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## **THE FIRST RUSSIAN INFORMATION SYSTEM — DATABASE OF CLINICAL CASES OF PERSISTENT BRONCHIAL ASTHMA IN PEDIATRIC PATIENTS**

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**Article received:** 23.11.2014. **Accepted for publication:** 24.12.2014.

*The article is dedicated to an urgent issue – implementation of information/communication systems to the modern healthcare. Information databases of clinical cases – registers – are currently in demand in various spheres of medicine, especially in pediatrics. Registers have deservedly become a crucial instrument of improving healthcare quality absolutely necessary both to determine effectiveness and safety of long-term therapy and conduct a clinical-economic analysis, as well as in cases of rare conditions and diseases, when conducting a randomized clinical trial is difficult. The authors give a preliminary assessment of works on design, creation and implementation of the first Russian information database of clinical cases of severe uncontrollable bronchial asthma, as well as results of analysis of omalizumab's (biopharmaceutical) effectiveness and safety in real clinical practice in children with asthma.*

**Keywords:** information system, database of clinical cases, register, allergic diseases, children, bronchial asthma.

### **INTRODUCTION**

Nowadays, the demand for *information databases of clinical cases*, or medical registers, is getting stronger [1-3]. It is reasonable to use them to determine effectiveness and safety of prolonged therapy both under conditions of long-term follow-ups and in the event of rare conditions and diseases, which make it difficult to conduct a randomized clinical study [4, 5].

A modern *register* is a complex system that carries out clinical monitoring of the patients grouped by the nosological principle, the medical intervention technology in use or any other factor. Patients are subject to such monitoring from the moment of diagnosis establishment until any certain outcome [2, 3].

At the same time, *medical intervention* is seen as a broad derivative term used to describe a program, an action, a measurement or a manipulation developed and used to impact disease in a patient or population-wide [6]. Any diagnostic or therapeutic action is aimed at prophylaxis as it prevents deterioration of the patient's health or prevents spread of an infection, which is why it is critical to accept the fact that prophylaxis is an inherent part of treatment or recovery. As defined by the U.S. Office of Technology Assessment, health technologies are “therapeutic devices, medical or surgical procedures used for medical care, and the organizational and supportive systems wherewith such care is provided” [7]. The concept of “health-affecting technology” is a lot broader as it includes measures to stimulate the patient's behavior, especially in terms of health-saving behavior, improvement of physical and psychological potential, preventive programs, and healthcare availability [6].

The basic points of the general utility analysis applied to most health technologies are *value*, *safety*, and *effectiveness* [6, 8]. Unfortunately, there is no real diagnostic or therapeutic technology that would not represent any potential danger. Most data on medical interventions are acquired from *databases of clinical cases*. Adequately planned register design makes it possible to acquire homogeneous data by means of long-term dynamic monitoring of a patient's status under conditions of the *real clinical practice* [2, 4].

High demand for registers in all areas of medicine is caused by the fact that evaluation and analysis of the data accumulated by means of highly specialized databases help to achieve clinical, scientific, economic, and social goals [2, 3]. Therefore, it is registers that make it possible to study real clinical practice, to evaluate peculiarities of healthcare provision at different healthcare institutions, and to identify region-dependent areal discrepancies. Registers may thereby be used for different purposes, e.g. to study peculiarities of the disease course or the clinical-economic effectiveness of different medical interventions, as well as to compare different diagnostic, pharmacological or invasive therapeutic techniques [2, 3, 9].

Thus, registers are nowadays classified by type, intended use, and design [2, 10].

## **TYPES OF REGISTERS**

The simplest register type is a real-time non-interventional prospective cohort study based on clinical cases. The data to be accumulated in such registers are population-wide. The design of such registers reflects general risks of diverse impact factors. The parameters under analysis are general clinical outcomes, i.e. mortality and morbidity. An example of this type are epidemiological registers (e.g. register of pregnant women), which make it possible to evaluate how manipulations correlate to the recorded clinical outcomes.

A **clinical outcome register** is a more sophisticated version of long-term monitoring in real clinical practice. It is prospective by design, as well as non-interventional. The data for such registers are collected population-wide: on a specific but considerably large group of persons. Such registers are aimed at evaluating clinical parameters (mortality and morbidity), which may serve as endpoints, as well as information awareness, healthcare availability or other parameters. Such registers may be aimed at studying the natural course of a disease in a patient cohort with common specific characteristics. Registers of this type may be used for social scientific research, population-wide or more detailed epidemiological monitoring.

A **medical technology safety analysis register** is prospective and non-interventional by design; it is based on clinical cases of patients undergoing a certain intervention or receiving a specific pharmaceutical. It provides an opportunity to analyze adverse events of different severity, including severe and unforeseen ones. It is widely used when pharmaceuticals or medical technologies are undergoing registration, as well as for field post-marketing studies.

A **risk management register** is aimed at analyzing clinical outcomes, acquired data on safety and adverse effects, commitment to the prescribed treatment regimen, and the impact that different factors have on commitment to therapy. The design of such research in real practice is prospective and non-interventional. The incoming data are limited to a certain intervention but are still collected population-wide, and one or more criteria are in place to achieve the goal of such monitoring. The advantage of such registers is the opportunity to collect broad data that may be outside the scope determined by data parameters for registration of pharmaceuticals. Pharmaceuticals are analyzed for risk-utility; such registers are aimed at evaluating measures of decreasing potential risks of a pharmaceutical or a medical intervention; this provides a possibility to minimize the already known risks, including corrections and changes of the current recommendations, without voiding the medical technologies under consideration of their advantages.

The design of a **nosological register** is prospective and non-interventional. Monitoring is conducted population-wide, and data are acquired on a patient cohort suffering a certain disease. Prospective studies allow analyzing results of use of a pharmaceutical or a medical intervention, evaluating safety, clinical outcomes (mortality and morbidity), as well as use of resources or

correctness of use of pharmaceuticals and management of the patients with such a nosology. Such registers help not only to understand principles of the natural disease course, but also to identify, compare, and evaluate different patient management strategies, determine the markers of safety, effectiveness, and clinical outcomes, reduce the disease burden quantitatively and define the patients' quality of life. Besides, it is possible to identify and compare the present approach to therapy during such monitoring and thus choose the best clinical practice. Such registers are suitable for clinical economic analysis.

A **register of pharmaceuticals in use** is designed prospectively; yet, it may include a significant amount of retrospective data. It is based on clinical cases observed in a cohort of patients receiving the same medicamentous treatment. Among the parameters under analysis are safety and effectiveness, clinical outcomes, use of resources or correctness of pharmaceutical usage, identification and analysis of management strategies and additional prescription. Such registers are used for post-marketing monitoring, to compare the actual effectiveness of a pharmaceutical with its expected effects, to study unapproved (contraindicated) use of a pharmaceutical, and to identify specific signs or markers conditioned by the intake of one or another pharmaceutical. The register allows analyzing economic effectiveness (cost-effectiveness), evaluating the patient's willingness to pay and the chance to reimburse the costs of the conducted therapy.

A register of clinical management strategy, or **therapeutic register**, is designed prospectively; however, it may include retrospective population-wide data and clinical cases. Keeping such a database of clinical cases provides an opportunity to analyze treatment and patient management approaches, to evaluate clinical and economic outcomes as well as how optimally resources are used, to calculate the amount of costs and the total disease burden, and also to evaluate the quality of provided healthcare. Such registers are used for economic analysis, i.e. as part of analytical methods employed to make decisions on distribution of resources within the healthcare framework. Such analytical methods include, but are not limited to:

- cost-minimization analysis used when the effect of interventions under evaluation is similar;
- effectiveness analysis used to determine the advantage of an effect measured in natural units, e.g. years of life;
- cost-utility analysis, whereby quality-adjusted life years serve as utility units to compare different interventions by several categories, e.g. favorable and adverse effects;
- cost-benefit analysis measured in monetary units. Evaluation may concern loss of labor capacity when a certain intervention is analyzed when used for different patient conditions.

Measuring the costs and utility of a medical intervention determined by direct and indirect costs that have both clinical-economic and "invisible" components important for the total profile of healthcare parameters (according to the patients' estimates) and for the analysis of cost consequences is a complex objective of economic analysis.

Likewise, a register of healthcare resource usage (as well as a register of clinical management tactics) is intended for economic analysis; however, the most attention is given to disease burden, the cost of healthcare under conditions of one or another nosology etc. Such registers are designed prospectively; however, they may involve retrospective data, and feature a determined sample of patients or clinical cases. Such registers are aimed at analyzing direct costs of healthcare service provision, hospital admission and pharmaceuticals, as well as evaluating indirect costs incurred by the loss of labor capacity.

It is crucial that any register is flexible. The scope and focus of data collection may be adopted over time to fit additional objectives [2, 9, 11]. New studies, such as randomized cluster studies or case-control studies, may be conducted within the framework of register maintenance. Meanwhile, information databases of clinical cases may be used for additional follow-up [10].

There is, therefore, no doubt that creation of a register is a difficult and labor-intensive process that includes multiple phases of researchers' and clinicians' work, from setting goals and

defining objectives to forming the group of parameters to analyze and defining the monitoring outcomes.

The technical aspect is of key importance.

### **IMPLEMENTATION OF THE FIRST RUSSIAN INFORMATION DATABASE AT THE SCIENTIFIC CENTER OF CHILDREN'S HEALTH**

The Scientific Center of Children's Health is the leading institution providing healthcare to children with different nosological forms, syndromes, and rare diseases. The Center maintains a pediatric register of patients with severe uncontrollable persistent bronchial asthma (nosological register).

Given the heterogeneity of clinical symptoms in different patients with bronchial asthma, it is reasonable to use prolonged clinical monitoring to evaluate effectiveness and safety of therapies applied to treat severe uncontrollable persistent asthma in the field.

When preparing the creation of the register, the specialists analyzed all the data on creation, structure, advantages, and possibilities of registers, or clinical databases. This analysis made it possible to predict the further possibilities for implementation and use of this systematic tool to optimize and increase the quality of healthcare provided to children suffering bronchial asthma.

Taking into account the set objectives, the techniques in use, and the nosological peculiarities, an informed consent was drafted for patients, as well as their parents and guardians, with the help of the Center's lawyers. Besides, an explanation sheet containing comprehensive information on the planned monitoring has been drafted.

The software, i.e. the electronic shell of the severe persistent bronchial asthma clinical cases database management program was developed and created in several interrelated consecutive phases as follows:

- setting goals and objectives;
- choosing appropriate solutions;
- determining the structure of input and output data;
- determining the hardware requirements;
- determining the software requirements, i.e. the requirements to software features, reliability, conditions of operation, informational and software compatibility, external interfaces, and data safety and protection;
- determining the stages, phases, and deadlines of development;
- choosing programming means;
- developing the general solution algorithm, building up the general structure and components;
- developing the logical structure of the database and external interfaces;
- developing separate (module) solution algorithms;
- determining how input and output data will be presented;
- developing the structure of the program, specifying the structure of components per module;
- programming and debugging;
- developing, agreeing upon, and approving the procedure and methodology of tests;
- testing the software modules and the database;
- making corrections based on the results of re-testing.

Thus, systematic programming and further debugging of the end product provided for the database of clinical cases, the register of pediatric patients with severe uncontrollable persistent bronchial asthma. One of the pharmaceuticals used for background therapy in such cases is omalizumab. The database contains data on 64 pediatric patients, 62.5% whereof are boys. The age of the patients ranges from 6 years to 17 years 11 months; the average age is 12.9 years. All the patients suffer severe uncontrollable persistent bronchial asthma and either receive or used to receive treatment based on omalizumab – a bioengineered pharmaceutical. As of now, this pharmaceutical continues to be administered to 31 patients, 70.9% whereof are boys.

The average duration of asthma in these patients was 10.9 years (from 3.9 to 15 years); an accompanying atopic pathology was observed in 100% of those children: atopic dermatitis – 36%, allergic rhinitis – all the patients, seasonal rhinitis – 84%, food allergy – 45% (anaphylaxis – 25%), previous urticaria – 25%, and drug allergy – 32%. The average daily dose of inhalational glucocorticosteroids was 1000 µg of fluticasone propionate, or 500-1,500 µg per day.

The duration of omalizumab therapy ranged from 1 to 70 months. The effectiveness was evaluated according to the accepted recommendations, i.e. only after 16 weeks or 4 months of therapy. The background therapy was reviewed, i.e. the dosage of inhalation glucocorticosteroids was decreased if the disease had become more controllable, though only after 6 months of treatment with the biological agent.

Over the course of treatment, asthma became more controllable in all the patients. According to the control tests, the improvement amounted to 36% on the average (from 9% to 64%). Clinically significant exacerbation frequency decreased by more than 80% (from 4.1 to 0.65,  $p < 0.005$ ) after six months of treatment.

Over the course of treatment, the biological agent was administered more than 5,300 times. Local adverse events were observed in one case per hundred and manifested themselves as erythemas and indurations at the site of administration. They would resolve without clinical intervention within 1 to 1.5 days after administration. Local allergic responses in the form of eruption were observed in two patients and were managed by administering the 2<sup>nd</sup> generation antihistamines. They caused no further concern.

It is planned to continue active maintenance of this clinical case database in the future not only to solve epidemiology-related problems, but also to achieve optimal outcomes of effectiveness and safety monitoring for both innovative state-of-the-art treatment techniques and conventional treatment approaches. The mixed system for monitoring of patients with bronchial asthma and maintenance of a register, or a clinical database, are a must for improving healthcare provision to such patients.

The peculiarities of clinical case monitoring implementation, further modification and transformation of the goals and objectives of the register will provide an opportunity for wider usage of the database and its accumulated data owing to methodological flexibility. The long-term outlook for integration of areal information system will help optimize and harmonize the development and management of patient registers, and create a unified protected database for personal health data of all bronchial asthma patients [3]. The obtained outcomes of clinical monitoring will help to make asthma more controllable, improve commitment to prescribed treatment, decrease the frequency of exacerbations, and improve the quality of life of patients and their families.

### **Conflict of interest**

The authors have indicated they have no financial support / conflict of interest relevant to this article to disclose.

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