INFORMATION TECHNOLOGY IN THE EVALUATION OF RWD / RWE (REAL-WORLD DATA/REAL-WORLD EVIDENCE)

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The features of evaluating data from real clinical practice are discussed. Approaches to material processing for decision support in medicine and health care are also given. The development of standardized methods of analysis with the possibility of obtaining a unified indicator for assessing data from routine clinical practice, combined with the development of information technology is the direction of development of the concept of result-oriented health care. The classification of information technologies used in medicine and public health is presented. The main characteristics and functioning features of the developed software modules for automated data evaluation of real clinical practice are presented: a program for the distribution of drugs on the levels of clinical efficacy, a program to assess the effectiveness of therapy for the specified period; a program to determine the interval of clinical efficacy of drugs.

Keywords: real clinical practice data, RWD/RWE, information technology, automated assessment, software module

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ИНФОРМАЦИОННЫЕ ТЕХНОЛОГИИ В ОЦЕНКЕ ДАННЫХ РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКИ

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Рассматриваются особенности оценки данных реальной клинической практики. Также приведены подходы к обработке материалов для поддержки принятия решений в медицине и здравоохранении. Разработка стандартизованных методов анализа с возможностью получения унифицированного показателя для оценки данных рутинной клинической практики в сочетании с развитием информационных технологий является направлением развития концепции результат-ориентированного здравоохранения. Представлена классификация информационных технологий, применяемых в медицине и здравоохранении. Приведены основные характеристики и особенности функционирования разработанных программных модулей для автоматизированной оценки данных реальной клинической практики: программа для распределения лекарственных препаратов по уровням клинической эффективности; программа для оценки эффективности терапии за расчетный период; программа для определения интервала клинической эффективности лекарственных препаратов.

Ключевые слова: данные реальной клинической практики, RWD/RWE, информационные технологии, автоматизированная оценка, программный модуль

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In different nosologies, medical aid is provided based on clinical recommendations. The conclusion about inclusion or non-inclusion of medicinal preparations (MP) into clinical recommendations is based on the principles of evidence-based medicine. Randomized controlled trials carried out at the pre-approval stage of MP registration constitute the framework of evidence-based medicine. They have an evidence level taken into account in clinical recommendations. MP effects are considered statistically significant here. However, it is not always possible to reproduce them in real clinical practice.

This occurs because when a medical technology or MP are widely applied, no estimate of effectiveness and safety of MP use is taken into account in patients with concurrent diseases and polypragmasy. The issue concerning principal and concurrent nosologies is unsolved in many cases. In the presence of many drug interactions which occupy a significant place in real clinical practice the values of MP effectiveness and safety can differ from those obtained in clinical research. The lack of long-term effects is a limitation for clinical trials. In its turn, this impacts on clinical and economic variables, as well as social and economic impact consequences. Thus, systematization of methods, development of methodologies and algorithms of complex estimation are essential in real clinical practice at the modern stage of healthcare development. The obtained outcomes can form a framework for introducing changes and additions into clinical recommendations and MP limited lists. Thus, non-interventional trials become significant now. The term ‘non-interventional trials’ was first mentioned in November 2016, when the Guidelines on Good Pharmacovigilance Practices and Guidelines on Good Clinical Practices of the Eurasian Economic Union (EEU) were approved [1, 2]. Due to the spread of coronaviral infection, the term has found a wider application at the federal level.

Government regulation No. 441 dated April 03, 2020 ‘On the Peculiarities of Regulation of Drugs Intended for Use Under Threat of Emergency Occurrence and Management and to Provide Medical Aid to Persons Injured in the Result of Emergencies, Prevention of Emergencies, Prevention and Treatment of Diseases that Constitute a Danger to the Public, Diseases and Damages Obtained as an Effect of Unfavorable Chemical, Biological and Radiation Factors’ states that ‘drug

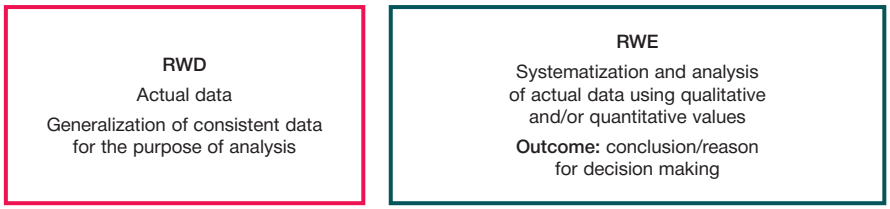


Fig. 1. Real World Data and Real World Evidence (RWD/RWE)

Table. Classification of information technologies applied in medicine and healthcare

Information technologies	Characteristics of information technologies
OLAP (online analytical processing) — technologies	Preparation of aggregate data based on big data structured following the multidimensional principle and their use to present the visualization means. Operates with retrospective archives with data stored for a long time.
Data mining technologies	Data analysis to find previously unknown values among numerical and text data. The key process of the ETL-technology (Extract, Transform, Load). ETL includes as follows: • extraction of data from external sources; • data transformation and clearance ensure their correspondence to the model requirements; • data upload to the repository.
SADT, RAD- and CASE-technologies	SADT (Structured Analysis and Design Technique) technology of structural analysis and design. It is the basis for CASE (Computer-Aided Software/System Engineering)-technology and RAD-(rapid application development) technology.
Simulation modelling	Computer technology to examine some real process parameters using a set of math tools, special simulation programs enabling focused research of a real complex process structure and functions stored in the computer in the mode of simulation.

effectiveness is examined during a low-interventional study following the principles of good clinical practice' [3].

Real World Data and Real World Evidence are estimated during the studies.

Real World Data (RWD) inform of a patient's condition and/or provision of medical aid. In the majority of cases, medical (primarily electronic) records, insurance company data, pharmacovigilance system data, patient registries are sources of RWD. RWD are collected beyond pre-approval clinical trials.

Real World Evidence (RWE) presents as an outcome of (qualitative/quantitative) use of a medical technology in a standard medical practice. RWE belongs to aggregate data obtained during the actual use of a medical technology/ MP (fig. 1).

RWD are actual data only. They carry no significant information about the use of a MP and form the basis for analysis, the outcomes of which enable to answer the questions about a routine usage of MP, and drug-drug interactions in polypragmasy (including long-term therapy effects).

In 2018, the FDA initiated the so-called Framework Program on Cumulative Evidence in Real Clinical Practice. This is the first step concerning systematization of real clinical practice data and algorithms of their estimation development in healthcare [4]. The approach can improve medical aid affordability and quality along with cost effectiveness in healthcare system. Implementing the principles of real clinical data analysis and development of information technologies must become a basis for healthcare system restructuring.

TECHNOLOGIES OF DATA PROCESSING FOR DECISION SUPPORT

Finding an optimal decision is the main task of using information technologies. The process of decision finding includes the system of decision support in the form of application programs and the controlling unit setting inputs and estimating the obtained result [5]. The widely used information technologies are as follows:

– OLAP-technologies (online analytical processing) or a data processing technology when aggregate data are prepared based on big data structured following the multidimensional principle;
– data mining technologies;
– SADT (Structured Analysis and Design Technique) methodology;
– RAD (Rapid Application Development);
– CASE (Computer-Aided Software/System Engineering) includes instrumental means used in system designing.

The information technologies mentioned embrace the entire range of works concerning creation and program maintenance (analysis and development, implementing project documents, system coding and testing) and technologies of simulation modeling (table).

SOFTWARE MODULES INTENDED FOR RWE AUTOMATED ASSESSMENT

1. **The program of MP distribution according to the levels of clinical effectiveness** (computer program). The program was developed using C++ Higher Level Programming Language in Borland Developer Studio (License Certificate Number: 24247). The software component is based on the methodology of weight coefficients calculation efficiency by the Fishburn's method (fig. 2).

MP names or schemes of pharmacotherapy are inputs recorded by users (can have code names such as 1, …, n); how many times every analyzed MP or scheme was prescribed (abs. number); number of positive outcomes obtained when a MP or pharmacotherapy scheme was used (abs. number). The values of clinical effectiveness defined as the ratio of positive outcomes with respect to the general number of prescriptions are calculated automatically. This is followed by clinical efficacy measures ranked from higher to lower values.

Then a user introduces a number of levels by which the available set of MP or schemes analyzed must be distributed into the 'Enter N' graph (fig. 3).

The program ranks a set of MP or treatment schemes from a higher to a lower level considering the value of weight coefficients.

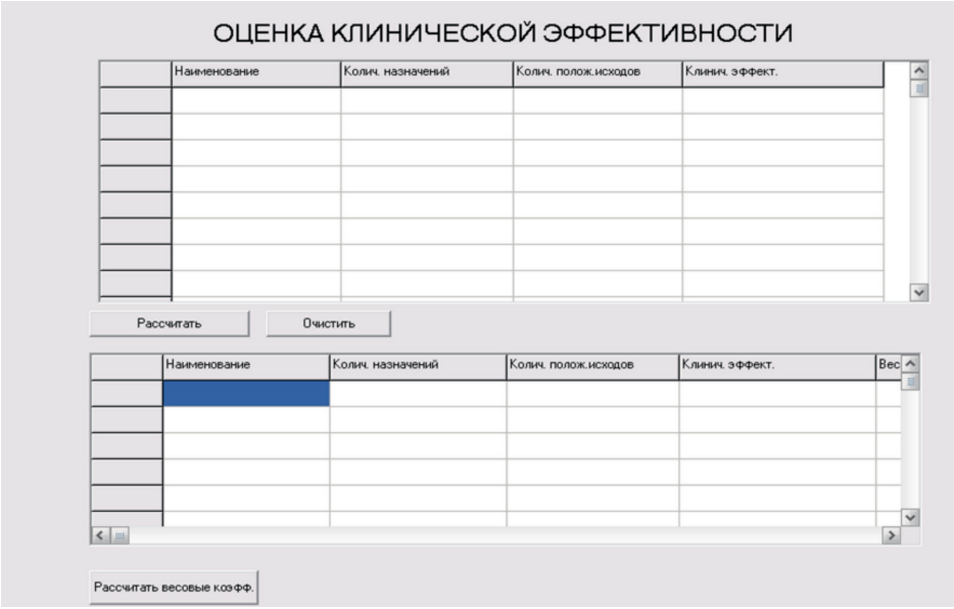


Fig. 2 Program interface to distribute MP based on the levels of clinical effectiveness

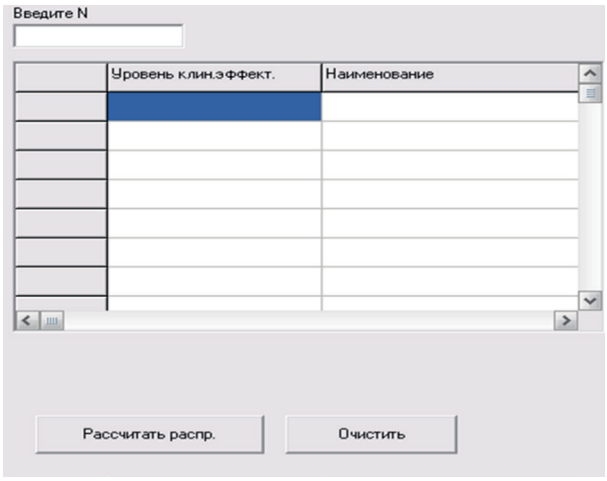


Fig. 3. Program interface to distribute MP based on the levels of clinical effectiveness when a number of levels is entered (N)

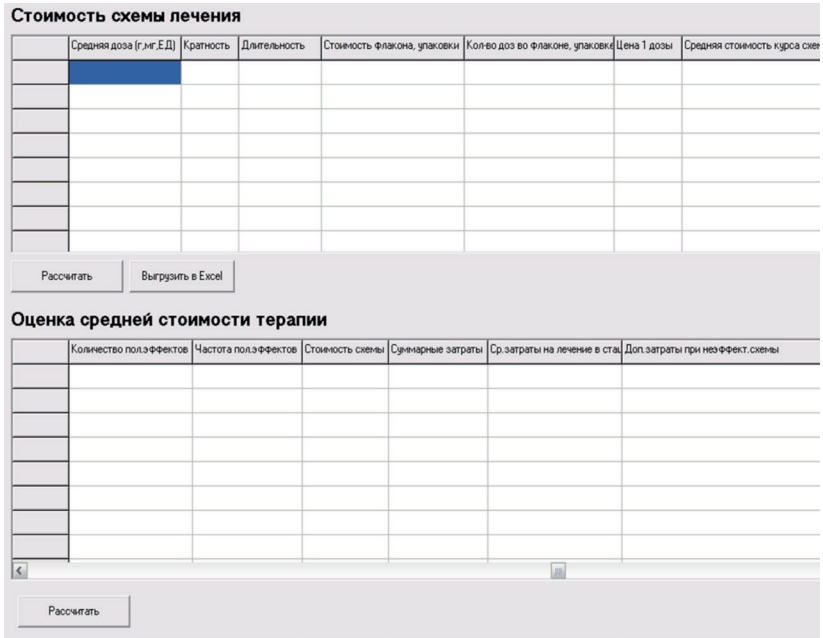


Fig. 4. Program interface to estimate therapy effectiveness

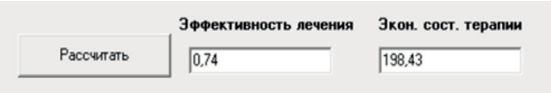


Fig. 5. Program interface to estimate therapy effectiveness when the analysis outcome is obtained

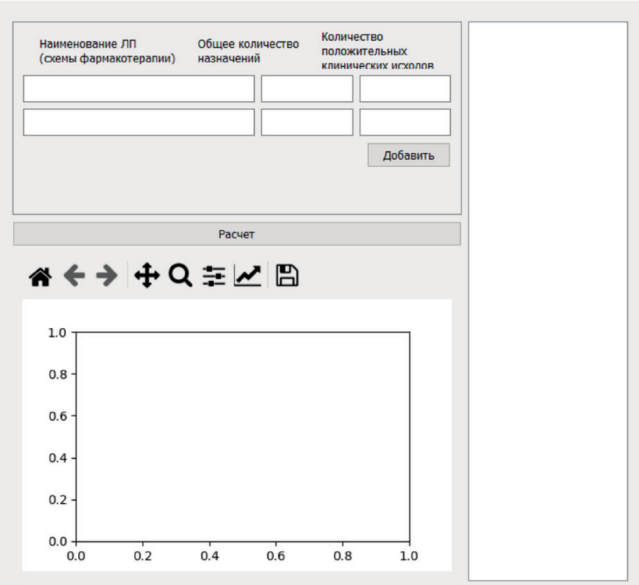


Fig. 6. Program interface to determine the interval of clinical effectiveness for MP

The program module can be used by clinical pharmacologists and health professionals when pharmacological support is planned. The module is optimal for comparison of outcomes of treatment with original and generic drugs.

2. **A program estimating the effectiveness of therapy for the specified period** (computer program) is developed to assess pharmacotherapy considering all MP used while treatment. The program is developed using C++ Higher Level Programming Language in Borland Developer Studio (License Certificate Number: 24247) (fig. 4).

13 subsequent mathematical operations form the basis for the algorithm of computer program implementation.

The user enters data on prescriptions (abs. number), positive clinical effects obtained when using MP (abs. number), expenditures for MP (RUB), additional expenditures associated with non-effectiveness of initially administered MP (RUB). The rest values are counted automatically.

This results in such values as 'Clinical Therapy Component' and 'Economic Therapy Component'. The Clinical Therapy Component is expressed as a percentage (%) and shows therapy effectiveness in a hospital, medical organization, city or region for the specified period. The economic component shows average expenditures per 1 case of the examined disease considering both positive, and negative clinical effects, the occurrence of which was associated with additional expenditure. This is how a patient's condition was improved. The economic effectiveness is expressed in rubles (fig. 5).

The program enables to compare MP or pharmacotherapy schemes in a medical organization; perform qualitative assessment of MP effectiveness, compare values obtained from different medical organizations in an objective way and find the best practice of MP prescription and usage (with the largest value of clinical therapy and the lowest value of economic therapy). The latter can be used by government health agencies during decision making.

3. **A program determining the interval of MP clinical effectiveness** (computer program) was developed. It was based on actual clinical practice to estimate the possibility to transfer the medical technology to another group of patients with this nosology. β-distribution was the program basis.

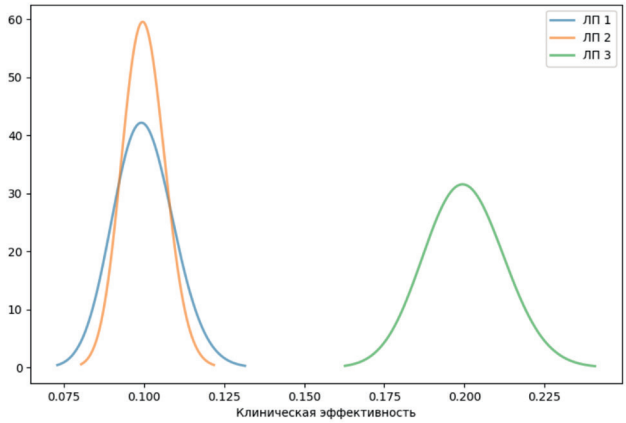
In theory of probability, it constitutes a two-parameter family of absolutely continuous distributions and is used when binomial probability distribution is described (for instance, 'ill-healthy', 'positive effect-negative effect'). It is limited by 0 to 1 interval and corresponds to the described occurrence of a clinical effect due to MP administration.

The values of effectiveness (average values) obtained in clinical practice can differ from those for another sample of patients. Beta-distribution allows to determine how significant the changes can be and which minimal intervals of values cover the actual exact values of the required clinical effectiveness with 95% probability. From a practical perspective, 95% confidence interval shows that 95% of all potential samples using the MP with the examined nosology will produce the values of clinical effectiveness within the set boundaries. In 5% of cases the values will go outside the found boundaries (fig. 6).

The user enters the MP or scheme name, a number of prescriptions for the specified period and a number of positive outcomes into the application. The analysis results are presented as a graph (curves of beta-distributions of clinical effectiveness with the probability of visual comparison) and a number (the interval of MP probable clinical effectiveness when it is transferred onto another group of patients with the same nosologies, 95% CI) (fig. 7).

CONCLUSION

The results obtained when the MP is used in routine clinical practice allow to obtain more exact data about its effectiveness and safety (considering polymorbidity and associated polypragmasy). It is necessary to develop methodologies and algorithms of non-interventional trials to improve validity of the obtained outcomes and for correct interpretation. Further development of standardized methods of analysis obtaining a unified value



(a)

label	a	b	mean	var	min	max
ЛП 1	100	900	0.1	0.0001	0.0822	0.1193
ЛП 2	200	1800	0.1	0.0	0.0872	0.1135
ЛП 3	200	800	0.2	0.0002	0.1758	0.2253

(b)

Fig. 7. Program interface to determine the interval of clinical effectiveness for MP when the graphical (**a**) and numerical (**b**) outcomes are obtained

to estimate the data of routine clinical practice combined with developed information technologies becomes an important step towards implementation and development of outcome-oriented healthcare. RWD/RWE are essential in acquisition, accumulation and analysis of data obtained while prescribing and using the MP and when an individualized approach to pharmacotherapy was developed. As a result, we deal with improved quality of rendered medical aid and optimization of expenditure on the system of pharmacological support.

Implementation of non-interventional trials into practice requires a more exact regulation of the legal part. The EAEU Guidelines regulate the trials with a human as a study subject presenting an ethical and scientific planning standard and conducting the trials. At the same time, they are not enough to organize non-interventional trials.

Expertise underwent by local ethics committees ensures an independent assessment of trial ethical aspects. It is considered by local ethics committees depending on standard operational procedures accepted. To simplify the organization of non-interventional trials, it is necessary to develop single approaches to planning and organization, as well as criteria to estimate the trial outcomes.

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