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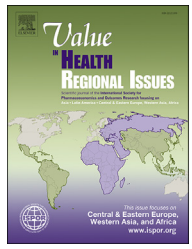

Systematic Review

Review of Pharmacoeconomic Studies in Russian Cancer Research: An Outside View

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ABSTRACT

Background: There is an increasing number of Russian economic evaluation studies in oncology, the scope and quality of which are unknown. **Objectives:** This study aimed to assess the scope and quality of economic evaluations in oncology, with the goal of elucidating implications for improving their use in Russia. **Methods:** Online databases were searched for oncologic economic evaluations written in Russian. Data were extracted and assessed with the Quality of Health Economic Studies (QHES) instrument. In addition, the QHES was modified to overcome double-barreled items in a single criterion. **Results:** Of 29 articles identified, 15 met study criteria and were included in the review. Most studies analyzed cost-effectiveness of first- and second-line therapies for lung and kidney cancer. The others analyzed prostate, breast, and colorectal cancers and lymphoma. The QHES mean quality score for the reviewed studies was 74 (and 69 with the modified tool). Comparison of the quality of different study types revealed that cost utility studies and studies that used decision trees and Markov models had the highest mean quality score. Clear statements regarding bias, study limitations, uncertainty, study perspectives, and funding source were commonly absent in the reviewed studies. **Conclusion:** Our review indicates that oncologic economic evaluations published in Russian are limited in scope and number. In addition, they demonstrate opportunities for improvement in several important technical areas.

Keywords: economic evaluations, oncology, quality assessment, QHES score

Introduction

Global healthcare costs continue to rise annually,[1] and this is a major challenge given the scarce resources and growing prices of innovative drugs and medical devices. These challenges are made more severe by the burden of chronic diseases and aging populations. Developed countries have been allocating a larger proportion of public expenditures to healthcare. Health technology assessment (HTA) is an important process to guide decision making on which drugs and medical devices should be publicly funded in the context of limited healthcare resources. An evidence-based HTA accounts for various determinants, including clinical benefits, harms, cost-effectiveness, budget impact, and patient preferences and values of an intervention. These processes can be especially crucial when making funding decisions for expensive treatment, such as cancer.

Cancer is a devastating disease, and its treatment is often costly. Many Russians with cancer do not have access to lifesaving treatments because of their high costs. It has been shown that the 5-year survival rate among women with breast cancer was 90% in the United States but only 71% in Russia.[2] Public funding could not cover all cancer treatments. Cancer drugs are procured for patients within the framework of the 3 major public programs: (1) the additional drug supply program for the elderly and disabled, (2) the regional benefit program with broader coverage principles, and (3) the 7 high-cost diseases program. Nevertheless, these programs have limitations. The regional benefit program has limited funding, while the 7 high-cost diseases program only covers a few oncology drugs.

Since the early 1990s, there have been discussions on introducing clinical and economic assessment into the process of developing an essential drug formulary list in Russia.[3] In the

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ensuring years, the selection criteria, listing procedures, and drugs evaluation process have changed.[4] The last government resolution No. 871 dated August 28, 2014, "On Approval of the Regulations for Preparation of the Lists of Drugs for Medical Use…," was a step forward to create and implement an HTA program in Russia. This decree defines the inclusion rules for formulary listing in the Vital and Essential Drug List. Points are given for the level of evidence strength based on clinical efficacy, safety, budget impact, and cost-effectiveness of each drug.

Economic evaluations of new drugs in Russia have been published since the 1990s. There were several attempts by local experts to develop guidelines to report economic evaluations systematically.[5-7] Nevertheless, none have been acceptable by health economists in Russia. The objective of our review is to evaluate the quality of published economic evaluations on oncology in Russian language. Although the choice of oncology may limit the scope of our review, cancer has a large disease burden on life years lost to healthcare costs. Our review will provide insights into the quality of published economic evaluation in Russia and to identify knowledge gaps for future research.

Despite the increase in the number of publications in Russian journals, our search of the PubMed database did not reveal any clinical and economic articles written by Russian authors and published in international journals, whereas the number of articles from other developing countries has increased steadily. This could be explained in part by the lack of interest to publish in international high-impact journals and the low quality of manuscripts submitted for publication. The goal of our review is to test the second hypothesis—to evaluate the quality of economic evaluations written in Russian and published in oncology.

Methods

We performed a literature search for the articles on economic evaluation in oncology in Russian clinical and economic journals. We used the search terms pharmacoeconomic analysis, clinic-economic analysis, cost-effectiveness, cost-utility, cost-benefit, economics AND oncology (cancer). We searched PubMed, Embase, E-library.ru, and the Society Pharmacoeconomics and Outcomes Research (http://www.rspor.ru/database/index.php) databases. We also reviewed the references of economic evaluations identified from the literature search.

For inclusion in our review, studies must have met the following criteria: full economic evaluation in oncology published from January 2010 to March 2015, using a decision modeling approach or primary economic evaluation using person-level data. We excluded editorials, surveys, reports, and essays. We

Table 1 – Overview of Russian economic evaluation in oncology.

#	Author, year	Clinical description	Treatment	Decision model	Time horizon	Incremental cost, rubles	Effectiveness	ICER, Rubles
1	Pavlish et al,[10] 2014, St. Petersburg	CRC	Eloxatin vs Exorum Eloxatin vs Platicad	Statistical analysis Statistical analysis	3 y 3 y	101 213 61 750	11.5% tumor regression 3.4% tumor regression	8801 18 162
2	Kulikov,[11] 2014, Moscow	Metastatic Kidney cancer	4 treatment strategies	Markov model	10 y	N/A		
3	Kolbin et al[12] 2014, St. Petersburg	Kidney cancer	Sunitinib vs bevacizumab Sunitinib vs sorafenib	Markov model Markov model	6 y 6 y	−2 946 960 518 629	0.31 LY 0.74 LY	Dominant 705 618
4	Kolbin et al[13] 2013, St. Petersburg	Hormone-resistant metastatic prostate cancer, second line	Cabazitaxel vs abiraterone	Decision tree	5 y	−159 200	0.267 LY Progression-free survival	Dominant
5	Rudakova[14] 2013, St. Petersburg	Advanced NSCLC, second line	Gefitinib vs docetaxel Gefitinib vs pemetrexed	Math. Model Math. Model	No No	−8270 197 860	0.13 QALY 0.23 QALY	Dominant 1230310
6	Belousov et al[15] 2013, St. Petersburg	Advanced NSCLC	Gefitinib vs docetaxel	Markov model	3 y	−11 089	0.015 QALY	Dominant
7	Rusakov et al[16] 2012,* Moscow	Metastatic hormone refractory prostate cancer, 2nd line after chemo	Abiraterone acetate vs Mitoksatron Cabazitaxel vs Mitoksatron	Math. model Math. model	No No	3 358 080 6 854 568	0.4 LY	8 760 209
8	Kolbin et al[17] 2012, St. Petersburg	Metastatic Kidney cancer 2nd line	Everolimus vs sorafenib	Markov model	5 y	22 250	0.05 LY	497 002
9	Kulikov[18] 2012,† Moscow	Advanced NSCLC, 2nd line	Erlotinib, docetaxel, pemetrexed, gefitinib	Markov model	3.3 y	N/A		
10	Procenko et al[19] 2012, St. Petersburg	Advanced NSCLC	Gefitinib vs chemo	Markov model	1 y	950 700	1.02 LY	934 800
11	Omelyanovsky et al[20] 2011, Moscow	Imatinib resistant chronic myeloleukosis, second line	Dasatinib vs nilotinib	Markov model	10 y	−3 434 025	0.1 LY or QALY	Dominant
12	Rudakova[21] 2011, St. Petersburg	Chronic lymphocytic leukemia	Bendamustine vs chlorambucil	Markov model	Lifetime	261 500	0.308 LY or 0.255 QALY	803 800/LY or 956 400/QALY
13	Rudakova[22] 2011, St. Petersburg	Non-Hodgkin lymphoma	Bendamustine vs CHOP-R	Markov model	Lifetime	366 200	0.901 LY or 0.823 QALY	406 500/LY or 445 000/QALY
14	Pavlish et al[23] 2010, St. Petersburg	Metastatic breast cancer, 2nd line	Taxol vs paclitaxel-lens	Decision tree	No	30 793		
15	Apolikhin et al[24] 2011, Moscow	Prostate cancer	radical prostatectomy vs brachytherapy	Statistical analysis	N/A	N/A	Remission increase by 18.5%	N/A‡

CHOP-R indicates Cyclophosphamide, Hydroxydaunomycin, Oncovin—Rituximab; CRC, colorectal cancer; ICER, incremental cost-effectiveness ratio; LY, life years; N/A, not applicable; NSCLC, non-small cell lung cancer; QALY, quality-adjusted life years.

* ICER recalculated by authors (months transformed into year).

† Incremental analysis of more than 2 technologies is not applicable.

‡ N/A— average value used instead of incremental.

also excluded articles where modeling and incremental analysis were not used (eg, cost minimization analysis) and articles that discussed several types of cancer.

We used the Quality of Health Economic Studies (QHES) instrument developed by Chiou et al[8] to assess the quality of selected economic research methodology. The QHES is a validated tool developed from a survey of 120 health economists worldwide. The survey includes the definition of criteria and their relative importance for assessing the quality of articles. After summing up all 16 of the QHES' quality criteria with assigned scores (100 as maximum), studies were divided into the following categories: (1) very low quality (0-24), (2) low quality (25-49), (3) moderate quality (50-74), and (4) high quality (75-100).[9]

A description of the QHES quality criteria and their weights is presented in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2019.04.008. We compared results of quality assessment for Russian economic evaluations in oncology with studies conducted in different disease areas. In addition, we conducted quality assessment by subgroups, including the methods of economic evaluation, model type, and place of study.

A limitation of the QHES instrument is that 2 or more questions are used to evaluate the quality of research from different perspectives within the same criterion (ie, compound questions). To account for this limitation, we modified the QHES instrument by dividing multi-criteria questions into sub-criteria with separate weights with the total weight of the criteria unchanged (see Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2019.04.008 for more details).

Data extraction and quality assessment on studies that met the inclusion criteria were conducted by 2 reviewers (S.D. and D.D.) separately. We used the modified QHES instrument to assess the quality of the included studies. Study characteristics, including clinical description, treatment, type of decision model, time horizon, availability of sensitivity analysis, incremental cost, and quality-adjusted life years (QALYs) gained, were extracted in a standardized form. After the independent reviews, the results were discussed to reach a consensus. A third reviewer (J.H.) was consulted if there were discrepancies.

Results

Despite the increase in the number of publications in Russian journals, our search of PubMed and Embase databases did not reveal any clinical and economic articles written by Russian authors and published in international journals, while the number of articles from other developing countries has increased steadily. The literature search identified 29 articles on economic evaluation in oncology. All of them were published in Russian language clinical and economic journals, and none in English-language international journals. Among these 29 articles, 13 articles were excluded for the following reasons: not a full economic evaluation (n = 4), no incremental analysis (n = 5) (eg, only the average cost-effectiveness ratio and not the incremental cost-effectiveness ratio were reported), and not original research articles (n = 4). A total of 15 studies are included in this review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the study selection is presented in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2019.04.008.

Most of the included studies (67%) were published by health economists from St. Petersburg, Russia. The remaining 33% were from Moscow, Russia. The main clinical and economic parameters of included studies are presented in Table 1.

Two-thirds of the economic evaluations were cost-effectiveness analyses, and the remaining were cost-utility analyses. The cancer types in the included studies are presented in Figure 1. The main method of economic evaluation was the state transition (Markov) model (54%). Other methods included mathematical modeling (20%), as well as statistical analysis of patient-level data (13%) and simple decision trees (13%). Clinical efficacy was reported as clinical outcomes (ie, % tumor regression), intermediate outcomes (ie, progression-free survival), and final outcomes (ie, life years saved and QALYs). New technology was dominant in one-third of the included studies. When not dominant, the incremental cost-effectiveness ratio ranged from 705 000 rubles to 8 760 000 rubles per life year (or QALY) saved.

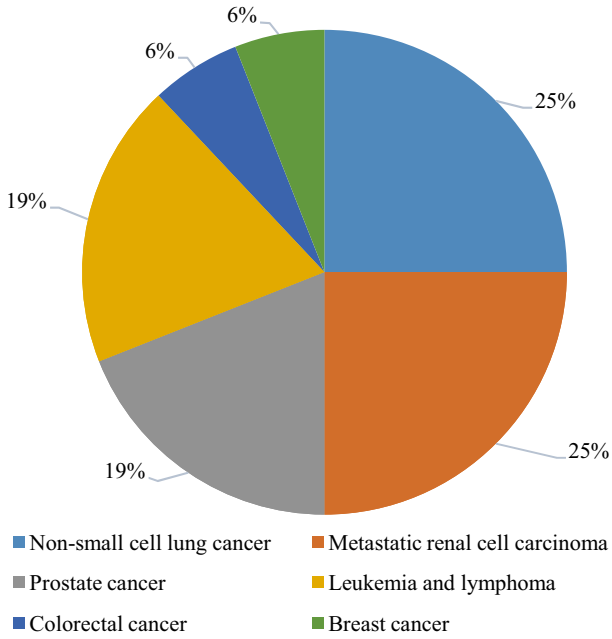

Fig. 1 – Cancer types considered in the review. Half of the economic evaluations were focused on NSCLC and metastatic renal cell carcinoma. Thirty-eight percent of studies were on leukemia or lymphoma and prostate cancers. NSCLC indicates non-small cell lung cancer.

The results of the quality assessment are presented in Table 2.

The average quality score was 74 points (range: 57-93 points) using the original QHES method and 69 points (range: 57-91 points) using the modified QHES. Forty-seven percent of studies reviewed were rated as high-quality, with the remaining 53% rated as moderate. None of the included studies was rated as low quality. In subgroup analyses, quality between studies that used cost-utility and cost-effectiveness methods was similar (1.2 vs 1.7 points on the differences between QHES and modified QHES instruments). Studies that used Markov models and decision trees had the highest-quality scores (75.6 and 76.5 points, respectively). Nevertheless, results should be treated with caution, because Markov models were used only in 3 articles. Our analysis showed that the place of study matters. The difference in quality assessment between studies carried out in St. Petersburg and Moscow was 12 points, which indicates regional differences.

Quality assessment by various characteristics is presented in Figure 2.

Table 3 shows QHES score comparisons of economic evaluations conducted in different diseases. Only 2 studies were country specific and reviewed economic evaluations published in Vietnam[26] and India.[29] We found that most studies published in Russia have moderate quality when compared to other quality assessment reviews (in other diseases), which indicates satisfactory quality of pharmacoeconomic studies (Table 3).

Table 2 – Quality assessment of Russian economic evaluations in oncology.

	No.	%	Range of quality score		Mean quality score	
			QHES	Modified QHES	QHES	Modified QHES
Type of economic analysis						
Cost-effectiveness	10	67	57-93	57-91	73.0	69.3
Cost-utility	5	33	65-82	62-75	74.2	67.6
Type of model						
Markov model	8	53	65-93	59-91	75.6	70.8
Statistical analysis	2	13	57-70	57-65	63.5	61.0
Mathematical model	3	20	63-88	61-81	72.0	68.0
Decision tree	2	13	67-86	62-77	76.5	69.5
Study location						
Moscow	5	33	61-78	57-71	64.8	62.2
St. Petersburg	10	67	65-93	62-91	77.7	72.0
Overall	15	100	57-93	57-91	73.4	68.7

QHES indicates Quality of Health Economic Studies.

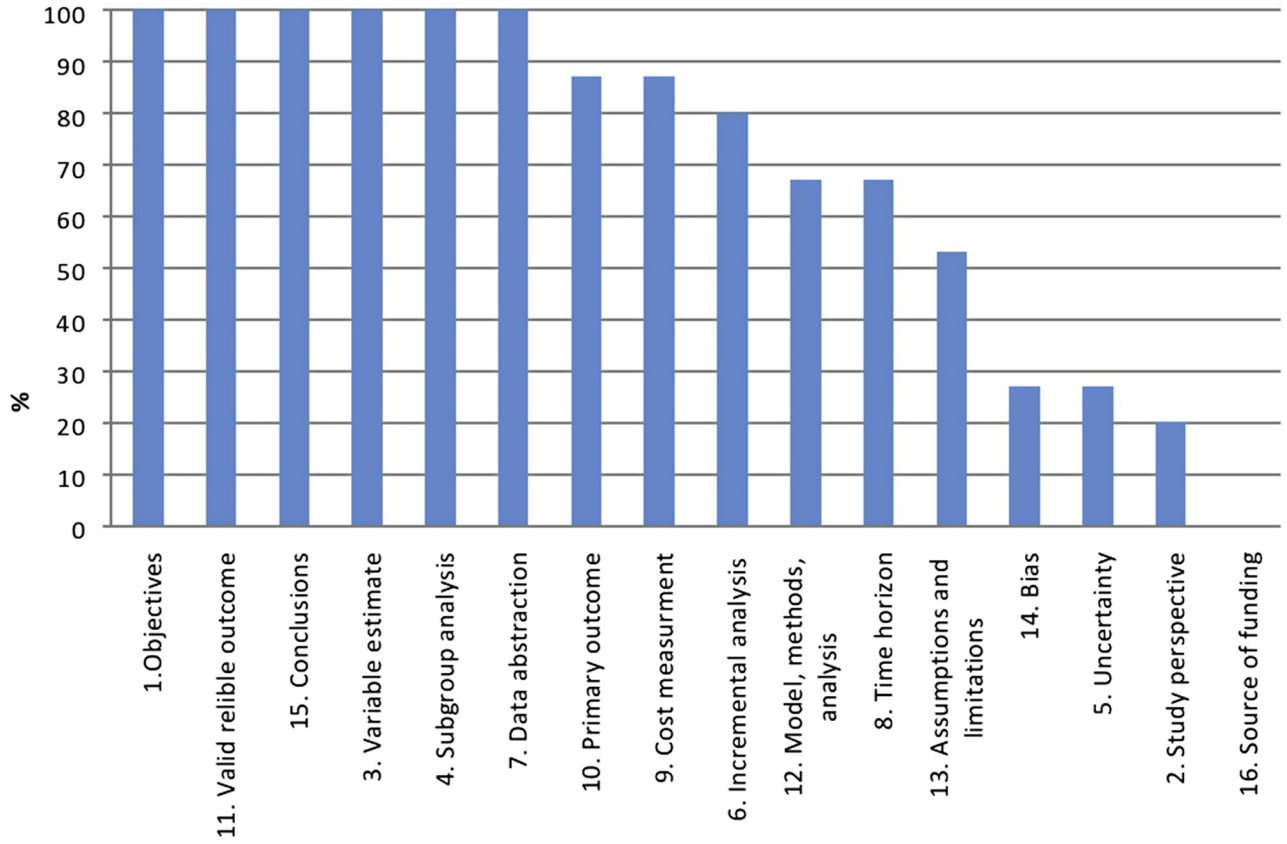

Fig. 2 – Proportion of economic evaluation that obtained QHES score. None of the studies reported source of funding, and only 20% reported study perspective. Less than 30% of studies reported bias and uncertainties, and less than 60% stated assumptions and limitations. QHES indicates Quality of Health Economic Studies.

Discussion

Our study was the first quality assessment of Russian economic evaluations in oncology. We found that the average quality score was depended on the quality assessment method with the QHES instrument yielded higher score than the modified QHES instrument.

The best quality study (93 points) was a pharmacoeconomic analysis of targeted therapy for metastatic renal cell carcinoma from St. Petersburg.[17] Among the studies from Moscow, the best quality one (78 point) was a clinical and economic analysis of the second-line treatment of chronic myeloid leukemia.[20] Most included studies in this review were conducted in St. Petersburg. It appears that there is a regional difference in the number of

Table 3 – QHES grade comparison.

Author, year	Description of economic evaluation review	QHES	
		Mean	SD
Lange et al[25] 2014	Metastatic NSCLC	66.5	17.2
Tran et al[26] 2014	EE published in Vietnam	67.3	22.9
	EE published internationally on Vietnam healthcare	88.7	13.3
Yong et al[27] 2014	Enhanced asthma management	73.7	9.7
Peterson et al[28] 2009	Physical therapy	82.2	15.8
Desai et al[29] 2012	EE based in India	86	6
Wong et al[30] 2010	Pharmacogenomics	77	range 29-99
Gerkens et al[31] 2008	Surgical treatment of obesity	95	range 75-99
Nwachukwu et al[32] 2015	Orthopedics Sports Medicine	81.8	range 70-94
Djalalov et al[33] 2011	Genetic testing services and interventions	89.8	range 41-100

EE indicates economic evaluation; NSCLC, non-small cell lung cancer; QHES, Quality of Health Economic Studies.

published economic evaluations, which may be explained by a higher degree of adherence to HTA guidelines developed by St. Petersburg University.[6,7] Most of the reviewed studies did not include probabilistic sensitivity analyses, which are commonly seen in economic literature published in international journals.

The reviewed studies could be categorized into 2 main categories for improvement: (1) reporting issues and methodological limitations, and (2) require an extra analysis and/or refinement of the Discussion section.

The first category includes (1) disclosing the source of funding (3 points), (2) stating the perspective of the analysis (4 points), (3) displaying the model structure and justifying the methods of analysis (8 points), and (4) stating the time horizon and justifying discounting (7 points). By meeting those requirements, it is possible to improve the quality of the published studies by more than 20 points. None of the reviewed studies disclosed the sources of funding. Such financial disclosure is mandatory for publishing in international journals. Only 3 authors stated the analytical perspective of their studies. Most authors used only the Russian Ministry of Health perspective, which is logical as the formulary inclusion decision is made by these authorities. The structure of the economic models and methods of analysis (eg, stimulation methods, Markov model, decision tree) were presented in only one-third of the reviewed studies. This makes it difficult to track the disease progression and to determine whether the models are realistic. Three studies indicated the use of a mathematical model, but did not describe the model type or analysis used. Accurate reporting of methods and results allows other researchers to replicate the studies to validate the results. A validated economic model could inform other jurisdictions' funding decisions. Time horizon and discounting were not presented in one-third of the reviewed studies. Duration of time horizon ranged from 1 year (lung cancer) to lifetime (leukemia). Discounting should be done not only for cost but also for clinical outcomes. The discount rate for outcomes, if not previously defined, could be equivalent to the cost. Reporting the methods and results of an economic evaluation accurately and transparently could greatly enhance the quality of a study.

The second category of studies (ie, those that require additional analyses and/or refinement of the Discussion section) includes articles that could benefit from the introduction of model assumptions and limitations (7 points), description of the direction and magnitude of potential biases (6 points), and inclusion of uncertainty analysis (9 points). Model assumptions and limitations were not reported in about half of the analyzed studies. In cases where there were inadequate clinical or economic data, it would be difficult to simulate the economic models accurately on the natural history of the disease, side effects, and patient characteristics. Therefore, reporting of the model assumption limitations ensures the integrity of the economic models. When explaining model limitations to decision makers and medical professionals, it would help them understand what factors affected the model and what has been done to reduce the impact of limitations on the results. Potential model biases (eg, deviation of research design and inappropriate conclusions) were not reported in more than two-thirds of the articles.[34] Explicit discussion of the direction and magnitude of potential biases could clarify model robustness and reliability. Uncertainty analysis was not presented in over two-thirds of the articles. Probabilistic analysis was not conducted in any of the studies, and deterministic analysis with 1- and 2-way sensitivity analysis diagram was presented in only 3 studies. All these studies were conducted in St. Petersburg. Sensitivity analysis is an important component of the model simulation, which shows how sensitive the results are in response to changes in assumptions. A graphical representation of the analysis results is extremely useful for those who are unfamiliar with the modeling.

In addition, Russia follows a World Health Organization standard for cost-effectiveness thresholds (ie, 3 times gross domestic product per capita). Only a few studies reported the threshold, but no studies provided a quantitative value for the threshold. Instead, most studies discussed comparative effectiveness of the interventions only.

Based on the analysis of Russian pharmacoeconomics studies in oncology, we provide recommendations to improve the quality of published studies and their compliance with the requirements of international journals (Table 4).

Our study has limitations. First, there is no unified clinical database of Russian articles, such as PubMed or Medline, to identify all pharmacoeconomic papers on oncology. We have made every effort, including an intensive internet search, a search in archives of clinical journals and databases, and a review of articles' references, to minimize this limitation.

Second, the QHES technique lacks focus in some criteria. We attempted to address this limitation by modifying the QHES. Young and Shafie used similar modification of the QHES and reported similar results[26] that the total QHES score was higher than that from the modified QHES.

The number of published economic evaluations of health technologies is rapidly increasing in international journals. Properly conducted economic evaluations are standard tools for technical appraisal, and they inform decision makers in determining funding priorities.[35] Nevertheless, despite the increased number of published economic evaluations, the quality of reporting is suboptimal. There have been many attempts to improve the quality of economic studies through the development

Table 4 – Suggested recommendations to improve quality of Russian economic evaluation studies.

#	Problem	Recommendation
1.	Results and Discussion sections mixed together	Results and Discussion sections of the study should be presented separately. Mixing 2 sections does not allow to summarize the key findings and to interpret methods of data obtaining.
2.	Model parameters plausible range and sources not performed and justified.	The details of all model parameters, including transition probability, mortality, cost, and utility, should be described in the Methods section. Justification of selected parameter mean, plausible range, and source should be clearly performed.[8]
3.	Discussion section is not meeting criteria of health economics journals (eg, medical decision making).	Discussion section should compare study results with relevant findings from other published work, and discuss the limitations of the study and any methods used to minimize or compensate for those limitations. In addition, the discussion section should include recommendations for future research directions.[40]
4.	In some models, the natural history of disease was not fully described. Studies use a simplified model consisting of only 2 health states, life and death.	Using 2 health states for the Markov model does not allow for properly modeling the costs and consequences of the implemented technology. A model should represent some aspects of reality at a sufficient level of detail to describe the transitions of a cohort of patients among a number of mutually exclusive health states to reflect a natural history of the disease and treatment pattern.
5.	Costing received significantly more attention than the clinical effectiveness. Studies provided excessively detailed analysis of drug costing, while information on resource utilization—medical and nonmedical—in many cases was absent.	When conducting a simulation, it is more important to show the cost of treatment cycle. Costs must be presented for all compared technologies. The modeler must specify the full range of values for each cost parameter. These data will be used in the sensitivity analysis to determine the uncertainty of the model.
6.	Values of some parameters used in the model presented per 100 patients.	Economic evaluation usually performs results per average patient. Performing clinical and economic indicators per 100 patients in some of the studies can confuse interpretations of the results.
7.	Some studies used median values for the clinical parameters obtained directly from clinical trials.	It is recommended to use mean values of clinical parameters such as survival and progression-free survival in cancer models. The results of clinical studies are mainly presented as median.[36]
8.	Sensitivity analysis was performed only in selected studies	One-way sensitivity analysis should not be limited to 1 or 2 parameters and should be conducted for all key parameters that might affect the result. The best way of presenting results of 1-way analysis is using the tornado diagram. The plausible range should be presented for all analyzed parameters.[37]
9.	Discounting with a longer time horizon (more than 1 year) was not performed, and the discount rate was not presented.	If time horizon of the model exceeds 1 year discounting of cost and outcomes should be presented.[39]
10.	In some models, hazard rate of the survival analysis was mistakenly used as a probability of the event.	The rate of the events represents a number of occurrences of an event for a given number of patients per unit of time. The probability of event is the likelihood that an event will occur for a single individual in a given period. The right way to calculate 1-year event probability (eg, from 5-year event probability) will be defining an annual rate and then converting it to the annual probabilities.[38]
11.	Some studies used the ratio of average values to compare the cost-effectiveness of 3 or more alternative technologies, which is a methodologically incorrect way of reporting CEAs results.	Incremental analysis can be used for a comparison of only 2 technologies. Using average instead of incremental values might mislead the decision-making process.[41]

CEA indicates cost-effectiveness analysis.

guidelines, checklists, and recommendations to inform economic evaluation and reporting results.[36-39] Nevertheless, most of these appraisal tools do not have weights for the quality criteria, thus it is impossible to quantify the study quality. Chiou et al developed the QHES grading system, a practical quantitative tool for appraising the quality of cost-effectiveness studies using validated criteria with specific weights.[8] This tool helps identify high-quality studies to be included in a systematic review.

In conclusion, our systematic review showed an average quality of Russian pharmacoeconomic studies in oncology, with a considerable number of studies that did not describe model assumptions and limitations, funding sources, or potential biases. Probabilistic sensitivity analysis was not routinely reported. As such, dealing with uncertainty by learning and conducting probabilistic sensitivity analysis is indicated as a key area of knowledge dissemination and capacity building. There is a great potential to improve the quality of economic evaluations by more thorough and transparent reporting.

The relatively few economic publications suggest that HTA development is still in an early stage in Russia. Developing Russian economic evaluation guidelines that are acceptable to Russian health economists would be helpful to move HTA development in Russia forward.

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Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2019.04.008.

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