new equipment or adjustments in the existing healthcare infrastructure, which cannot be achieved in a short time. Besides, the resignation of a leader or new priorities set by the senior managers may also hamper the implementation of innovations.

There are also a number of external barriers which have to be taken into account but which it may be difficult or impossible to control, such as the general political and economic situation. If the financial resources of the healthcare system are insufficient to implement changes, the motivation system does not encourage innovation and the accountability system does not include indicators of compliance with guidelines, it becomes even harder to make change happen. According to the NICE, there is evidence that implementing regulations and setting goals at the national level with mandatory monitoring and continuous professional development improve the quality of medical care and lead to better treatment outcomes.

The methods recommended by the NICE include talk with key individuals, surveys (questionnaires), direct observation, brainstorming, and focus groups.

Key individuals are the leading experts who have enough knowledge, skills and authority to evaluate the current practice. Individual or group discussions with such persons may be regarded as an informal way to study the problem or review the situation. This method works well for the introduction of a particular new procedure to a single department or unit: meetings with the key persons will help to predict how the life of the department will change after the implementation of the new procedure and which problems are likely to arise.

In some cases it may be more effective to use the method of direct observation. It is particularly appropriate when the behavior in routine situations is analyzed (e.g. how the staff wash their hands).

Another method is the survey (with the help of questionnaires), useful for estimating the opinions, knowledge, views and habits of a large, geographically dispersed group of people. Both paper and electronic questionnaires are currently used in surveys. A well-prepared questionnaire is essential for obtaining useful results, since the quality of answers directly depends on the quality of questions (“as the question, so the answer”).

Brainstorming is a creative method of problem solving which can be used informally in small groups or as part of the work of focus groups. First the problem is described, and then all the participants have to propose different solutions that occur to them. A clear advantage of brainstorming is that the participants “catch” each
other’s ideas and subsequently develop and hone them. Unfortunately, sometimes this method is hard to apply, since a number of people with busy schedules and a specially trained moderator have to be present at the same time.

Finally, the focus group is a method of controlled discussion and interviewing of a small group of experts (6—10 people). The moderator poses open-ended questions, listens to the ensuing discussion and summarizes its results. The NICE considers focus groups to be useful for innovations that concern several departments within the same organization.

Each of these methods has its advantages and disadvantages, which need to be considered when change is planned (see the Table).

The third section of the manual suggests how the barriers to change can be overcome. There is no ideal method that would overcome all the barriers at once, and every particular situation demands its own individual intervention. It may be expected that multifaceted interventions will be more effective compared to any single method, although the authors of the systematic review which forms the basis for these guidelines did not find enough evidence to prove this contention.

As may be expected, educational interventions, such as production and distribution of educational materials, visits and workshops held by experts, are of great importance in overcoming the barriers. Apart from education, clinical audit, reminders and information for patients and the society at large can also be effective.

### The pros and cons of the methods of identifying the barriers to change in medical practice

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Shortcomings</th>
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<tbody>
<tr>
<td>Talk with key individuals</td>
<td>Low cost</td>
<td>Highly dependent on the key individuals</td>
</tr>
<tr>
<td></td>
<td>Rapid collection of information</td>
<td>High risk of subjective results</td>
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<tr>
<td></td>
<td>The possibility of obtaining detailed information and discussing the problem repeatedly</td>
<td>Possible difficulties in finding the appropriate key individuals</td>
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<td></td>
<td></td>
<td>The need to prove the identified tentative trends</td>
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<td>Direct observation</td>
<td>Minimal bias in data collection</td>
<td>People may refuse to be observed</td>
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<tr>
<td></td>
<td>Thorough, detailed knowledge of the existing stereotypical habits</td>
<td>Besides, since the subjects know that they are being observed this may change the habitual behavior</td>
</tr>
<tr>
<td></td>
<td>With repeated observation, may subsequently become the basis for monitoring</td>
<td>Observers must have special skills in order to minimize their effect on the workers</td>
</tr>
<tr>
<td>Survey with a questionnaire</td>
<td>Rapid collection of data from a large number of subjects; statistical analysis of standardized data</td>
<td>A good questionnaire takes a long time to compile</td>
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<tr>
<td></td>
<td>Relatively low cost</td>
<td>Low response rates may cause a bias towards the relatively more active and qualified workers</td>
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<tr>
<td></td>
<td></td>
<td>The core methodology does not exclude subjectivity</td>
</tr>
<tr>
<td>Brainstorming</td>
<td>Easy and fast to perform</td>
<td>The need for a highly qualified moderator</td>
</tr>
<tr>
<td></td>
<td>Generates a great number of ideas</td>
<td>The more active group members may dominate the less active</td>
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<td></td>
<td>Involves people in the process of change</td>
<td>It is hard to involve physicians, since they are busy with their clinical practice</td>
</tr>
<tr>
<td>Focus groups</td>
<td>Groups of experts may exchange opinions and provide valuable information</td>
<td>The need for a highly qualified moderator</td>
</tr>
<tr>
<td></td>
<td>Encourages new ideas</td>
<td>It may be hard to find a convenient time to suit all participants</td>
</tr>
<tr>
<td></td>
<td>Involves people in the process of change</td>
<td>Participants may need incentives to take part</td>
</tr>
<tr>
<td></td>
<td>Relatively easy and fast to perform</td>
<td>Analysis of the expressed opinions takes time and careful planning</td>
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Educational materials include booklets, flyers, journal appendices, compact disks, software, etc. For instance, in addition to the full text of the report, the NICE always publishes a short version that summarizes the key recommendations for the target audience. There is evidence that such educational materials improve public awareness of the planned changes, that their perception is affected by the type of materials used, and that the greatest effectiveness is achieved when this method is used in combination with other interventions. Moreover, published materials can be distributed at relatively low cost, which is important for rational resource management.

Educational meetings (conferences, courses, lectures) can be arranged for small groups or large audiences. With larger audiences more people can be reached, but then the possibility of using interactive techniques is lower. However, interactive encounters are scientifically proven to be much more effective compared to formal lectures.

Educational outreach visits of experts were originally suggested by pharmaceutical companies and used for changing prescribing practices. Specially trained professionals visit physicians in their offices to offer information, support and assistance in implementing superior treatments. Such visits have been proved to be effective in implementing specific changes in general clinical practice, such as prescribing preferences, preventive measures and methods of solving commonly occurring problems. Repeated visits are more effective than single visits. Besides, their effectiveness can be improved if in addition to visits reminders and information
for patients are also provided. Unfortunately, it is not known whether such visits can be useful for the task of implementing more complex changes, such as new diagnostic procedures or algorithms for referral to specialists. Furthermore, the results depend on the personal qualities of the visiting expert, and the method is rather expensive in terms of time and money.

Involving highly respected professionals, the so-called opinion leaders, can also assist in implementing an innovation. Their role may vary from signing the introduction in clinical guidelines to lecturing at a conference, writing an article or participating in educational visits. It must be pointed out that it is not always easy to find the appropriate opinion leaders: a scientific degree and high position are no guarantee of respect and high professional standing.

Clinical audit with feedback is based on collection and analysis of data on the actual clinical practice. Data collection may be performed by physicians employed by the medical organization itself (internal audit) or by external experts (external audit). Feedback may relate to the evaluation of clinical outcomes, the costs of medical care, or the application of particular techniques of treatment and diagnosis. Audits may be effective in implementing changes, but a lot depends on the type of data collected and its quality. Physicians are more willing to participate in collecting clinical data. Thus an audit becomes more effective if the medical staff becomes actively involved in data collection but the analysis is performed by a respected expert, who also reports the results. The effectiveness of feedback may be improved if the medical workers are provided with the results of analysis in good time, and the method works best in combination with financial incentives and educational interventions.

Reminders may be both very simple (stickers with key recommendations for use/avoidance of particular techniques) and very complex (software that suggests to the physician the optimal course of action). These methods may be effective if they are applied at the time of making a specific decision. Repeated reminders are more effective than single reminders. Automated systems of assisting in making clinical decisions have been proved effective in implementing preventive interventions and changes in prescription practice. It is hard to influence more complicated decisions using these methods.

Strategies aiming at informing patients have also been proved to affect the work of physicians, because well-informed patients are more active in discussing their treatment with the physicians and more willing to try a new treatment if there is evidence of its superiority. Mass educational campaigns are also effective methods of educating large sectors of the population. Interestingly, both meticulously planned and unplanned mass educational campaigns have been proved effective. It is important to remember that well-informed patients are better at complying with treatment guidelines and achieve better outcomes, which in turn motivates the medical workers.

The manual ends with recommendations for using various methods of overcoming specific barriers. For example, if the knowledge of prospective changes is poor, it is important to disseminate information and ensure that healthcare professionals are aware of the innovation. An educational workshop would be an effective measure in this situation. To understand what exactly needs to be changed, it is necessary to perform clinical audit to reveal the current practices and determine which stereotypes differ from the new guidelines, then forward its results to the medical workers and use opinion leaders to promote the innovation. For instance, the opinion leaders could participate in an educational seminar or outreach educational visits.

The motivation of physicians is very effectively shaped by feedback from their patients. Patients may be asked to complete a questionnaire about the care they receive (patients also need to feel motivated to complete the questionnaire, and this issue also demands attention), and the results may be submitted to medical workers.

Another way to improve the motivation is to offer successful examples from real-life clinical practice. Respected professional may organize an educational seminar and share their experience. If necessary, some selected physicians may receive training in leadership skills, so that in future they can take part in promoting innovations.

Naturally, both administrative and financial incentives can provide effective means of encouragement. The NICE suggests accountability and rewards for complying with national standards as effective motivating techniques. In addition, compliance with national guidelines may be stipulated in the contract or in the plan for individual development of employees.

Where the guidelines developed by the NICE contradict the recommendations of a respected professional association, it may be expedient to arrange a meeting and discuss a common plan for the implementation of innovations. If the physicians are convinced that the guidelines are based on scientific evidence, this will also promote their acceptance. The NICE suggests that physicians should be provided with detailed information concerning the scientific evidence that the guidelines are based on. It may be helpful to explain the principles of developing guidelines, hold open discussions involving opinion leaders and more actively involve physicians in the creation of new guidelines.

The manual contains two examples of successfully overcoming the barriers and implementing the NICE guidelines. The first example concerns the involvement of medical workers in implementing the NICE clinical manual. Several methods were employed to overcome the barriers. Opinion leaders were chosen, and they took part in
educational workshops; a short version of the manual was prepared and disseminated; physicians were surveyed. There were monthly educational workshops, and compliance with the manual was studied using the audit method.

The second example refers to involving professionals and organizations that are not part of the National Health Service (NHS) into the implementation of the manual for obesity prevention. The prospective participants were informed with the help of leaflets distributed through pharmacies, placed on posters and sent to all HNS workers and to local authorities together with their salary slips. The manual was mentioned in the annual report of the Director of Public Health. Educational meetings were organized for nurses, junior physicians and provisors. Leaflets targeting school teachers were prepared and disseminated. Opinion leaders were also involved in promoting the guidelines. Finally, external pressure was also applied: various agreements and programs (such as the plan for working with children and adolescents) included recommendations for the implementation of the guidelines.

To summarize, the NICE has developed a tool for planning and performing the implementation of measures aimed at changing the current medical practice. Unfortunately, there have been no serious studies that could provide evidence for the effectiveness of various methods of change management in Russia, therefore for the time being all we can do is hope that the recommendations developed by the NICE will work in this country as well. Changing the current practice is obviously a long and difficult process which demands careful planning, persistent implementation and regular adjustment. The guidelines developed by the NICE once again set a good example of a conscientious, explicit and judicious approach to solving an important problem.

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Whereas the Western countries have made considerable progress in the development of pharmaceutical and medical industries, which allowed them to ensure a broad public access to innovative drugs and advanced health technologies (HT), the same problem has not been resolved in Russia so far. The share of the most science intensive and innovative component of the latest treatment technologies — innovative drugs — in the total drug consumption is rather small and, according to Pharmexpert, accounts for about 12% in value terms and about 2% in natural units [1]. At the same time, the vast majority of innovative drugs in the Russian market are import products, while the share of domestically produced innovative drugs is negligibly small. A yet more substantial lagging from the West is observed in the industry manufacturing the medical equipment and devices, which in certain high-technology segments are 100% covered by import supplies.

Why do hundreds and even thousands of ideas in the HT sphere, suggested in our country 15 and more years ago, have never been put into practice and failed to interest the business community? How did Western countries manage to build a powerful innovative industry manufacturing drugs, medical equipment and devices? What is the role of the state in the adoption of innovations in pharmaceutical and medical industries? The answers to these and many other questions are given by the international experience of state incentives for innovation in healthcare industries, particularly the experience of state regulation of the biopharmaceutical industry in the USA.

**SIGNIFICANCE OF STATE SUPPORT OF INNOVATIONS FOR GLOBAL PHARMACEUTICAL AND BIOPHARMACEUTICAL INDUSTRY**

Over the past few decades, the global pharmaceutical industry has become a leader both in the volume and the rate of growth of expenditures for the research and development (R&D). From 1996 to 2009, the total annual expenditure for R&D in the pharmaceutical industry increased nearly threefold up to around 100 billion dollars (Fig. 1). Whereas the R&D expenses in the most of other industries were substantially reduced due to the economic crisis, pharmaceutical companies continued boosting the expenditures for science and research.

According to FiercePharma, the aggregate R&D expenditures by 15 leaders of the so-called Big Pharma

![](image-url)

The most dynamic and science intensive segment of the pharmaceutical industry is biotechnology, although the leading biopharmaceutical companies (BPC) yield to the Big Pharma companies in respect of the aggregate R&D expenditures. Thus, the aggregate R&D expenditures by 15 leading BPC in 2009 totaled about 7 billion dollars. The commanding lead in the global biotechnological industry is held by the USA, where 5 largest and 11 out of 15 world leading BPC are located. The United States are also the leader as for the total number of BPC — about 2000, including 300 state-owned companies. Canada is second with 500 BPC, followed by Germany, Great Britain and France. The United States’ biopharmaceutical industry employs 200,000 people.

Biopharmaceutical industry is a high-cost industry which may entail risks. By estimates of different Western sources, the total input into R&D of a usual drug ranges from 500 million to 1 billion dollars, while the introduction of a new drug to the market takes 10 to 15 years [5]. The market launch of a biopharmaceutical (BP) costs substantially more. According to the Tufts Center for the Study of Drug Development, in 2005 the expenses for the market launch of a new BP with an allowance for financial risks totaled 1.24 billion dollars [6]. The heavy expenses for the development of innovative drugs, especially biotechnological preparations, are conditioned by the peculiarities of their formulation. Despite the conventional formulation by chemosynthesis, which takes no more than several days, the BP development often takes many months of work, and only singular projects prove a success.

The recent years have been marked by an increase in the cost of inputs into development of a new drug, which is due to the complexity of development of drugs for the new chronic, serious and rare diseases, a rapid growth of the scope of the current clinical trials (CT), the difficulties with recruiting a sufficient number of patients for CT, and a high rate of failures revealed in the final stages of the drug development. However, the drug market’s peculiarity is that the notion of “too expensive” is a relative concept for it. Such an idea was pronounced in the speech by Andrew Rudman, Vice President of the Pharmaceutical Research and Manufacturers of America (PhRMA), at the 1st Adam Smith Conferences’ International Forum “Innovative Drug Research & Development in Russia”.

In his opinion, the market of innovative drugs, particularly biotechnological preparations, has a great future ahead, despite the fact that only two out of ten projects in this sphere pay their way and bring profit. At the same time, a drug properly selected and included in the reimbursement system, for example an antihypertensive drug, can provide a substantial budget saving for hospitalization [4].

It’s difficult to imagine the progress of pharmaceutical and biopharmaceutical companies in the majority of developed countries without a wide state support, including massive injections from the federal and regional budgets for scientific R&D, which together with venture capital and private financing create favorable conditions for the invention and commercialization of new drugs and biological substances. In these countries, special institutions function under health ministries, having rather substantial budgets and authorized to provide fund rising for the projects concerned with the R&D of new drugs and health technologies. Among these are, for instance, the National Institutes of Health Research of USA, the Canadian Institutes for Health Research, the National Institute for Health Research of Great Britain.

The support of medical research in Germany and France is lined up rather differently. In Germany, substantial means for medical research are assigned not only through the Ministry of Health, but also through the Ministry of Education and Research. The support of medical research in Germany and France is lined up rather differently. In Germany, substantial means for medical research are assigned not only through the Ministry of Health, but also through the Ministry of Education and Research. In recent years, stress have been laid on the construction of new medical research centers in separate therapeutic areas. Two of such centers, for degenerative diseases and diabetes, were opened in 2010. Four others are scheduled for opening in 2011. In France, the main state agency in charge of health research is the French National Institute of Health and Medical Research (Inserm), being under the authority of two ministries — the Ministry of Labour, Employment and Health and the Ministry of Higher Education and Research. Inserm coordinates activities of 10 lower institutes in different therapeutic areas.

Despite the different approaches, the mentioned agencies are similar as to their key role in setting the priority lines of research in the sphere of development of new drugs and HT in their countries. The field of their competence covers the creation and support of the infrastructure of Researchs Development centers, the formation of a research pool and the competitive selection of specialists and investigators, and the distribution of funds aimed for support of this research. Specialists and investigators are given a wide access to the necessary information resources and the consultations on the study design, as well as the possibility to exchange opinions within the framework of different working groups and councils; they are given awards for particular achievements and results. The ultimate aim is forming a base of clinical and non-clinical evidence, with regard for the best
practices of making informed managerial decisions at different levels of the healthcare system. The evidence base developed in that way is employed during the conduct of another important type of research — health technology assessment (HTA). The HTA studies based on the results of clinical and non-clinical research, make it possible to carry out a comparative analysis of clinical efficacy and economic acceptability of new technologies with respect to the drugs and technologies already being part of the reimbursement system, in order for making rational decisions in public health. In some countries of Eastern Europe, HTA studies also receive substantial allocations from state budgets.

Moreover, the most of developed countries provide special measures for support and financing of small businesses engaged in the development and commercialization of new drugs and HT. The regional units (states, provinces, counties, lands) implement their own support programs aimed at innovative pharmaceutical and medical businesses.

All the mentioned measures of state support of R&D in public health work in combination, supplementing each other and providing a firm basis for development and commercialization of innovations, and for optimization of the diagnostic, treatment and organization methods, which make it possible to get the highest results with the available limited resources.

STATE SUPPORT OF INNOVATIONS IN HEALTHCARE IN USA

The experience of the USA, an undoubted leader as for the volume and number of innovation support programs in public health, and first of all its most science intensive segment — biopharmaceutical industry, deserves special attention. The most substantial allocations from the federal budget for support of R&D of new drugs and HT are provided to the United States National Institutes of Health (NIH). These institutes form a structural unit of the US Department of Health and Public Services, which unites 27 separate institutes dealing with different types of diseases and managing the system of federal financing of R&D, related to a wide range of diseases. R&D covers oncology, diseases of hematopoietic system, heart, lungs, gastrointestinal tract, kidneys, teeth and maxillofacial area, eyes, musculoskeletal disorders, skin and mental diseases, hearing impairments, neural disorders, diabetes, strokes, allergy, infections, children diseases, diseases caused by injurious environmental effects, aging, alcoholism and drug addiction. The National Institutes of Health finance the human genome studies and the bioengineering research. R&D is financed through grants and contracts to individual investigators, research groups and development centers, allowances to students and scientists, through the support of educational and modernization programs, and also construction projects.

In 2011, the NIH budget will amount to 32.2 billion dollars that exceeds the level of 2010 by more than 1 billion dollars, or 3.2 %. Over 80 % of the NIH budget will be spent for support of R&D concerning 218 aggregative groups of diseases, including the most common as well as rare diseases. The R&D support program involves over 300 000 scientists and investigators from more than 3000 organizations, including universities, medical colleges, hospitals, clinics and development centers located in all of the fifty American states, in the District of Columbia, Puerto Rico, Guam, and Virgin Islands. The NIH budget structure by items is presented in Fig. 2.

The research grants are awarded on a competitive basis to the investigators who have presented the most promising and well-grounded applications. The competition has two stages to ensure the inclusion of the best projects into the program. In 2009, NIH approved of 43 125 research projects financed at the expense of their own budget. The other 23 000 grants were approved and financed within the framework of the American Recovery and Reinvestment Act of 2009 which is executed by NIH. In 2011, the NIH budget provides over 17 billion dollars for research grants. In addition, 8.2 billion dollars will be allocated for such grants in accordance with the American Recovery and Reinvestment Act. The act also stipulates an allocation of one billion dollars for the construction, expansion, repair, modernization and re-equipment of development centers and laboratories.

A sum of 400 million dollars is allocated for the new line of research financed by the state budget — the Comparative Effectiveness Research (CER) of the drugs and HT used by the great masses of population in the same clinical cases [7].

In 2009, within the framework of the healthcare reform actively supported by President Barack Obama, a special private nonprofit institution was established to carry out such kind of research — the Patient-Centered Outcomes Research Institute. The governmental allocations for the institute foundation and for CER support in 2009 totaled 1.1 billion dollars. The results of this research are to be used for elaboration of recommendations when making decisions on the reimbursement of the

Fig. 2. NIH budget structure by items of expenditure, %. Total expenditure — 32.2 billion dollars [7]
cost of treatment and drugs under the budget programs. Among these are first of all the medical care financing programs aimed at the aged and low-income groups — Medicare and Medicaid. These results may be also used when forming the medical insurance programs. The Institute Board includes the directors of the NIH and the Agency for Healthcare Research and Quality (AHRQ), a key government department in charge of financing the state HTA programs. Besides, the board enlists representatives of patient organizations, consumer societies, physicians, investigators, manufacturers of drugs and medical equipment, insurance companies, and other stakeholders.

The main task of the new institute is to determine the priority lines of research and sources of financing, and providing assistance for the new comparative effectiveness studies of HT on the basis of systematic review of the available evidence and new studies, including the clinical and observational studies. A special methodological committee established as the part of the Institute has to develop shortly the standards and requirements to the selection and financing of CER projects, as well as the recommendations to investigators concerning the study design. The research grants to be provided through the Institute will be aimed at the broad spectrum of performers, including federal agencies (first of all NIH and AHRQ), academic universities, and private research institutions. The investigators will get access to the database of the Medicare and Medicaid Centers. The results of all studies concerning the HT health effects, pursued by the Institute, will be opened up to the general public.

The United States National Institutes are also in charge of the grant program aimed at small-scale research companies, with an amount of financing equal to 672 million dollars in 2009 [8]. In addition, about 10 % of the NIH budget is aimed for financing the CT program carried out by NIH themselves, which involves 1250 staff principal investigators, as well as outside experts and consultants. Substantial funds are also appropriated by NIH for support of the National Library of Medicine, the largest and constantly growing store of biomedical literature for physicians, investigators, and the general public. The library’s two most important information resources are the Medline/PubMed and PubMed Central databases, providing access to more than 1.87 million scientific articles. Among the library’s latest projects are the creation of a new search system to facilitate the access to the results of comparative effectiveness studies of drugs and HT, and the launch of a Twitter-based medical resource aimed at general public, medlineplus4you, in addition to the widely popular and confidential consumer website MedlinePlus.gov. Besides, the ClinicalTrials.gov database has been considerably expanded lately.

Practically all the American states to a certain extent are recipients of the NIH-financed research grants. However, the main funding recipients in this line are California, Massachusetts and New York, which started formation of the American-largest biopharmaceutical clusters nearly from scratch 30 years ago. Thus, in 2009 California received NIH grants to a total sum of 3.2 billion dollars, Massachusetts — 2.3 billion dollars, and New York — about 2 billion dollars [9].

The R&D financing within the NIH framework exerts a great positive influence on the economic growth of the country and the total employment of the population, as well as on the similar indicators of separate states, particularly those whose prosperity depends on the state of the biopharmaceutical industry. Amid the crisis and scantiness of resources, the competition for grants and NIH support becomes more intense. The state administrations are forced to give more attention to the interaction with federal authorities when grounding the priority importance of the NIH grants not only for the economic performance of the given territories, but also for the local development of advanced health technologies aimed for satisfaction of the growing needs of the patients in the country as a whole.

Special mention should be made of the federal grant programs run through the US Small Business Administration (SBA), being of enormous importance for commercialization of new technologies and inventions in the pharmaceutical and medical industries of the country. The grant recipients are small and medium businesses with a headcount not above 500 people. The SBA programs provide low-interest loans, grants, and other types of support to small new businesses, the so-called start-ups, thereby encouraging them to concentrate their efforts not only on the basic and other types of research, but first of all on the commercialization of their results.

**CREATION OF FAVORABLE REGULATORY ENVIRONMENT FOR INNOVATION IN HEALTHCARE AT REGIONAL LEVEL**

The policy of separate states regarding the arrangement of favorable conditions for the development of innovations in public health is another subject worthy of attention. For example, the state of Massachusetts, which enjoys the highest level of NIH funding per capita, has drawn up a program of bio-parks development and support of investments in the biopharmaceutical industry, stipulating the measures for consultation and support of businesses, first of all the start-ups, which only project their investments in the state’s biopharmaceutical industry. Although the main funding recipients in this line are California, Massachusetts and New York, which started formation of the American-largest biopharmaceutical clusters nearly from scratch 30 years ago. Thus, in 2009 California received NIH grants to a total sum of 3.2 billion dollars, Massachusetts — 2.3 billion dollars, and New York — about 2 billion dollars [9].

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training personnel in the field of biotechnology, such as the Massachusetts Institute of Technology and the University of Massachusetts. Besides, the state administration provides financing for the educational programs aimed to training and retraining of personnel in the field of biotechnology, involving senior school students as well as persons of mature ages.

The state administration renders assistance to local BPCs by sponsoring their participation in exhibition activities and conferences held within the country and abroad. An important role is also played by the state’s programs concerned with the development of transport infrastructure, the allocation of unused lands for the expansion and construction of hospitals, medical research centers, as well as the other infrastructure and construction projects. The state stimulates development of the industries allied to biopharmaceutic industry, such as metallurgy, the plastics and new materials industry, the production of telecommunications equipment and services, as well as the industries producing the needed equipment facilities, microscopes, machines and tools. The state is fertile in research resources — the top institutes of higher education, such as the Harvard University and the Massachusetts Institute of Technology, are located in its territory, as well as a large number of other specialized educational institutions, research laboratories, medical centers and clinics. Consequently, that’s just the place where the most of pharmaceutical and medical companies prefer to locate their research units.

According to Jeffrey Kemprecos, Director of Public Policy and Corporate Responsibility of the American company Merck Sharp & Dohme, his company as many other companies in the industry has established an effective interaction with local authorities by holding biweekly meetings with them. At the same time, the state administration involves special officers in charge of nothing but pharmaceutical industry, having a good understanding of industry specifics and trying to administer to companies’ needs [10].

Another goog example is the development of Californian biopharmaceutical clusters. These clusters are situated near three Californian cities — San Francisco, San Diego and Los Angeles. It should be noted that the Californian biopharmaceutical clusters had emerged due to the huge private initiative, enterprise and unopposed business development. However, the achievements of the state administration, which had succeeded in creating an atmosphere of creativity and intellectual freedom, should not be disregarded, too. The foundation for the clusters development was laid several decades ago, when the administration launched a program of concessional lease of unoccupied lands for siting of high-technology businesses and enterprises, and undertook a heavy investment in the state’s transport infrastructure, in the construction of superhighways and airports. The state administration actively facilitated the attraction of the NIH grants and contracts to finance the biopharmaceutical research projects in the state’s territory, and on its part provided grants to scientists and financial support to students and graduates of the top universities located in the state’s territory. For today, the state administration has awarded about 300 research grants altogether worth 765 million dollars [11].

The most critical factors of biopharmaceutical industry' success in California were the diversified economic set-up of the state and the presence of a scientific laboratories network developed with the local administration’s assistance. Another factor was the nearness of the Silicon Valley, the state’s main high-tech area situated near the US-largest Stanford University, where the most cutting-edge information technologies, used among other areas in medicine, had been developed.

The success of Californian BPCs had been preceded by the massive investment on the part of the state administration in the educational infrastructure, in the development of universities and other educational institutions, and scientific centers as well. As a result, California began drawing professional people and highly sought specialists and scientists from other regions of the country and from abroad, who had aspired to fulfill their potential in the context of the unique favorable climate for private initiative and enterprise. Many of those scientists later established their own biotechnological firms, which undertook commercialization of scientific research results.

In the 2000s, the state administration implemented two important initiatives on stimulation of scientific research in biopharmaceutical industry, namely the foundation of the Californian Institutes for Science and Innovation and the California Institute for Regenerative Medicine. These research centers were established by decision of local residents, who made a substantial financial contribution, having collected several hundred of million dollars from private donors in addition to the funds allocated by the state administration. The state residents set up a supervisory committee to exercise monitoring of the proper use of the funds allocated for the research projects carried out using the facilities of the mentioned centers. According to plans, the state administration is to provide grants for the stem cells research projects, run by the California Institute for Regenerative Medicine, to a total sum of three billion dollars within a period of ten years [11].

Due to the massive support, thousands of small high-technology biopharmaceutical and medical start-ups now operate successfully in California. At the same time, such Big Pharma companies as Pfizer, Johnson&Johnson, Eli Lilly, Novartis and others, have chosen the Californian cluster for opening their research units in its territory.
MODERN RUSSIAN MODEL OF STATE FINANCING OF INNOVATION IN HEALTHCARE AND ITS BOTTLENECKS

The modernization and the innovation development are the two key economic guidelines declared by the President of Russian Federation Dmitry Medvedev, which are expected to transform the country and wipe out the lag in the sphere of establishment of high-technology industries. At the same time, an essential role in the adoption of innovations is assigned to the pharmaceutical industry. In his recent address to the Federal Assembly, the President set the task of increasing the share of innovative drugs up to 60 % by 2020.

The emphasis in fulfilling the task of conversion of the pharmaceutical and medical industries to the innovative development model is put on the more efficient use of the result-oriented approach, the venture capital and private financing facilities, and the opportunities of cluster development. The government laid out the Federal target program “Development of pharmaceutical and medical industries of the Russian Federation for the period until 2020 and further perspective”. The program stipulates a substantial budget allocation, of about 123 billion rubles (4 billion dollars), for modernization of the specified industries. The total amount of allocations within the program approaches 188 billion rubles (6.3 billion dollars). The program is to be started in 2011 and to be implemented within a period of ten years [12]. A simple arithmetical calculation shows that the average annual expenditure within the program amounts to 630 million dollars, while the average annual budget expenditure for the program comes to 400 million dollars.

According to the developers’ plan, the innovative nature of Federal Program consists in the fact that over a half of the total program expenditure and 78 % of the related budget expenses will be directed to the support of investment in R&D. The aggregate investments in R&D within the program will amount to 95.6 billion rubles (3.2 billion dollars, i.e. 320 million dollars a year on the average).

The program stipulates cooperation with foreign companies, research and educational institutions, which is to provide a strong incentive to development for Russian applied science, engineering and education. The task is set for building up small innovative businesses and training highly skilled personnel for the pharmaceutical and medical industries. The program implies foundation of respectively ten and seven Researchs Development centers of international standard to develop new drugs, medical devices and equipment using among others the facilities of the specialized innovative clusters. Many of these research centers will be established as parts of the top universities of the country.

Besides, the program is designed to create for the first time the favorable conditions for a broad participation of the budgets of RF entities and municipal formations in the financing of R&D concerned with the development of new drugs, medical equipment and devices. Such participation will consist in the co-financing of separate items of the program, as well as in the provision of conditions necessary for the arrangement of pharmaceutical clusters in specified locations.

The importance and timeliness of the tasks of modernization and adoption of innovations, set by the country leadership in front of the pharmaceutical industry and the industry manufacturing the medical equipment and devices, are beyond any doubt. The program gives a general outline of the model of transition to the innovative way of development, including such factors as the role of state financing and regulation of innovations, training of personnel for the pharmaceutical and medical industries, and the formation of clusters.

At the same time, the question of sufficiency of the proposed measures and financial resources for the provision of transition of Russia’s modern healthcare system to a qualitatively new, innovative level remains undecided. First, the amount of funds allocated for innovation is still insufficient, it’s incomparable with the R&D budgets of neither the leaders of pharmaceutical business, nor the state programs of financing of R&D in healthcare of the developed countries. The funds allocated within the aforementioned Program can so far serve only as “initial capital” for the industry modernization. It’s obvious, however, that achieving a qualitative innovation breakthrough would require much bigger injections. As Premier Vladimir Putin fairly remarked during the Program draft discussion held on December 8, 2010 in Khimki (Moscow Region), “As a matter of fact, we’ll have to build up a new industry, attractive for investment, able to generate innovations and create efficient jobs” [13].

The creation of a new, investment-attractive high-technology industry would obviously require formation of an efficient mechanism of state financing of scientific R&D in healthcare through a system of grants and other instruments of support of scientists and researchers. It’s necessary to build up a branching network of up-to-date educational and research institutions and laboratories, and to provide an effective assistance to small business following the best practices of the world. It would be necessary to develop and implement the state innovative educational programs relating also to professional education, and the professional development programs relating to innovative ventures. Distinct improvements should be achieved in the performance of state academies of sciences, Russian science foundations and universities.

It should be appreciated that Russia still remains a small market for innovative drugs since only 5 to 6 million out of 140 million’s population of the country
can actually afford the use of modern drugs, and those are mainly upper-income persons and groups entitled to various benefits. To start producing innovative drugs, business would require a substantial effective demand, which can not be catered for without taking decisions on the development of state reimbursement programs covering the entire population, similar to those adopted in the developed countries. The currently effective programs of pharmacological support cover no more than 5 to 6 % of the population, they are inefficient and don’t apply to the majority of rare diseases.

There is no doubt that the transition to an innovative healthcare development model will require the creation of an adequate regulatory system to provide the support of investment in healthcare both at federal and regional levels. Special laws and rules must be adopted, concerning the state support of innovative activities and the creation of state institutions for the management and financing of R&D in health care.

All of these basic preconditions for the transition to an innovative model of development of the pharmaceutical and medical industries would yield actual results only on condition that a fundamentally new mentality is formed, which assigns primary importance in social development to the technological progress, adoption of innovations, and development of business initiative. Another indispensable condition is maintaining a cooperative and constructive interaction among the business, the authorities and the society in order to create a rational managerial decision making system in health care.

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Strategic Planning Workshop: Methodology and Results

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The strategic planning workshop as a method of arranging team work goes back only a few years, when it was created to improve the effectiveness of events and activities arranged in the health care system of the Russian Federation. This format was suggested by the communicative team “Praktika” (“Practice”) for the staging of events organized by the Expert Group for Health care at the Federation Council Committee for Social Policy and Health care and has been successfully applied.

The need for new approaches to organizing team work was felt because the traditional methods of event organization were seen as inadequate in the face of the goals and limitations of the modern medical community, researchers and managers involved in designing innovative management techniques in the Russian health care system. Some of these specific goals and limitations are described below.

1. **Multiple audiences involved in discussions, debates and decision-making.** Health care is not an isolated sector: firstly, it is closely related to a number of other sectors, and secondly, medical issues are of relevance to many aspects of social, political and economic life and public well-being. In addition, the health care system as such is not homogeneous. It is not enough to consider the opinion of only one party, such as health care officials or doctors, in the process of debating, discussing, and solving the problems of the Russian health care. Such problems must be considered with respect to the positions of various professional and social groups.

2. **High social status, time cost and busy schedules of the majority of participants in such events.** The task of gathering both the leading medical experts and representatives of paramedical organizations in the same room, at the same time is inherently problematic. There is a further complication: the higher an expert’s ranking, the more expensive their time and the busier their daily schedules. These people can only devote a limited amount of time to the event, therefore one of the major tasks facing the organizers is to intensify team work, increasing its “efficiency coefficient”.

3. **The participants differ in the extent of their knowledge** of the innovative issues under discussion, and as a result, they may not have strong opinions and positions. Certain recent topics in the Russian health care are so novel that only a handful of people are fully informed. However, to promote these issues, many more people must become involved. Accordingly, in many cases the audience may be extremely heterogeneous in the degree to which participants are informed. Because of this peculiarity, the organizers face the additional task of quickly providing information. In the course of the event participants must be given exhaustive information relevant to the topic, absorb it, have their questions answered, and form an opinion. Only then will they be in a position to take part in fruitful discussions with other participants. This task necessitates a particular structuring of events.

4. **Strong, often uncompromising positions** of some representatives of the medical and paramedical communities. As any other sector, the health care system harbors some insuperable conflicts of interests. Discussions of such clashes often end in a stalemate, with the search for a compromise hampered by serious obstacles. Hosting events aimed at consensus achievement in such situations calls for a special effort on the part of the organizers.

5. **Complex topics, with low public awareness.** Some of the recent issues in the Russian health care are extremely complex and hard to understand. Besides, even when considerably simplified, they do not easily yield themselves to everyday reasoning. Here is a classical example: a medical specialist often has great trouble trying to appreciate the logic of a health care administrator in discussions of the modern management techniques.

6. **Incompatibility of communicative and cognitive goals of the event.** A person performing cognitive tasks is disinclined to communicate, and vice versa. Absorbing
knowledge and engaging in a productive discussion depend on two different mental processes, relying on completely different mechanisms. But events are commonly expected to solve both of these tasks at once.

7. **Time compression, shortening the path to acquiring positions.** Time compression is one of the key issues in our lives in general. How can we do more in a given period of time? Can an event be organized in a way that will be many times more effective than a traditional lecture or conference? This question concerns the effectiveness of human labor, the speed at which our brains and the scientific community can process particular kinds of information, and the satisfaction of participants with the event.

8. **The need for unconditional positions**, for shaping the opinion of the professional community. *Quot homines tot sententiae* (there are as many opinions as there are men), this has been known since the Roman times. On some occasions dozens and hundreds of attitudes to the same issue arise in the course of the discussion. The goal is to highlight the main, unconditional points in this polyphonic mental image, because this is the way forward.

9. **The need for direct contact between the representatives of different sides.** The discussion of certain issues calls for a direct contact between the opposing parties. Sometimes it is an open conflict, but sometimes the different sides never communicate in the ordinary social life. To make such events fruitful, the contact between the opposing sides has to be properly arranged, leading to a constructive and productive discussion.

10. **The need for sharing the expertise and teaming up different specialists.** Often a task remains unsolved as long as people work within the field of their own expertise. But finding a solution becomes more likely if the experience and various opinions of different people are combined. One of the goals of sophisticated, complex events is to ensure direct experience sharing among people of completely different opinions, professions and occupational groups.

Strategic planning workshop is a method of managing the work of large groups to reach a prompt and effective solution to the current problems in the health care sector. The main advantage of using strategic planning workshops rather than traditionally organized events is that the new method offers gains in effectiveness and time.

The original search for new, more productive and time-effective methods of managing team work is usually associated with the name of Alex Osborn, one of the founders of the advertising company BBDO (the final letter actually stands for Osborn). As the person in charge of creative work at the company, Osborn designed the “brainstorming” technique and in 1953 published his book “Applied imagination” [1].

In the scientific circles, these issues have been researched within the framework of the so-called “social facilitation” [4]. As early as 1898, Norman Triplett published his results showing that people tend to work faster and more efficiently in the presence of others rather than alone [2]. His conclusions were confirmed by several other studies, at the same time the phenomenon of social inhibition (the opposite to social facilitation) was discovered but at that time no consistent model of the latter effect was developed.

A resurgence of interest in facilitation occurred after 1940, and at that time Robert Zajonc became involved in this research. By 1965 he had created a consistent scientific model that predicted whether a particular type of activity would follow the inhibitory or facilitatory pathway [3]. Zajonc’s hypothesis was investigated and confirmed in more than 300 studies. The ideas of Zajonc and other researchers working at that time laid a firm foundation for practical application of the facilitation effect, e.g. for effective management of team work in organizations.

Training courses and short educational programs for adults, which proliferated in the 1970s, provided the perfect milieu for the development of new effective techniques of management and personal growth. Many of the management techniques that are now to be found in the toolkit of every practicing business coach, moderator or facilitator were originally created during that period. For example, new and highly effective methods and techniques of team work management relying on cycling of team work were developed at that time [4].

One more researcher must be mentioned in any discussion of the modern scientific approach to improving the effectiveness of individual and team work. This is Mihaly Csikszentmihalyi, who described the effect of mutually dependent kinds of experience and current personal goals on work productivity [5].

To recapitulate, the strategic planning workshop is a method of managing team work which applies the modern scientific insights, such as the facilitation effect and Csikszentmihalyi’s flow theory, to the task of improving the effectiveness of team work.

The strategic planning workshop offers an effective way to educate (inform) 30 to 80 participants with various backgrounds and various, if any, positions prior to the event, and to manage their team work. The organizers carefully think through the work of different teams and the audience as a whole, taking into account the purposes and particular features of the event, and design the event aiming at a structure in which all the elements are interconnected and mutually supportive. As part of the workshop, the participants representing the viewpoints of different groups exchange opinions in the course of joint brainstorming, active debates, team analysis, etc.

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1 Facilitation, social: improving the effectiveness (in terms of productivity and time-effectiveness) of individual work in the presence of other people, who may be cognized by the individual as simply observers or as a competing person or persons.
Often the teams are formed randomly rather than based on professional affinities, allowing for more objective solutions.

The workshop is managed by the facilitator in close cooperation with a number of experts on the issues being discussed. As an option, an expert moderator, well informed and with a personal stake in devising an action program, may be present and may take an active part in the workshop activities in order to make the search for solutions as effective as possible.

The whole procedure is recorded to produce audio- and video-tapes that are then transcribed. The participants place the results of their work on large sheets of paper, which are also used as aids for presenting their results to other participants. The results of every workshop are analyzed and summarized in a report, which is sent to all the participants and used in future for development, planning and practical application of the debated subject.

Two examples of the issues recently tackled by the organizers of strategic planning workshops are given below.

**THE FIRST EXAMPLE**

*The discussion of alcohol policy of the Russian Federation for the period up to 2020.*

Background: for about twenty years it has proved impossible to reach an agreement regarding the production and sale of alcohol in Russia due to serious disagreements among various parties, such as the medical community, state officials, manufacturers of alcoholic drinks, and public representatives, including unions of radical abstainers. The goal of the event was to reach a consensus and define the main features of the future alcohol policy in the RF. There were over 60 participants, more or less equally representing all the interested parties. The actual event lasted for 8 hours. All the opposing positions were known prior to the event (from completely free alcohol market to the introduction of prohibition laws). The main challenge was presented by non-constructive conflict between the participants due to inflexible entrenched positions.

The event was structured as follows:

1. Groups were formed to team up participants of sometimes similar and sometimes different views. This technique both crystallized the various opinions and allowed the participants to communicate, debate and look for points of agreement in a free way.

2. The educational part of the event was entirely based on the experience of those countries that have already gone through an alcohol crisis (there are more than 15 such countries) and the various models that might be applicable in Russia. The option of “inventing” something new also remained open. The content field for discussions in mixed groups was structured so as to avoid ready-made solutions and invite the participants to take part in a lively discussion.

3. Both homogeneous and mixed groups were given the task of reaching a consensus, so that each group would have a single consolidated opinion. In some cases dissenting opinions were also considered and recorded.

4. The rules of debating postulated that every opinion was important and had to be recorded, therefore every participant could express their opinion and be certain that it would be considered. However, the overall goal of group discussion was to reach a consensus.

5. Team work was organized in accordance with the cycle normally used in facilitation practice, which consisted of the following stages: activity (the actual discussion of the issue in groups), publication (preparing and delivering a presentation of the group’s opinion), processing (all the participants evaluate the work of the group and suggest corrections), summarizing (highlighting the common and consensual elements in the overall work), application (the general discussion turns to practical matters and each participant checks how well the decision suits them). The workshop organizers think that this cycle of team work (which originates from the work of William Pfifer mentioned above and remains little known in Russia) affords maximum integration of the collective experience of the participants.

The results of the workshop:

1. Although the initial positions were known in advance to be antagonistic, the participants of this workshop managed to arrive at a common solution to the problem of Russian alcohol policy and suggested a number of practical steps towards its implementation.

2. No conflicts arose in the course of the 8 hour long workshop.

3. There were no spells of waving attention in the course of the event; the participants felt tired but highly satisfied with the results of their work in the end of the workshop.

4. The records of the strategic planning workshop were forwarded to the appropriate public authorities of the RF as the background content for the new concept of alcohol policy currently under preparation.

**THE SECOND EXAMPLE**

*The discussion of the acceptability and desirability of introducing DRGs into the Russian health care system.*

One of the greatest challenges facing the organizers was the incompatibility of cognitive and communicative aspects of the event: the 62 participants differed greatly in the extent of their familiarity with the principle features

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2 The method of diagnosis-related group (DRG) is successfully used in a number of countries to facilitate financing and forecasting and to ensure greater transparency in health care provision. The method is based on known correlations between the diagnosis and treatment costs. It makes the financial relations in health care more transparent, clear and predictable, which has a positive effect on the overall performance of the health care system and improves the relations between medical centers and insurance companies.
The DRG method, from complete ignorance to firsthand experience in introducing DRGs in some Russian regions. At the same time, all participants had a profound practical interest in understanding how the issue of introducing DRGs will be resolved in Russia. Therefore the event was designed to include a large educational component: within a short time, it was necessary to level out the familiarity with the issue among the participants. They had to receive and absorb the information, incorporate it into their own professional views, and develop informed opinions and attitudes to a whole range of key issues. It was only after this preliminary procedure that they were ready for a productive discussion of the central question of whether Russian conditions were suitable for the introduction of DRGs.

The task facing the organizers of this strategic planning workshop was solved with the help of three stratagems. Firstly, the speakers were selected to provide information and meet the educational target. The selected speakers represented all the aspects of DRGs, both theoretical and practical. These were the leading experts from a number of countries who have created and introduced DRGs or were actively working with DRGs.

Secondly, anticipating that the participants would have many questions, the organizers had planned in advance a system for managing questions. Allowing direct questions to the speakers, this system allowed to process, analyze, classify the questions raised by participants and to adjust the subsequent presentations accordingly. This system for managing questions saved a considerable amount of time and produced a thorough understanding of the problem, so that the participants had no more questions left.

Thirdly, a facilitated transition from cognitive to communicative activities was an in-built component in the structure of the event. During the first part, the participants were simply an audience, i.e. they were randomly distributed in the hall. During the second part, they were re-seated in accordance with their occupational groups. When it was time to ask questions, participants were requested to ask one or two questions that were particularly essential for their sector, thus letting them appreciate their common interests and self-identify as members of occupational groups. The actual communicative part of the event (discussions, debates) was performed in mixed groups. Thanks to the previous seating arrangements, each participant’s “baggage” included both a personal layer of thoughts, ideas, and doubts, and a clear perspective of the position of their “guild”. As a result, the work in mixed groups turned out to be particularly intensive and productive.

The results of the workshop: 62 key experts concerned with the issue of introducing DRGs in Russia left the workshop with the following: a thorough understanding of the subject; an informed personal opinion on every aspect of the problem; an understanding of the whole range of opinions and attitudes found among the professionals. Moreover, in the course of team work the initial views of professionals influenced each other and became crystallized into consensual unconditional positions. At present the analysis of this event is being submitted to the competent public authorities in charge of strategic planning of the development of the Russian health care system.

The method of strategic planning workshops of the communicative group “Praktika” is constantly developing, but even now it is already possible to highlight the main features that distinguish it from the traditional methods of team work management:

1) combining cognitive and communicative tasks;
2) staging group activities in accordance with a particular cycle of team work;
3) using both homogeneous and mixed groups;
4) purposefully managing the content of the event;
5) recognizing the importance of all opinions and positions;
6) prioritizing procedures aimed at reaching consensual positions;
7) recording and then analyzing the event.

The strategic planning workshop is a method designed for the management of professional discussions and debates that has been applied to the most complicated problems of the Russian health care for the last few years. Its great effectiveness has been noted by participants and organizers alike. Wider use in the health care system will promote its development, considerably facilitate decision-making and streamline the introduction of innovative management techniques.

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ABOUT THE JOURNAL

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The system of health technology assessment (HTA) has found a widespread application around the world, and its active development is starting in Russia. Over 60 countries have set up HTA agencies and research centers for optimization and rational reallocation of the state funds, for achieving transparency in the managerial decision making process.

CONCEPT OF THE JOURNAL

The major goals of the journal are:
— development of the effective professionally-oriented information resource — a foundation for the integration of knowledge and experience of researches and practitioners;
— promotion of the HTA principles in Russia;
— making expert opinion an important part of the decision making process in healthcare.

MAIN OBJECTIVE

The main objective of the journal is the improvement of the medical and social effectiveness and efficiency of the healthcare system, and the quality of medical and preventive care. Implementation of the optimal organizational methods and innovative technologies will contribute to the quality of life improvement in the Russian population.

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