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Department of Internal Diseases 1

S. M. Kyselov

MAIN PRINCIPLES OF EVIDENCE-BASED MEDICINE

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Author:

S.M. Kyselov, MD, PhD, DSc, professor of Department of Internal Diseases 1 of ZSMU

Reviewers:

S.Ya. Dotsenko, professor, MD, PhD, DSc, head of Department of Internal Diseases 3 of ZSMU;

V.V. Syvolap, professor, MD, PhD, DSc, head of Department of Multimodal Diagnostics and Propedeutics of ZSMU.

Kyselov S. M.

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In tutorial have been highlighted main issues and principles of evidence-based medicine, determined its role in modern clinical practice. It will be useful for students of medical high schools of III-IV accreditation levels.

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Table of Content

List of abbreviations

DB – database

OR – odds ratio

WHO – World Health Organization

EBM – evidence-based medicine

EP – etiological part

CT – clinical trial

CE – clinical epidemiology

CR – clinical recommendations

MPH – Ministry of Public Health

IEC – independent ethics committee

DTG – diagnostic and treatment guideline

RCT – randomized controlled trial

CV – curriculum vitae

GCP – Good Clinical Practice

GIN – Guidelines International Network

GMP – Good Manufacturing Practice

GLP – Good Laboratory Practice

ICH – International Council for Harmonisation

Intro

The tutorial «Basic principles of evidence-based medicine» contains materials for practical classes and independent work of students by the topic «Principles of evidence-based medicine» of content module 5 «General issues of internal medicine» of module 1 «Fundamentals of internal medicine (endocrinology, gastroenterology, pulmonology, hematology, physiotherapy, general issues of internal medicine)» in accordance with the requirements of the programs of the discipline «Internal Medicine», specialty: 7.12010001 «General Medicine» and 7.12010002 «Pediatrics».

The tutorial describes the actuality of evidence-based medicine (EBM) nowadays, modern concepts, principles and aspects of evidence-based medicine, its role in real clinical practice, the requirements for conducting of clinical trials, key points of clinical epidemiology – the background of EBM, probable types of trials design, possible options and limitations, principles of clinical guidelines and protocols creation. There are necessary tests to verify the assimilation of the material, the glossary contains basic terms of this tutorial. Resources with links to leading global evidence-based medical databases are published at the end of the publication.

Actuality

The globalization of information processes in all areas of knowledge, and, in particular, in medicine, has posed qualitatively new problems in choosing a solution for a doctor, a healthcare organizer, and a patient [1, 2, 3, 5, 6]. Even newer issues often provide outdated information, and expert recommendations in textbooks and reviews which do not supported by evidence. [1, 6]. The flow of medical information is constantly increasing - around 40,000 medical and biological journals are published in the world, in which approximately 2,000,000 articles are published annually [6, 9]. Practitioners and healthcare managers urgently need critical assessment of information [1].

Only evidence-based medicine can solve these problems. Now it is in the focus of clinicians, healthcare managers, lawyers, patients and the public. [2, 3]. Доказательная медицина предусматривает добросовестное, разумное и разумное использование лучших современных доказательств для лечения каждого пациента [5]. According to another definition, evidence-based medicine is a branch of medicine that is based on evidence, which involves the search, comparison, generalization and dissemination of evidence for use in the interests of patients [4, 6]. The practice of evidence-based medicine means combining individual clinical experience with the best available independent clinical evidence from systematic research [9]. Individual clinical practical experience means professionalism and judgments that were obtained by an individual clinician, means of his clinical practice [5]. The best independent clinical evidence is understood to mean the data of clinically relevant studies, often in the fundamental areas of medicine, but mainly clinical studies with the accuracy and accuracy of diagnostic tests (including clinical examinations of patients), the assessment of the adequacy of prognostic markers, and the effectiveness and safety of therapeutic, rehabilitation and preventive measures [3]. Doctors should use both individual clinical practical experience and the best available clinical evidence and never only one thing [1]. Without individual clinical experience, practical decisions are significantly influenced by evidence obtained even from impeccably conducted

studies that may be inadequate for an individual patient [7]. On the other hand, making practical decisions without taking into account independent practical decisions can also harm the patient [9].

Origin of evidence-based medicine

When considering the situation in medicine during the 20th century, it turns out that a huge amount of information fell upon the physicians in the form of lots of new books, magazines, Internet sources, etc. [1, 3, 5]. The development of new information technologies (electronic databases and magazines, multimedia training programs on optical discs and on the Internet) is constantly expanding the ability of doctors to obtain timely information. Naturally, there was a need to comprehend the capabilities of these technologies, to determine their place, role and relationship with traditional print media [4, 6].

A good doctor always strives to be on the cutting edge of the latest medical advances. In search of an answer to a clinical problem, a doctor can use different sources of information and at the same time receive various, and sometimes opposite, recommendations. Such findings do not solve problems, but strengthen them. [1].

Nowadays, there are more than 20 thousand drugs on the pharmaceutical market and against this background, there is aggressive marketing by pharmaceutical companies, a massive impact on television consumers of drugs, prepared by authors incompetent in medical matters [9]. As a result, both the doctor and the patient became in a difficult position, since several methods of treatment are offered for the treatment of the disease at once and all of them, according to these sources, are the best [1]. How to distinguish dubious information from really truthful and objective in this situation?

For example, a short digression into the history of medicine will show that the search for answers to such questions worried the minds of many prominent

scientists and people who have nothing to do with medical science, long before the term “evidence-based medicine” came to light in the 1990s [2].

It is known that the Roman emperor, King of Sicily and Jerusalem, Frederick II (1192-1250) was interested in how physical exercise can affect digestion. To find out, he ordered the two knights to give the same food and sent one to hunt, and the other to sleep. A few hours later they were killed and the contents of the digestive tract were studied. It turned out that in the stomach of a sleeping knight digestion was more intense [6].

In the 17th century, physician and philosopher Jean Baptiste Van Helmont proposed the first clinical trials involving a large number of participants, with their randomization and statistical analysis in order to assess the benefits of bloodletting. It was envisaged that 200-500 poor people should be included in the research, dividing them into 2 groups by lot, where phlebotomy was not performed in one group and bloodletting was done in the other as much as the doctors considered necessary. It was supposed to evaluate the effectiveness of bloodletting by the number of burials in each group, but, unfortunately, there are no data on the implementation of this experiment in history [4].

In the middle of the 19th century, in Paris, in his works, Pierre Charles Alexander Louis described the principles of statistical analysis for evaluating medical treatment and showed that bloodletting is a useless type of treatment. True, this did not change the attitude of doctors to bloodletting at that time and during the next stages of the history of mankind. This problem - the transfer (translation) of research results into practice - remains relevant today. [6].

In the 1920s, Ronald Fisher first introduced the principles of statistical planning and analysis of experimental studies. After World War II, thanks to the work of Austin Bradford Hill and his followers, British epidemiologists Richard Doll and Archibald Cochrane, this area of science began to have a significant impact on clinical practice and public health. [4].

Finally, at the end of the 20th century, thanks to the joint efforts of more than fifty specialists, primarily from McMaster University of Canada, as well as from

other universities and institutions in different countries, the basic principles of evidence-based medicine were formulated [5].

Since in real clinical practice when solving problems related to the treatment of a particular patient, the doctor often cannot rule out doubts about the correctness of his judgments, as a result, not all of his actions are correct, that is, they correspond to the modern level of scientific knowledge. At the same time, with different tactics of medical care, the clinical consequences may be the same. From the combined experience of clinical medicine and the development of clinical epidemiology, an understanding has come that treatment should be evaluated according to the final outcomes (clinically important, important for the patient). These are the key points of evidence-based medicine. [1, 4, 5, 6].

DM from the way of thinking of a group of advanced doctors and epidemiologists has transformed into a variant of generally accepted medical practice. Moreover, the principle of evidence has taken a key place in the assessment of all medical technologies, moreover, not only in the patient management, but also in management decisions and financing. Now it is obvious that such a transformation extends beyond medicine, encompassing all spheres of human activity [1].

Knowledge of the basics of evidence-based medicine over the past 10-15 years has developed very intensively, has become absolutely necessary for researchers and doctors, as it facilitates the adoption of clinical decisions [2].

By the last quarter of the twentieth century, a situation had developed where, every 5 years, the amount of medical information doubled, and experts actually did not have time to get to know it for use in everyday practice. In order to assist physicians in examining clinical trial results for practical use, a team of epidemiologists from McMaster University, led by David Sackett, wrote a number of articles published in medical journals, starting with a series published in the Canadian Medical Association Journal in 1981. [6].

The authors used the term “critical appraisal” to refer to the critical use of medical literature by physicians trained to evaluate the quality of research. In the

future, they became convinced of the need to implement a large-scale program that would teach doctors how to use the information obtained to solve problems that arise in the treatment of specific patients. Then the process of practical application of published data in the literature D. Sackett called "the transfer of a critical assessment to the patient’s bed." Now it is clear that obtaining scientific results in fundamental medicine, as well as in clinical medicine, is not enough for scientific achievements to be part of everyday practice; systematic efforts are needed to transfer into practice, "translate" the research language into the practice language. This area of research and practice is designated as translation [9].

The term "evidence-based medicine" was used in 1990. In the newsletter for applicants for internship at internal medicine at McMaster University. It said: “In everyday use of diagnostic, treatment and prognostic methods, residents should observe educated skepticism. The EBM approach is a thorough study of relevant evidence-based data, an assessment of their reliability and practical significance. The doctor must be able to clearly formulate the clinical question, search for an answer to it in the medical literature, conduct a critical assessment of the facts found, determine the possibility of using them in the treatment of a particular patient and directly apply the data found in practice” [1, 4, 6].

In 1991, the term “evidence-based medicine” appeared on the pages of the new ACP Journal Club. In those same years, the development of questions of practical implementation of the principles of EBM and training in its basics continued. An international working group was also created to prepare materials to familiarize doctors with the principles of the practical application of medical literature data. [8].

The result of their work was the publication of a series of articles under the general title “Recommended Approach to the Study of Medical Literature (Reader's Guide)”, which have been published in the JAMA journal since 1993. These articles have been collected in the most comprehensive publication on EBM published and available in the internet (http://www.cche.net/ usersguides / main.asp) [9].

Main principles of evidence-based medicine

Evidence-based medicine (EBM) – section of clinical medicine that seeks, compares, analyzes, and puts into practice evidence obtained for use in the interests of patients. DM involves the usage of the most modern evidence of the effectiveness and safety of diagnostic, preventive or therapeutic measures obtained during randomized controlled clinical trials to make a clinical decision on their use for each patient. Existing evidence is searched, compared, generalized and widely disseminated for use in the interests of patients [1,4, 7].

DM solves the following tasks [4]:

1. Standartisation the activities of scientists, doctors and healthcare organizers according to the principles of EBM.
2. Increasing of the effectiveness of pharmacotherapy of acute diseases and syndromes and stabilizing of long-term remission of chronic pathological conditions, reduce mortality and improve the quality of life of patients.
3. Increasing the safety of treatment and reduction the risk of complications and worsening of the course of the disease by rational prescribing of drugs and treatment methods.
4. Optimisation of national health systems.
5. Optimisation the economic provision of treatment, preferring less expensive and at the same time quite effective drugs, diagnostic methods and treatment.

Basic principles of EBM:

- The principle of using scientific and medical information of only the highest level of evidence. Such information is concentrated in the results of clinical trials that are conducted exclusively on humans, and summarized in clinical guidelines, systematic reviews, meta-analyzes, international consensus, etc. [6].

- The principle of continuous updating of information on the achievements of medical science and clinical practice. It helps to accelerate its

use to optimize the diagnostic process, increase the efficiency and safety of any medical interventions, improve the activities of scientific institutions and national health authorities. This is facilitated by professional publications, electronic databases accessed through the Internet, and the frequent reprint of modern leading directories [4].

- The principle of constant acquaintance of all participants in the medical industry with the achievements of science and practice. The conditions are created for the daily control of their professional activities by comparing it with world achievements. It contributes to improving the results of scientific and clinical research, increasing the professionalism of scientists, practitioners, employees of public health authorities at all levels. [2].

- The principle of optimal diagnostic feasibility. It provides for the maximum use of all currently accepted methods for examining patients, in particular anamnestic, physical, instrumental and laboratory, and in a single diagnostic complex [8].

- The principle of rational pharmacotherapy as the basis for individual programs of highly effective, safe and economically viable treatment of any disease. It is based on the optimal use of three groups of drugs and resuscitation measures (pharmacotherapy algorithm) [5]:

a) the main (basic) drugs that can radically change the course of the disease, stabilize its development, eliminate dangerous manifestations, prevent a catastrophe;

b) drugs according to special indications in the presence of clinically threatening syndromes in patients, complications, exacerbations of concomitant diseases, which also requires medical intervention. Often these are existing encephalopathies or comas, respiratory failure, or cardiovascular, renal or liver failure, and so on;

c) additional funds that are added to the treatment program in order to complete the pharmacotherapy of acute diseases, or to ensure long-term remission of chronic pathological conditions.

- **The principle of evidence-based disease prognosis.** The doctor is not always able to cure the patient, but to relieve him and his relatives reliable information about the inevitable adverse outcomes of the disease is obliged in any cases. Therefore, the prognosis, that is, the prediction of possible clinical outcomes of the disease and the likelihood of their occurrence in the future, should be based on the results of the same studies carried out for diagnosis and treatment [6].

- **The principle of continuous improving the safety of medical interventions** (diagnostic, medical, physiotherapeutic, surgical, organizational). It is achieved by conducting the same clinical trials as establishing their effectiveness (mainly randomized) [8].

- **The principle of standardization of medical interventions** in order to use only the most effective, safe and economically viable methods of diagnosis, prevention and treatment, taking into account the type of medical institutions. It is based on the results of clinical studies that are conducted to establish the effectiveness of drugs, certain methods of medical interventions, as well as the results of studies on the effectiveness of organizational technologies. According to the results of such studies, appropriate clinical recommendations are created, that is, standards for medical interventions, for example, for the treatment of heart failure, arterial hypertension, stroke, epilepsy, infectious diseases, etc. These standards include, first of all, the minimum amount of necessary care for patients, which is mandatory for all medical institutions of the country, as well as optimal care, is carried out as far as possible [7].

- **The principle of minimizing the economic costs of diagnosis and treatment of diseases.** Therapeutic tactics should be based on pharmacoeconomic approaches [5].

- **The principle of collective responsibility for the high efficiency of diagnostic and medical technologies.** First of all, this refers to such common diseases as stroke, myocardial infarction, acute poisoning with toxic substances and so on. From the position of EBM, the conscious action of not only the doctor, but also the patient, who has the right to complete information about his health,

origin of the disease, the level of risk for life, real approaches to treatment, the positive and negative consequences of each of the existing ones, becomes the leading in the treatment process methods [2].

- The principle of continuous optimization of national health systems with the goal of rational use of public resources and patient opportunities, organization of promising national projects and programs, special training and retraining of personnel. It contributes to the improvement of the results of the work of direct performers (scientists, doctors, managers), the activities of medical institutions and the medical industry as a whole, the formation of the state health policy as a whole [3].

In 1948, British doctors published results of the first clinical trial of the effectiveness of streptomycin in tuberculosis. One group of patients was treated with streptomycin, the other - according to the then standard pharmacotherapy regimens. The distribution of patients into groups was carried out according to a table of random numbers. **Randomization principle** – «randomly selected groups» – became golden standard of medicine. The most acceptable and reliable is a randomized trial with the principle of double blind control [6].

When conducting a **randomized study** of the effectiveness of a drug for a particular disease, groups of patients (at least two) are distributed randomly. This achieves the practical identity of groups of participants in quantitative and qualitative indicators. Analyze and evaluate the effectiveness of a certain type of medical intervention. **Non-randomized trials** suggest the distribution of patients into groups in a nonrandom manner if random distribution is not possible for technical or ethical reasons [9].

Cohort trials include formation of two or more groups (cohorts) of patients, of which only one assesses the appropriate medical or therapeutic intervention, although the clinical result is recorded in all groups. Observations can go on for years (for example, the effect of smoking on lung cancer) [7].

Tansversal (or sumilteneous) trials are carried out by the method of questioning, examination, collecting answers to a specific question among doctors

and patients. Examination and collection of information about the patient (or group of patients) is carried out once. This makes it possible to establish a picture of the disease in one patient (or group of patients), to clarify the symptoms, to determine individual manifestations and the severity of the disease. The final result is a description of the disease in an individual patient, and in the aggregate of options - this is a study of the connection of some signs with a variant of the disease [5].

«Case-control» trials are performed in situations where the expected clinical effect is recorded very rarely, develops slowly. A group of individuals is formed from individual cases of the corresponding disease or clinical effect. Next, a control group is selected from individuals without such a disease or condition, but similar in important prognostic characteristics - age, gender, and concomitant pathologies. Calculate in all groups the number of patients exposed to certain adverse and undesirable effects. The results are correlated taking into account the known and measured prognostic factors. [8].

Description of a case or series of cases – short reports of successful treatment or manifestations of threatening complications of pharmacotherapy, which is essential for timely medical information. The value of the method is to receive prompt messages about the complication of treatment, the occurrence of side effects and so on, because waiting for years for relevant more reliable information is often inappropriate [3].

Recommendations for patient management should be systematized on the basis of the degree of reliability of the effectiveness and feasibility of use.

Levels of evidence and degree of recommendation

In practice, healthcare providers can use a wealth of potential sources of information about medical interventions:

■ materials of studies conducted by medical specialists or specialists from other areas;

■ research materials and other information from pharmaceutical and other companies;

■ research reviews and clinical guidelines;

■ opinions of experienced professionals (experts);

■ opinions of colleagues;

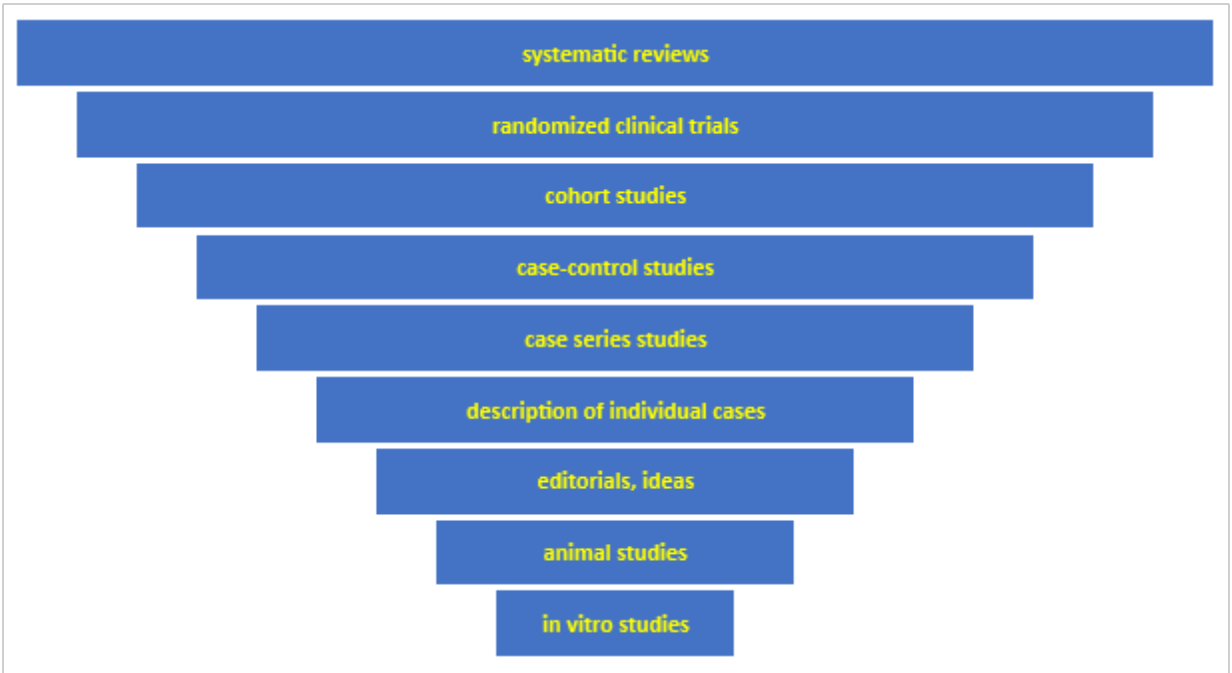
■ personal experience;

■ first-hand patient evidence [2].

For the doctor, studies published in scientific medical journals are of most value. This is due to the fact that articles in magazines undergo rigorous selection and editing, which reduces the likelihood of receiving poor quality information, or an incomprehensible, uninformative message [1].

Scientific reports in journals do not always contain the results of original scientific research. It can also be comments, discussions. Along with medical journals, biological studies, as well as studies performed on animals, are published in journals. [1].

The most evidence-based information is scientific research, characterized by the presence of a systematic process, which is carried out according to a clearly developed protocol, which seeks to exclude or explicitly identify the researcher's own preferences and to obtain results that are relevant for patients / clients and medical practitioners working in this field [9].



Picture 1. Evidence hierarchy of information sources

Research data have varying levels of evidence. Using the “pyramid of evidence” (Fig. 1), the doctor should always give preference to the results of the most evidence-based studies. With regard to the effectiveness of therapy and prevention, these most evidence-based studies are randomized clinical trials (RCT) [2]. When there are many RCT, systematic reviews allow you to take into account the differences between them and conduct a generalized assessment based on the entire set of RCT. Therefore, it is generally accepted that the conclusions of systematic reviews are more conclusive than the results of individual RCT. [1].

Graduations (classes) and levels of evidence were developed in Oxford [9]:

Class I - the presence of consensus and / or evidence regarding the effectiveness, appropriateness of application and the beneficial effect of the procedure;

Class II - conflicting evidence and lack of consensus on the effectiveness and appropriateness of applying the procedure;

IIA - the “balance” of evidence / consensus is inclined to the effectiveness and appropriateness of the procedure;

IIB - the balance of evidence / consensus tends to be ineffective and inapplicable;

Class III - the presence of consensus and / or evidence of inefficiency and inappropriateness of the application of the procedure, and in some cases even its harmfulness.

In turn, the degree of evidence of the effectiveness and feasibility of applying the procedure is divided into three levels of reliability [5]:

Level A – data from at least two randomized trials;

Level B – data obtained in one randomized clinical trial and / or in a meta-analysis, or in several non-randomized trials;

Level C – expert consensus based on research and clinical practice.

EBM is a method of medical practice; it differs by the usage of the most reliable information for making medical decisions. The main goal of EBM is to constantly increase the effectiveness of medical services for the diagnosis, treatment and prevention of diseases, as well as the use of methods leading to the rational use of limited resources [3].

EBM uses the achievements of a relatively young science - clinical epidemiology. Clinical epidemiology (CE) is developing the scientific basis for medical practice. The main postulate of CE: every clinical decision should be based on a rigorous scientific justification. This is “evidence-based medicine”, literally translated as “evidence-based medicine” or, which more accurately reflects the meaning of the term, “evidence-based medical practice” or “scientific evidence-based medicine” [9].

The concept of "evidence-based medicine" implies the following:

- providing the most effective and safe treatment based on the most reliable evidence available;
- collection, interpretation and integration of reliable clinical data obtained as a result of observations of specialists and during testing, patient communications;
- technology for the search, analysis, synthesis and application of medical information to make optimal clinical decisions;

- the process of continuous learning, allows you to integrate the most reliable of the existing evidence with individual experience;
- the new paradigm of clinical medicine differs from the previous one by a smaller impact of subjectivity on the choice of criteria for diagnosis and therapy and requires a doctor to critically evaluate the opinions of various experts and the results of clinical trials;
- information technology for choosing the best options for medical activities [10].

By the definition of well-known experts, DM is a conscious and consistent use of the best proven results of clinical trials in the treatment of a particular patient. The terms used in this definition have the following meanings [1, 4, 6, 10]:

- conscious: the conscious application of the results of the study to each patient;
- consistent: taking into account in each clinical case the ratio of risk and benefit from the treatment method used, taking into account the uniqueness of each patient, including his general condition, concomitant diseases and preferences;
- best proven research results: on the basis of a critical approach, a specialist selects the best from the entire spectrum of ongoing studies to diagnose or treat a specific disease [1].

An objective prerequisite for the emergence of EBM was an increase in the amount of scientific medical information, as well as a lack of financial resources associated with an increase in health care costs. Every year, more and more new methods of diagnosis, treatment and prevention are being introduced into medical practice. These methods are more or less actively studied in numerous clinical studies, the results of which often turn out to be dissimilar and even opposite. So, from a large number of methods, it is necessary to choose the one that has the highest efficiency and safety. It should be remembered that the novelty or high cost of a new intervention is not a guarantee of its superiority over others [9].

Thus, for practical use, the information obtained must be carefully analyzed and summarized. The EBM methodology provides a critical analysis of all data in

order to discard substandard, unprovable, and rely on reliable results obtained using effective scientific methods [10].

EBM to date has significantly changed the attitude towards diagnosis and therapy, as new, more effective interventions have been proposed for many diseases. At the same time, evidence of inefficiency, worthlessness, or even damage to the patient's health of some old interventions is given [1].

Currently, a lot of research is being conducted, the purpose of which is to improve the quality of medical care. Each year, the MEDLINE database is updated with the results of approximately 10 thousand randomized controlled trials (RCTs). The Cochrane Collaboration trial registry (The Cochrane Collaboration; http://www.cochrane.org) contains references to approximately 850,000 such studies [13]. However, the data obtained are not always implemented in everyday clinical practice. The results of studies conducted in the USA and the Netherlands show that 30–40% of patients do not receive treatment in accordance with international recommendations, and 20–25% of patients receive treatment that is not indicated to them [16].

The introduction of EBM in the daily activities of a doctor also has an economic aspect. Even in highly developed countries, the resources allocated by the state to health care do not fully meet the needs of society. Therefore, it is undoubted that it is most efficient to direct these resources to the development of methods of prevention, diagnosis and treatment, the practical benefits of which are confirmed by studies that meet the criteria of evidence-based medical practice [9].

When analyzing the results of clinical trials, it is customary to evaluate their reliability, which determines the levels of evidence [10].

Key concepts for clinical epidemiology

Clinical epidemiology (CE) - the methodological basis of EBM. She studies the patterns of the spread of diseases, predicts them in each individual patient based on the study of the clinical course of the disease in similar cases [6]. CE solves all its problems directly on people and in no case on animals or elements of the human body - tissue culture, cell membranes and the like. CE provides EBM methods of biostatistics, objective criteria for the reliability of objective laboratory and instrumental studies and methods for their generalization [3, 4]. CE studies the complications and prognosis of diseases, the results of multicenter placebo-controlled studies to determine the objectivity of various treatment methods and side effects of drugs [2].

The term “clinical epidemiology” arose from the names of two “related” sciences of clinical medicine and epidemiology. It is called clinical because it solves clinical problems, answers a variety of medical questions, and recommends appropriate clinical solutions [6]. It is called epidemiology, since a significant number of its research methods were proposed by epidemiologists at one time and help to a specific patient is considered in the context of a large population, to which the patient himself belongs.

Clinical epidemiology is based on the following statements:

- in most cases, the prognosis, diagnosis and treatment results for a particular patient are not uniquely determined and therefore they should be expressed in terms of probability;
- these probabilities for a particular patient are best evaluated on the basis of previous experience accumulated by doctors regarding groups of similar patients;
- since clinical observations are carried out on patients who are free in their behavior, by doctors with different levels of knowledge and personal opinion, systematic errors in the results that lead to biased conclusions cannot be ruled out;
- any observations, including clinical ones, are influenced by chance;

- in order to avoid incorrect conclusions, the doctor should rely on studies based on strict scientific principles [6].

The essence of clinical epidemiology in the English version is reduced to five D:

- Death of the patient, especially when it is premature;
- Disease, which is always perceived by the patient as a dangerous disease;
- Discomfort in the form of pain, nausea, shortness of breath, itching, tinnitus, etc.;
- Disability - inability to normal activities at home, on the robot, during rest;
- Dissantispation - an emotional reaction to a disease or treatment, such as longing or anger [6, 9].

Diseases should be considered as hypotheses that must pass clinical trials [1].

The past century was marked by intensive improvement of epidemiological analytical studies of the causes of the spread of noncommunicable diseases (cardiovascular and oncological, associated with environmental degradation, etc.). Their results have become widely used in clinical medicine. At the same time, epidemiological studies of social impacts on human health developed [2]. Epidemiology was transformed into science not about the prevalence of infectious diseases, but about the prevalence of pathogenic factors affecting the spread of diseases. The object was not the epidemic process, but the process of the spread of diseases. Clinical research methodology has also deepened. They made it possible to obtain reliable information about the causes of morbidity and the effectiveness of certain medical interventions [4].

The methodology of DM is based on epidemiology. Currently, clinical epidemiology (CE) has been singled out from general epidemiology as a science that "allows forecasting for each individual patient based on the study of the clinical course of the disease in similar cases using strict scientific methods for studying groups of patients to ensure the accuracy of the prognosis." It is even called the “science of the methodology of medicine” [4, 6].

The main goal of CE is “the introduction of methods of clinical research and data analysis, ensuring the adoption of correct decisions”, because any science seeks to cognize some phenomenon, process or subject using an adequate method [6].

The epidemiological method is a set of techniques designed to study the causes, conditions of the onset and spread of diseases and other conditions in a population of people [2].

In the process of evolution of the epidemiological method, 3 main groups of epidemiological techniques have been distinguished:

- descriptive (descriptive),
- analytical,
- experimental [5].

The main scientific categories in CE is the concept of random and systematic errors that came to medicine from statistics. Biostatistics - the application of statistical methods in biology and medicine - is an important scientific tool for epidemiological research. Knowledge of its fundamentals is necessary for the practice of EBM, since it operates with quantitative data. Sometimes they try to reduce CEs to statistical research methods, but this is erroneous, since statistics, on the one hand, is just a research tool, and on the other, a completely independent science [6].

The main task of CE is to apply the principles of clinical trials to obtain reliable knowledge and critically evaluate research results in order to improve medical practice [7].

The main thing in assessing the results of a clinical trial is to evaluate its design, which should be adequate to the subject of the study. The quality of the developed design characterizes the methodological maturity of the researcher who plans to implement it. Understanding the types of research designs is, in essence, understanding the essence of clinical epidemiology [6].

A key element in the approach of CE to clinical research and in the practice of EBM is the approach to the consequences of diseases. The CE draws attention to

the fact that in order to evaluate interventions, it is necessary to study their effect on such results as death, discomfort, disability, patient dissatisfaction. These results are called clinically important or important for patients. Results in the form of changes in concentrations, density and other characteristics (surrogate results) in EBM are considered as those that do not have significant value for practice [1].

Fleming T.R. i De Mets D.L., who conducted special studies using the results of cohort studies as an example, showed that for various diseases the use of surrogate results as criteria for the effectiveness of treatment can lead to erroneous conclusions compared to subsequent clinical results [9].

It must be remembered that EBM technologies cannot and should not completely replace the previous principles of clinical practice, they only complement them and offer new, more effective solutions. From this perspective, it is interesting to analyze the use of EBM technologies in developed countries. It shows that real clinical decisions are made under the influence of a number of factors, such as the characteristics of the medical institution, the level of preparation of the doctor, the patient's preferences, etc. The basic principle for making a clinical decision remains the patient's choice when the latter is fully informed. This principle is confirmed by the Sicilian Declaration on the use of EBM technologies [6].

CE is relatively difficult to study. However, without realizing its foundations, a modern specialist cannot evaluate the quality of a scientific publication, navigate the current information, determine the value of the decision made (risk / benefit ratio), the reliability of the study, and critically evaluate clinical recommendations. As a result, a doctor who does not focus on CE cannot methodically correctly apply the results of scientific research to a specific patient [1].

In his daily activities, the doctor solves the problem of a particular patient and at the same time, the task facing the doctor is to find the answer to the clinical question. He knows in the face of all his patients, collects an anamnesis, conducts research and bears personal responsibility for each patient. As a result, the doctor evaluates, first of all, the individual characteristics of each patient, and he

reluctantly combines his patients into groups according to risk, diagnoses, treatment methods and evaluates the patient's membership in these groups within the framework of probability theory [4].

The physician’s personal experience is also important for making clinical decisions. However, the vast majority of doctors do not have sufficient practical experience to recognize all processes characterized by severity for perception, a long course, complex interaction and occur in most chronic diseases [6].

The subject of clinical epidemiology is the medical aspects of disease. For example, how are symptoms and diseases, interventions, and outcomes related. To assess how much you can trust the results of research, the doctor must understand how medical research should be carried out [3].

Thus, in order to judge the reliability of medical information, a doctor needs to know the basic concepts of clinical epidemiology, as well as anatomy, pathology, biochemistry, pharmacology. Therefore, at present, clinical epidemiology is considered as one of the fundamental sciences on which the building of modern medicine rests [6].

In connection with the introduction of the achievements of modern science, new technologies and medicines into practical medicine, the cost of medical care has reached such a level that even the richest groups of the population are not able to pay for all the desired types of services. At the same time, the use of new types of medical interventions is not always accompanied by a proportional improvement in clinical results. In this regard, methods are being developed for a more thorough, generalized assessment of scientific clinical data that healthcare managers can use to improve the provision of medical care. [7].

Nowadays, few people deny the fact that medical care should be based on the results of correctly conducted research and evaluated according to the final results, taking into account the financial costs that society can afford. Also, each patient is considered as an integral part of large groups of similar patients, helping not only to make accurate individual forecasts, but also to choose the best way to use limited financial resources to improve care for as many people as possible [4].

The main goal of CE is the introduction of clinical research methods that ensure the adoption of the right decisions. In this case, of course, personal experience and knowledge of the mechanisms of the development of diseases are important. However, other important aspects must be taken into account [6].

■ In most cases, the diagnosis, prognosis, and treatment outcomes for a particular patient are not accurately determined and therefore should be expressed in terms of probabilities.

■ The probabilities for a particular patient are better determined based on previous experience gained in a similar group of patients.

■ It should always be borne in mind that clinical observations should be carried out on patients who are free in their behavior, who are observed by doctors with different qualifications and their own opinions, which can lead to systematic errors and erroneous conclusions.

■ Any clinical trial is subject to chance and the result of each trial may be distorted by an accidental error.

■ To reduce errors in decision-making, the doctor should use the results of studies based on clear scientific principles, using methods to minimize systematic and taking into account possible random errors [6].

Clinical questions and answers to them are based on the principles and concepts below. The main issues posed by CE are deviation from the norm, diagnosis, frequency, risk, prognosis, treatment, prevention, reason, costs. These are the questions that arise both in the patient and the doctor. They are most often discussed among themselves by doctors and patients [5].

For CE, the most interesting are the results that are of vital importance for patients, as well as for medical personnel - death, illness, discomfort, disability, dissatisfaction with treatment. It is these phenomena that doctors want to understand, predict, interpret and change in the treatment of patients [6].

CE differs from other medical sciences in that all these phenomena are studied directly in humans, and not in experimental animals or elements of the human body, such as tissue cultures, cell membranes, receptors and mediators,

nucleic acid sequences, etc. Biological phenomena cannot be considered the equivalent of clinical results until direct evidence of their relationship has been obtained [2].

In benign clinical trials, the correct measurement methods should be used, since the results of less reliable measurements give less reliable evidence. The frequency and severity of clinical outcomes, such as death, illness, or disability, can be represented in numerical terms. Functional defect and loss of quality of life can be measured. In benign studies, the unreliability of subjective assessments made by a person should be taken into account, and this unreliability must be corrected [9].

Clinical outcome is rarely predicted with high accuracy. Most often, based on the results of previous studies on such patients, the probability of a particular result is determined. With the clinical and epidemiological approach, it is assumed that the clinical prognosis is uncertain, but can be quantified in the form of probabilities. For example, symptoms of coronary heart disease occur in 1 out of 100 middle-aged men per year; smoking doubles the risk of death at any age [4].

Population – large group of people who live in a certain geographical region (for example, in Ukraine) and reproduce themselves in a series of generations. This is a general biological definition of a population, in relation to humans it is a synonym for population. In epidemiology and in the clinic, a population is also called any group of people who have some common characteristics (for example, people over 65, or hotel workers). A population can only represent a certain part of the population (for example, in epidemiological studies of the causes of diseases). It may consist of patients hospitalized in a particular clinic or patients with a specific disease (more often in clinical trials). Therefore, we can talk about the general population, the hospital population, or the population of patients with a specific disease [4].

Sample – specially selected part of the population. Clinical trials are usually performed on samples, as it is impossible and usually not necessary to examine the entire population. In order for the sample to reflect the population correctly (be

representative, i.e. representative), it must be correctly created. In the simplest case, this is a random sample from a population. In fact, for various reasons, randomly selecting members of a population is not always easy, therefore more or less complicated (compared to a simple sample) techniques are used. In addition, the sample must be large enough for the estimates obtained to be sufficiently accurate. It is advisable to determine the required sample size before starting studies using standard statistical formulas [6].

The main goal of TBE is to introduce methods of clinical observation and data analysis that ensure the adoption of correct and adequate decisions in the treatment of patients, taking into account economic support [5].

To obtain evidence of the effectiveness of medical technologies, DM operates with such basic pharmacoepidemiological concepts:

- actual (final) clinical result (clinical outcome) - a phenomenon that is important for changing health indicators (recovery, disability, mortality, life expectancy) and / or quality of life;

- an indirect (indirect) criterion of effectiveness - a laboratory indicator or symptom, the dynamics of which directly characterize the patient's condition and affect the final clinical result;

- absolute risk (absolute risk) - the absolute difference between the frequency of development of an undesirable effect when using a medicinal product (PM) and the frequency of development of the same effect without the use of drugs;

- relative risk (relative risk) - the ratio of the frequency of development of an undesirable effect among people exposed to the factor being studied (drugs were used), to the frequency of development of a similar effect in the group of people not exposed to this factor (drugs were not used) [4].

The search for new drugs is carried out first on experimental animals. After the completion of the experimental studies, their result goes to the State Pharmacological Center of the Ministry of Health of Ukraine [5].

Clinical trials are carried out in 4 phases [9]:

The **first** phase is carried out on 20-80 healthy volunteers in order to establish the range of doses of the drug, its tolerance and safety.

The **second** phase of clinical trials is the first experience of using the active substance in patients with the disease. The main goal is to prove clinical efficacy in the study of 200-600 patients, to determine the levels of therapeutic doses of the substance, dosing regimens.

The **third** phase of clinical trials is a rigorous controlled study that is conducted to determine the safety and effectiveness of the active substances in conditions close to their use for the treatment of patients. Such studies involve more than 2,000 patients. They study the effect of a substance in combination with other drugs. Conducted controlled studies with a placebo, reference drug or treatment standard. Uncontrolled clinical trials (blind and open) may also be conducted.

The **fourth** phase of clinical trials is conducted after registration (licensing) of the drug in order to obtain additional information in terms of safety and effectiveness.

During a clinical trial establish:

- improvement of the dosage regimen and timing of the drug;
- interaction with food or other drugs;
- the influence of individual factors of the drug on survival, etc.

In a clinical trial, the goal of treating patients is determined by surrogate endpoints — disease parameters that determine the short-term or long-term outcome of a factor.

There are three types of endpoints [6]:

- primary endpoints are leading indicators that indicate a possible extension of the patient's life (reduction in overall mortality, mortality from disease)
- secondary endpoints are characterized by an improvement in the quality of life of the patient due to a decrease in the number of non-lethal forms of complications or due to the relief of the clinical signs of the disease;

- tertiary endpoints are indicators that are not related to improving the quality of life or its extension, but may indicate the possibility of preventing the disease by eliminating risk factors.

Clinical predictions based on knowledge of the pathology are just hypotheses that must pass the test in clinical trials. CE has developed criteria for assessing the scientific level of publications. Scientific research can be divided into two categories: some are conducted to put forward hypotheses, others - to test them. To test hypotheses, randomized controlled trials (RCTs) are more appropriate. Others are needed primarily for hypotheses [5].

From the point of view of evidence-based medical practice, the information used to make clinical decisions can be divided into:

• primary (data from original studies published in peer-reviewed scientific journals) and secondary (review and editorial articles, textbooks, expert opinions);

• direct (obtained in the course of clinical work) and indirect (obtained in the experiment);

• strong and weak (depending on the design of the study) [4].

Scientifically based medical practice gives priority to primary, direct and strong information as the basis for making clinical decisions [6].

The implementation of the principles of evidence-based medical practice can be implemented in two ways:

1. Traditional approach: in the case of a “non-standard” clinical situation, the doctor seeks advice from senior colleagues and leaves the patient with a rather vague list of diagnostic procedures, treatment regimens, and prognosis for the future.

2. A scientifically based approach: the doctor asks himself what he knows about the etiology, pathogenesis, differential diagnosis, principles of pharmacotherapy and prognosis for life, and understands that he does not know the answer. Then he in the library makes a request in the MEDLINE database, finds information via the Internet [9].

It should be borne in mind that at least 80% of medical publications in the world are published in English, the doctor is not able to absorb a huge amount of new information (approximately 4 million articles are published annually, and the doctor needs to review about 100 articles per day). The ability to critically assess the likelihood and feasibility of applying the results to practice is important. The optimal solution is to attract experts who, based on the principles of evidence-based medicine, will prepare an information product for practitioners in the form of clinical recommendations, systematic reviews, and literature digests of the most pressing health problems [5]. Such activities are developing in several directions:

1. Development of evidence-based clinical recommendations on the most important medical problems. The initiators of the clinical recommendations are professional medical associations or government organizations that create expert groups. The International Journal of Medical Practice regularly publishes clinical recommendations on critical issues of practical medicine prepared by the American College of Physicians [9].

2. Formation of a database of systematic reviews of randomized controlled trials. For the first time in the world in 1979, the famous English epidemiologist Archibald Cochran justified the need to use in medical practice only the data obtained in the process of properly organized and time-tested scientific research. A. Cochran suggested creating medical reviews based on a systematic collection and analysis of facts and regularly replenishing them with new data. Cochrane collaboration is an international community of scientists whose goal is to identify, systematize, and synthesize the results of all published randomized controlled trials. Systematic reviews of the centers of the Cochrane Association provide a comparative assessment of the effectiveness and safety of drugs for individual nosological units, but, as a rule, do not contain specific recommendations. Using Cochrane reviews, scientists summarize the results of various studies on a specific problem. The result is an objective, statistically substantiated coverage of information, an assessment of the degree of usefulness of various therapeutic, diagnostic and preventive interventions (the resources of the Cochrane Library are

electronic databases of systematic reviews published by the Cochrane Association) [1].

3. Creation of international journals of medical practice and abstract digests. American College of Physicians in 1991. Released the first issue of ACP Journal Club. Since 1996, a subsidiary of the US-British publication, the Evidence-Based Medicine magazine, has been released. International journals of medical practice publish abstracts of leading medical journals. The selected articles are presented in the form of structured summaries, which contain the same sections as the original publications (purpose, methods, important results and practical conclusions). Then the article is sent to an expert in a certain field of medicine, comments on the main results, helping the reader to understand their strengths and weaknesses, and determines how useful the results are in practice [9].

Systematic Reviews summarize scientific data and explain the reasons for the discrepancy between the results of various studies. Meta-analysis is a type of systematic review in which statistical methods are used to combine and summarize the results of several original studies. Systematic reviews are used in medicine as a source of information for making clinical decisions, planning future research and developing health policies [2].

Review articles – it is a kind of synthesis of information. Clinical recommendations, economic analyzes and analyzes of clinical decision-making algorithms include the results of systematic reviews. Evidence-based clinical recommendations are based on systematic reviews, appropriately adapted to local conditions and characteristics. In economic analyzes, the cost and effectiveness of various treatment measures are compared; performance data considered in such analyzes are most often obtained from systematic reviews of original studies. In the analysis of clinical decision-making algorithms, both the probability and significance of the expected clinical situations are quantified when making a decision [1].

A systematic review allows us to conclude that:

- the intervention is undoubtedly effective and should be applied;

- the intervention is ineffective and should not be used;

- the interference is harmful and should be prohibited;

- the benefit or harm is not proven and further research is required [2].

The benefits of systematic reviews of DM are as follows:

- well-defined methods limit bias in the inclusion and exclusion of research from the review;

- conclusions are more reliable and accurate in connection with the methodology that is used;

- Doctors, researchers, and healthcare administrators may receive more information in a short time;

- the time delay between the discovery of patterns and their implementation in practice is reduced;

- quantitative assessment of systematic reviews (meta-analysis) increases the evidence of the result [4].

The positive effects of evidence-based medicine should be considered in terms of the following aspects [3].

Medical and ethical aspects. Doctors prescribe only those diagnostic procedures that give real information about the patient's condition, which are not harmful to health and allow you to choose the most effective treatment. Doctors prescribe only those treatment methods that have previously proven effective in correct research on thousands of such patients [6].

The patient is informed about what is happening to him, participates in making decisions about his health and can always check the correctness of the appointments. Evidence-based medicine makes the communication between the doctor and the patient honest, open and transparent [2].

The economic aspect. Payment for medical services can be carried out from various sources: the state budget, funds of compulsory or voluntary medical insurance, and, finally, personal funds of citizens. These four sources are united, first of all, by the reluctance to pay for an extra examination and unreasonable and ineffective treatment. On the other hand, it is desirable to get the maximum effect

from those funds that are spent. Evidence-based medicine prevents the use of excess funds and helps to use them effectively [7].

The legal aspect. Citizens, insurance companies, the state, public organizations have the only tool in the form of standards for the provision of the most adequate medical services. Evidence-based medicine allows you to control any activity in the field of medicine [5].

Educational aspect.

1) The concept of continuous distance postgraduate education of doctors. Continuous adherence to the standards of evidence-based medicine would make it possible to efficiently and professionally train medical personnel and timely improve their qualifications.

2) The concept of a single standard for postgraduate training of doctors. Moreover, there will not be such striking differences between diplomas and certificates obtained in various medical institutions and, accordingly, in the qualifications of doctors.

3) The concept of a unified approach to the treatment of patients. Evidence-based medicine allows treating patients accordingly with the single most effective approaches, while the doctors themselves understand each other better [6].

Conditions for the effective functioning of evidence-based medicine [1]:

- conducting research with a high level of evidence;
- the availability of scientific journals of the so-called "high citation level" in which publications of only high scientific importance are published;
- the presence of doctors who know what, in which journals and how to read;
- the possibility of applying knowledge in practice;
- the interest of patients themselves in the implementation of the principles of evidence-based medicine;
- State interest in the dissemination of reliable scientific knowledge among doctors, pharmacologists and patients;

- the interest of doctors in the dissemination of evidence-based medicine, which is expressed in the creation of powerful medical associations that create standards of medical care and monitor their implementation [1].

Epidemiological Trials Design

Design, methods of conducting and organizing research - these terms are synonymous with the term structure [4].

Under the design of an epidemiological study, we understand all the features of a specific study provided for in its plan. These features are indicated by numerous terms, and only their combination allows you to see all the characteristic features of the study [6]. A variety of species and differences in the organization and conduct of epidemiological studies are given in table. 1.

Continuous trials. Continuous epidemiological studies are studies conducted within the scope of the general population, which in epidemiology is more often referred to as the term population. In the general case, a population is called an object of observation, which represents the totality of all units of observation that have certain characteristics, they are often called signs of inclusion / exclusion in the population.

In epidemiology, as noted earlier, these signs relate to the signs of time, place and “personality”. The idea of conducting a continuous study is associated with the desire to obtain comprehensive information about the phenomenon being studied. The volume of the population, and therefore the volume of continuous research in scientific and routine research, are significantly different.

If we assume that the purpose of a scientific study is to find out the causes of the onset and spread of this disease at present as a whole, and not in some territorial population group, then the population in this case should be the entire population that is prone to the risk of this disease [6].

Table 1

Key concepts that characterize features

of epidemiological trials

Classification sign	Trial name
Trial name	
- Describe the incidence or other phenomenon that belongs to the subject area of epidemiology - Explain the established manifestations of incidence, etc.	- descriptive - - analytical (case-control trial and cohort trial)
General scientific method	
- observation - experiment	- observational - experimental (randmozed field and clinical trial)
The volume of the studied phenomenon	
- total fenomenon (general population) - specially selected part of the phenomenon	- continuous - selective
Type of cognitive activity	
- scientific (special) - daily	- scientific (special) - routine
The presence of the studied events at the beginning of the study:	
- event already happened - events are predicted - events have occurred, but new events are predicted	- retrospective - prospective - combined
Study time	
- definit moment - definite time period	- instant (transversal) - dynamic (longitudinal)
Study Location	
- in the clinic or other health care facilities - out of clinic	- clinical - field

If the purpose of scientific research is to study the causes of diseases only in a given country or city, then a population is the corresponding population of a country or city. The total population in routine analytical studies is even smaller in volume, for example, when investigating an outbreak of a disease in an “organized” group of children. In this case, the population is all children and all

personnel of this institution or one (several) groups, depending on the initial hypothesis about the cause of this outbreak [4].

Despite the full study of the phenomenon, one should not think that the results of a continuous study are a priori more accurate than a selective one. The accuracy of continuous research data depends on many factors. For example, if a continuous study is large-scale, then a lot of employees participate in its conduct, it is rather difficult to standardize their qualifications, this will affect the results of the study. The main disadvantages of continuous research are the large expenditures of time, effort and resources, often the impossibility of their implementation [7].

Overcome the shortcomings of continuous allow selective studies, which are the main special tool of many sciences [2].

Selective trials. Selected epidemiological studies are based on data obtained in the study of the incidence of a relatively small part of the population - the sample. Based on them, conclusions are drawn about the features of the studied phenomenon in the entire population (general population) with which this sample was formed. Thus, the purpose of sample studies is to obtain representative information that could be extrapolated to the entire population [5].

The correctness of the data directly depends on the representativeness of the sample, which, first of all, is determined by the correct choice of the general population. Subsequently, part of the units of observation is selected from the general population. At the request of the researcher, the general population can be limited by various signs (time, territory, age, profession, and other social and biological characteristics of people) [3].

In addition, sample representativeness is provided by:

• the required number (volume, size) of the sample;

• compliance with the principle of randomization [2].

The size of the sample depends on many components, and primarily on the nature of the study. If the purpose of the study is to estimate the incidence among the population, then it is necessary [6]:

• select (set) the degree of reliability of the measurement of incidence, ie the value of the possible deviation of the sample data from the data of the studied population;

• approximately know the frequency of diseases that can be established.

If the population size is unknown, the sample size is calculated by the formula [4]:

$$n = \frac{T^2 \times (I \times q)}{\Delta^2}$$

If the population size is known, the sample size is calculated using a different formula [2]:

$$n = \frac{I \times q \times t^2 \times N}{(N \times \Delta^2) + (I \times q \times t^2)}$$

where (for both formulas)

n – sample size;

N – population size;

t – критерии вероятности (often about 1,96);

I – expected incidence rate;

q = R – I, where R – dimension of I index, which is used;

Δ – selected maximum permissible error of the indicator, which usually is not more than 25% of the indicator I.

Suppose that in the city of N it is planned to conduct a simultaneous selective study to study the frequency of new cases of hypertension among men aged 20-29 years. The population of this group in the city of N is 15,400. According to a study conducted several years ago, the incidence of new cases of arterial hypertension in this group of men in the city of N was about 70.0 ‰ (I = 70.0 ‰). That is, Δ is 25% of 70.0, i.e. Δ = (25 x 70.0) / 100 = 17.5 ‰. Δ2 = 306.2 ‰. As a result

$$n = \frac{(70{,}0 \times (1000 - 70{,}0) \times 22 \times 15\,400)}{(15\,400 \times 306{,}2) + (70{,}0 \times (100000 - 70{,}0) \times 22)} = 806$$

Thus, to obtain vibration data, respectively, of the necessary reliability, out of 15,400 people of 20-29 years old, 806 people should be examined [10].

The second condition for achieving representativeness of the sample is the principle of randomization (from the English. Random - case). Randomization provides random selection from among individuals representing the general population. In other words, randomization is an equal chance for each unit of observation from the general population to fall into the sample, which reduces the risk of inadvertently distorting the composition of the sample, but cannot exclude the dishonesty of the researcher during its formation [3].

Compliance with the principle of randomization is provided by various sampling methods. The choice of method depends on:

• from research design;

• expected accuracy of the results;

• total population;

• the possibility of using the most accurate method and other objective and subjective reasons [6].

At present, the ideal principle of randomization is the use of random number tables or similar computer programs for sampling observation units. This method provides random selection in which the unit of observation is selected from the population only once. This approach is mandatory for the formation of an experimental and control group during the majority of RCTs of various means and methods of treating patients. This contributes to adhering to the principle of impartiality of research and minimizing unintentional distortion of group composition. And to a large extent, subject to research design, it provides reliable conclusions. However, it should be remembered that no design can completely exclude dishonesty of a particular researcher [5].

The following methods are based on a certain plan in the selection of units of observation, which, of course, reduces compliance with the principle of randomization [4].

Mechanical selection. First, the units of observation are arranged in order based on some random sign: the number of the medical history, outpatient card, the first letter of the surname, etc. Then it is necessary to determine the interval after

which the units of observation will be mechanically selected from the list of the population (for example, every fifth). To determine the interval, the size of the population should be divided by the size of the required sample [2].

Typological (typical) selection. First, the general population is divided into groups according to some typical characteristic. Most often, various individual characteristics of people are used, such as age, profession, influence of perceived risk factors, illness, etc. Next, the required number of observation units is selected randomly or mechanically from each group. The sample size from each group should also be predetermined, and the ratio of sample sizes (for example, by age) should correspond to the structure of the population. Such a sample is often called a weighted typological sample. This method is most often used in observational analytical studies [5].

Series (socket) selection. Series (socket) selection is almost like typical. The difference is that during serial selection from the general population, not individual observation units are randomly selected, but their entire groups, which are called series, or “sockets”. “Sockets” can be individual institutions, workshops, medical stations, departments, wards, etc. Then, in each “socket”, a continuous study of all observation units is carried out [3].

Directional selection method. The method of directional selection provides, even at the stage of determining the general population, to exclude from the analytical study some factors whose influence is well known. For example, the effect of smoking on the risk of lung cancer is well known, but this is not the only factor. Therefore, researchers who aim to identify other additional risk factors for lung cancer should not be included in the population, and therefore in the sample of people who smoke. The advantage of a selective study over a continuous one is that with the right organization, reliable data can be obtained by spending much less effort, money and time. When conducting sample studies due to their smaller volume, it is much easier to control the receipt of unified information and minimize possible errors. However, for objective reasons, in many studies, the so-called biased samples are studied, which are insufficiently representative of the

entire population, which should be taken into account when assessing the conclusions of such studies [6].

Description of some of the terms defining the design of epidemiological studies.

Descriptional study involves obtaining descriptive epidemiological data, that is, data on incidence. Such a study may be independent, but the new descriptive epidemiological data obtained encourage the same or other researchers to continue the study in order to explain the manifestations of the incidence. Therefore, a descriptive study is, as a rule, only the first part of a full-fledged epidemiological study; it necessarily also includes the analytical part [2].

Analytical study is dedicated to identifying the causes of the onset and spread of diseases. The search process corresponds to general scientific ideas about two methods (directions) of revealing the connection between the alleged cause and effect. The first trick is from investigation to reason. When using it, starting from a preliminary investigation (for example, illness), they try in the past to find events that could be considered as the causes of this consequence. Another trick is from cause to effect. Focusing on the impact of the alleged cause, they expect the appearance of a causal effect [4].

According to the methods of searching for causes, two types of analytical studies have been developed: case-control and cohort study. Study **case-control** – analytical retrospective study, the purpose of which is to identify risk factors for the studied disease. The main group is selected from people with a disease that is being studied, the control group consists of people who do not have this disease. The fact of the influence of the studied risk factors is determined by a survey of persons in the compared groups, their relatives, according to archival data. A comparison of the frequencies of individual factors in the main and control groups allows us to calculate the odds ratio indicator (OR), the value of which tentatively assesses the presence of a causal relationship [6].

Observational study does not include interference in the natural process of the onset and spread of diseases. They also include the study of incidence in

situations where intervention has become a mandatory practice. For example, a routine study of the incidence of immunosuppressed infections [7].

During **experimental** study, vice versa, it provides for controlled intervention in the natural course of the incidence in order to identify its causes. Moreover, the epidemiological experiment must fully comply with other general scientific requirements for any experiment. In this regard, some authors use the terms "natural", "uncontrolled epidemiological experiment" are incorrect. Since as a result of the experiment it is necessary to answer the question why it happened as described in the experiment, any experimental study is always analytical [9].

Scientific (special) study is organized specifically to obtain (confirm) new data [2].

Routine – any epidemiological study, in the framework of official duties. It does not provide for the receipt of new scientific data; on the contrary, a routine study is carried out within the framework of the currently existing scientific ideas about the causes of the onset and spread of the disease. A typical example is the investigation of an outbreak of an infectious disease, when the search for the cause of its occurrence is based on the existing scientific understanding of the possible causes of such outbreaks [3].

Retrospective study is based on the study of information about cases of the disease that occurred at any time in the past, and the first method of searching for cause-effect relationships is used - from investigation to cause. The main source of information is the existing system of registration and registration of patients. A retrospective study can be either descriptive or analytical [6].

Prospective study involves the study of information as new (fresh) cases of the disease do not exist before the start of the study, the study of cause-effect relationships is based on the second method - from cause to effect. In this case, the study is based on the likelihood of new cases of the disease (consequence) among the population affected by the risk factor (cause). Prospective studies are always analytical [4].

Instant (transversal) studies can be both descriptive and analytical. Apparently, therefore, in various epidemiological publications they are referred either to descriptive or to analytical studies. In any case, the main goal of these studies is to obtain information about the incidence of a population of a disease for a limited period of time, if necessary, such studies can be repeated. Since a simultaneous study involves identifying all current cases of the disease, it is also called a prevalence study (incidence), and the results of a simultaneous study are often provided in terms of prevalence. If cases are identified that are associated with exposure to any risk factor, the study may become analytical [2].

Dynamic (longitudinal) the study involves a systematic study of information on incidence among the same population. In this case, the study can be continuous or repeated at short intervals. A typical example of a dynamic study is a routine operational and retrospective analysis of the incidence of the population, conducted by specialists of the centers for sanitary and epidemiological surveillance [3].

Although the concept **«clinical»** associated with the location of the epidemiological study, it is used only to indicate experiments conducted in the clinic, to assess the potential effectiveness of drugs, diagnostic methods, treatment regimens for patients. Such studies are called RCT [5].

Field considered a study conducted outside of health care facilities. Its scope is very diverse, from an investigation of a small fire to a nationwide study [4]. Field research may be:

- descriptive and analytical;
- observational and experimental;
- continuous and selective;
- routine and scientific;
- retrospective and prospective;
- instant and dynamic.

None of the above terms can independently reveal all the features of an epidemiological study. For example, studies of an outbreak of a disease are not

only observational, but also analytical, most often routine, continuous, simultaneous, retrospective or combined clinical or field research [3].

The organization of the research is a coordinated, ordered, interconnected set of various actions leading to the achievement of the intended goal [10]. Consists of several stages:

• preparatory;

• collection of information and initial statistical processing;

• statistical and logical analysis of the information received;

• formulation of vivods (final stage).

The preparatory phase includes:

• justification of the relevance (necessity) of the study;

• formulation of the final (final) and intermediate goals;

• formulation of a working hypothesis;

• selection of an object and unit of research;

• compilation of a program;

• planning;

• conducting a pilot study [10].

Most epidemiological studies provide for the achievement of an analytical goal, that is, they are aimed at identifying the causes of the occurrence and spread of the investigated pathology. The first part is a descriptive section. No less important are studies devoted to assessing the potential effectiveness of the proposed means and methods of combating the spread of diseases. In practice, it turns out not potential efficiency, but the real quality and effectiveness of executive activity [6]. According to the data obtained in the analysis of the literature and the goal, a working hypothesis is made - a possible explanation of the phenomenon being studied. For example, a hypothesis about the causes of the occurrence and spread of an insufficiently studied disease, or (for routine research) a hypothesis about the causes of an outbreak of some disease, but within the framework of the possible causes known to science of its occurrence. The working hypothesis determines all further actions and a significant part of the entire research design.

During the study, adjustments may be made to the working hypothesis, but if this leads to a change in the program, then the study should be started from the beginning [3, 4].

The object of research (observation) in epidemiological studies are comparison groups, which are called differently in different studies:

- exposed and unexposed;
- sick and healthy;
- main and control;
- test and control, etc.

These groups consist of sick and (or) healthy people - observation units, each of which is subject to mandatory registration. It is extremely important, both in scientific and in practical studies, already at the preparatory stage to determine the criteria on the basis of which a person will be considered sick, that is, to formulate the signs of a standard case of a specific disease. Sick and healthy people (units of observation) are carriers of various accounting signs. Those. signs that are supposed to be taken into account (registered) are called accounting [6].

The research program includes a data collection program and a program for summarizing and grouping data. An information collection program is a registration document that exists or is specially designed, which contains a list of accounting features necessary to fulfill the intermediate and final goal of the study. Accounting features are used in the following steps to group the received data, therefore they are grouping features. There are various classifications of accounting (grouping) features [7].

The main epidemiological classification of grouping signs is based on the allocation:

- diagnosis;
- signs of time;
- signs of a place (territory);
- signs of “personality” (individual signs) [5].

With the help of such signs, it is possible to make distributions to groups of patients and healthy individuals. In addition to this classification, accounting features are divided, in particular, into factorial (factorial) and effective. Factor - these are the signs under the influence of which the state of human health changes. Effective signs are different assessments of a person's health status, including test results and a diagnosis [4].

The separation of accounting signs into factorial and effective should be justified by the working hypothesis of a causal relationship of the alleged risk factors and morbidity. Often, all signs are divided into those associated with the unit of observation - a sick or healthy person, they are called personality factors, and environmental signs - environmental factors [8].

In addition to accounting signs, each registration document must contain a "passport" part [7]. It indicates:

• number of registration document (this unit of observation);

• Date of completion;

• insurance policy number;

• identification;

• name of the patient;

• increase other data required for any research. The registration document ends with the signature of the person who completed it [7].

A program for summarizing and grouping data is a set of layouts of tables that are often called developed ones. They are supposed to be used in the second stage of the study. They will enter the accounting signs from the registration documents. The layout should be such that the table after filling contains all the features of the studied phenomenon that are supposed to be detected. Thus, the layouts of the tables should correspond to the goals and working hypothesis of the study [6].

Table layouts are not just technical work, but mainly focused, thoughtful actions. The main thing is the choice of features for grouping, necessary to build a specific table. In epidemiological studies, all three types of statistical tables are used: simple, group and combined [5].

A research plan is a document that reflects all the basic actions necessary to achieve goals. At the same time, the plan indicates the place, time of the study, the necessary financial and technical means, personnel, the level of their training, the timing of individual actions, etc. As a result, the design of this epidemiological study is finally determined, which should contribute to the achievement of the goals [3].

Currently, when organizing scientific epidemiological studies, great importance is attached to the so-called pilot (trial, oriented) studies [7].

Pilot studies, in particular, allow:

• clarify goals and a working hypothesis;

• clarify the program for collecting information and layouts of tables;

• check the methods of collecting information and methods for its study;

• assess the preparedness of staff;

• get an idea of the variability of accounting features;

• evaluate the correctness of the choice of research design;

• clarify the amount of necessary funds and forces;

• specify the time [8].

An important stage is the collection of information and its primary statistical processing.

Information collection refers to the process of obtaining the necessary data and filling out registration documents. It is necessary to strictly observe the rules developed by the information collection program, not to allow violations of the rules for the selection of observation units, exclusion of accounting signs, changes in the methods and methods of collecting information. In the process of collecting information, its quality is periodically evaluated, and compliance with established rules is monitored [4]. The information that is collected is repeatedly summarized and grouped in accordance with the layouts of the tables. Such actions are called primary statistical processing of research data. The duration of the stage, depending on the design of the study, can range from several hours (outbreak investigation) to several tens of years (prospective cohort study). In general, data

collection lasts as long as necessary to obtain the necessary amount of information provided by the research program [6].

The final stage of the epidemiological study includes further statistical and logical processing of the information received, the organization of the obtained epidemiological data and a description of the study, the formulation of conclusions (conclusions) [2].

Further - after erection and grouping - statistical data processing can be quite diverse and include a significant number of statistical methods. These methods make it possible to comprehensively and reliably describe the dynamics and structure of the incidence rate, as well as measure the causal relationship of the alleged risk factors and the incidence rate. Despite the variety of statistical methods, the choice of a particular method should be strictly statistically and logically justified. Violation of this rule will inevitably lead to erroneous conclusions [3].

To study the information collected and present the results of the study, the so-called organization of epidemiological data, that is, their tabular and graphical display, is of great importance. During the final stage, new tables are created in which the results of a statistical evaluation of the differences of the compared values are necessarily indicated [5].

A graphical display of the information obtained allows us to demonstrate the features (patterns) of the dynamics and structure of the phenomenon under study that are available in the table. However, it should be borne in mind that incorrectly constructed diagrams can substantially or even completely distort the regularities in the tables [4].

The description of the study (report) should reflect in detail the entire course of work.

Formulation of conclusions (conclusion) is based on the results of statistical and logical study of the collected information [4].

Study case-control. The purpose of the case-control study is to determine the causes of the occurrence and spread of diseases. In case-control studies, the

probability of a causal relationship is justified not by a different incidence rate, but by the different prevalence of the putative risk factor in the main and control groups [6].

In a case-control study, the search for causal relationships goes in the direction from the investigation to the alleged cause [4].

Case-control research can only be retrospective, since it is based on archival data. Most often, the source of information in case-control studies is the medical history stored in the archives of medical institutions, the memories of patients or their relatives in an interview or according to a survey [3].

This type of study can be carried out as a preliminary study of causal relationships between the alleged risk factor and a specific disease. In the future, this issue can be studied in cohort studies [2].

Stages of conducting a case-control study. A case-control study (Fig. 2), like a cohort study, begins with the definition of the general population, that is, that part of the population over which the research will be conducted. The inclusion and exclusion criteria approved at the preparatory stage of the study are taken into account. Here, one should take into account such individual characteristics of potential participants as gender, age, race, place of work, bad habits, etc. The territory of the studied population and the exposure time of negative factors are important [4].

Then carry out the formation of the sample. In case-control studies, participants with a specific pathological condition are recruited [5].

<table>
<tr><td rowspan="4"></td><td rowspan="2">Sign (disease) is present (group of study)</td><td>Hypothetical factor (F+) – a</td></tr>
<tr><td>Hypothetical factor (F-) – b</td></tr>
<tr><td rowspan="2">Source population</td><td colspan="2" rowspan="2"></td></tr>
<tr><td rowspan="2">Sign (disease) is absent (control group)</td><td>Hypothetical factor (F+) – c</td></tr>
<tr><td></td><td>Hypothetical factor (F-) – d</td></tr>
</table>

Picture 2. Case-control sample study algorithm

These persons will be represented in the main group. The control group includes conditionally healthy participants who do not have the studied disease. As a result, the sample in cohort studies is half composed of patients, and the other half is represented by relatively healthy participants [7].

One of the methods for the formation of the main and control groups is the method of matching pairs. The meaning of this approach is to individually select each participant in the main group of the control group participant, taking into account a number of anthropometric, gender, social, ethnic and other characteristic features. As a result, researchers get approximately the same comparison groups with the only difference: the presence or absence of the studied disease [6].

The next stage of the study is the determination in the main and control groups of people who were and were not exposed to the expected risk factors [5].

Then the data on the presence or absence of the studied risk factor in the main and control groups are summarized in the contingency table (Table 2). The stage of the distribution of the main and control groups into subgroups (a F +, b F-, with F + and d F-) can be repeated as many times as the risk factors were identified as a result of the study of archival data [3].

Table 2

Layout of a four-field table for case-control studies

Groups	History of risk factor		Total
	Present	Absent	
Sick	a	b	a + b
Conditionally healthy	c	d	c + d
Total	a + c	b + d	a + b + c + d = N

According to the rule of constructing tables in the rows of the table indicate the group: the main - people with the studied disease, the control - relatively

healthy people. The column lists the criteria by which groups of participants are compared (presence or absence of the influence of a risk factor) [6].

The final stage of the study is a statistical and logical analysis of the data obtained and the formulation of conclusions [2].

Statistical processing of data in case-control studies. Since incidence and relative risk indices cannot be calculated in case-control studies, the severity of causal association in case-control studies is determined by differences in the frequency of exposure (detection frequency) of risk factors in the comparison groups, and not by differences in the frequency of diseases in the compared groups [4].

The frequency of exposure to risk factors in these groups is calculated using the same formula as the absolute risk in cohort studies, i.e. a / (a + b) for the main group (cases), and c / (c + d) for the control group [6]. The estimated frequency of exposure reflects the value of the probability of influence of the studied factor in the compared groups. Further calculations of the odds ratio are carried out according to the methods considered in the example of cohort studies [5].

A simplified formula for calculating the odds ratio is:

$$OR = \frac{(a \times d)}{(b \times c)}$$

However, there is a difference between the odds ratio obtained in cohort studies and case-control studies. In cohort studies, the odds ratio for the presence or absence of a risk factor is calculated, and in case-control studies, the odds ratios for the expected risk factors for patients and healthy participants are estimated [6].

In case-control studies, it is possible to calculate the indicator of the etiological part (EP) according to the formula:

$$EP = \frac{OR - 1}{OR} \times 100\%$$

In this situation, the indicator indicates the proportion of the number of cases of the influence of the risk factor, which leads to the studied disease [4].

The reliability of differences in the results of a case-control study in the compared groups is assessed using the criteria used in cohort studies: confidence

intervals are calculated for the Pearson criterion (chi-square) or Fisher's exact test [6].

The positive aspects of the case-control study are the possibility of their implementation, regardless of the prevalence of the disease under study, the relatively small expenditures of time, effort and funds necessary to create the main group of patients, select a control group for them, interview and create indicative conclusions. When studying such diseases in a cohort study, one would have to select a cohort from hundreds of thousands of people and observe them for a long time. This would lead to significant time, material and moral costs [4].

Case-control studies have a relatively short duration. The duration of the study depends on the performance of the personnel participating in the study. To obtain conclusions, it is not necessary, as in a cohort study, to monitor for a period exceeding the latent period of the development of the disease [7]. It is possible to simultaneously detect several risk factors for one disease. Case-control studies are characterized by relatively low economic costs. This makes them attractive when the researcher is limited in funding. However, we should not forget that each study has its own limitations [2].

In a case-control study, it is not possible to identify rare causes of the disease. In such cases, scarce data do not allow us to assess the reliability of differences in the frequency of the risk factor in the comparison groups and, therefore, draw conclusions about the presence or absence of a causal relationship [7]. Another drawback of this study is the inability to quantify the risk of illness (death) from the alleged cause. In the study, only the OR index is quantified. As a result, the researcher receives a low reliability of conclusions due to the high propensity for systematic errors [5].

Transversal studies (prevalence studies, simultaneous studies)**.** The goal of a cross-sectional (one-stage) study is to describe the relationship between a disease (or other health conditions) and factors that exist in a particular population at a particular time and have both a beneficial and a negative effect on people [9]. Concurrent studies often form the basis for addressing operational management

issues in healthcare. This is due to the possibility of constant updating of data on the health status of individual contingents by examining small groups of the population [2].

This study is performed at a certain point, but facts gathered may relate to past events (for example, examining outpatient patient records to examine how often blood pressure was measured over the past 6 years). A cross-sectional study assesses the prevalence of cases and the prevalence of risk factors, as well as their combination [10].

In fig. 3 it is shown the comparative characteristics of case-control studies, cohort studies, and cross-sectional studies.

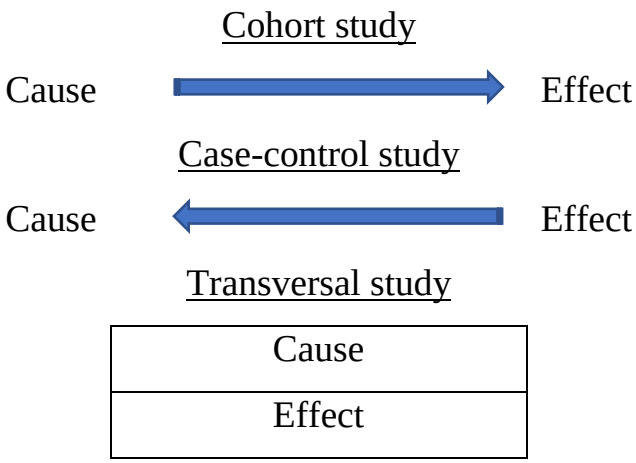


Figure 3. Comparative characteristics of three analytical studies

Unlike cohort and case-control studies (i.e. longitudinal studies), in a transversal study (transverse to the time axis), risk factors and diseases are studied simultaneously [9].

Stages of a transversal study

- Formation of a sample (cohort) from the general population, taking into account signs of inclusion and exclusion. The sample should be qualitatively and quantitatively representative [8].
- Collection of information on the prevalence of risk factor and disease. Each study participant undergoes a medical examination using a physical examination, laboratory tests and the necessary methods of functional diagnostics. Experts most often learn about the influence of risk factors from patients themselves, relying on their memory and awareness. They collect

industrial history, information on the socio-economic and domestic status of participants, heredity, etc. [2].

As a result of a simultaneous examination of the sample (cohort), four groups of participants are formed [4]:

- sick people who are affected by the studied factor;
- sick people who are not affected by the studied factor;
- healthy participants affected by the studied factor;
- healthy participants who are not affected by the studied factor;

• Description of the clinical picture of the disease, as well as the establishment of cases of the influence of the alleged risk factors [4].

• Formation of hypotheses about risk factors, diseases and their relationship [4].

• Calculation of indicators. In simultaneous studies, as already mentioned, the prevalence (prevalence) indicator is calculated [4].

• Assessment of significance of differences [4].

Advantages of the study: a description of the clinical picture of the disease while recording the fact of the influence of the studied cause; simple algorithm of carrying out; informational content; low economic costs [3].

Disadvantages of the study: lack of a comparison group; the inability to unambiguously establish causal relationships, since during cross-sectional studies they do not receive direct data on the sequence of events [8].

Example. A cross-sectional study revealed that overweight is more common among women who are diagnosed with arthritis and, accordingly, less common among those who have no arthritis. Could overweight exert an excessive load on the joints, as a result of which arthritis developed, or, conversely, women with arthritis showed low physical activity, which caused them to accumulate excess body weight? It is impossible to get answers to these questions in cross-sectional studies [1]. This type of study is not suitable for the analysis of the prognosis, since in prevalence studies it is impossible to identify the incidence of new cases of the disease (as in cohort studies), which means that the indicator cannot be used to

calculate the likelihood that people with similar characteristics will have the same event in future [4].

Analytical studies. In medicine, analytical studies are necessary to quantify the causes of the onset and spread of diseases of various etiologies. The results of these studies are used in the development of preventive measures aimed at eliminating or reducing the degree of exposure to factors leading to illness or other consequences [5].

Analytical studies have made a significant contribution to the development of modern medical science and practice, identifying the leading risk factors for the development of many diseases. For example, a link has been established between lung cancer and tobacco smoking, a higher prevalence of cerebral stroke among people with hypertension, a direct relationship between rubella in pregnant women and congenital malformations in children, a causal relationship between hypertension, smoking, high blood cholesterol and coronary heart disease, etc. [2].

Analytical studies are part of a group of observational studies, the main condition for which is non-interference in the natural course of the processes of the onset and spread of diseases (in contrast to experimental studies) [4].

At the stage of organizing any scientific research, a working hypothesis is formed, which implies the prediction of the result for which this research is organized. In analytical studies, the working hypothesis implies the difference between the research group and the control one, that is, it is assumed that the studied factor has a causal relationship with the investigated result of exposure, for example, by a disease. There is an alternative to the working hypothesis - the null hypothesis, which experts refute during the study. According to the null hypothesis, the studied groups of people do not differ from each other or the differences between them are statistically unreliable, and the putative risk factor or etiological factor is not such [3].

William Farr (1807-1883) - an English scientist, one of the founders of medical statistics, identified signs of personality, place and time, according to

which they systematize and analyze data obtained in studies [9]. Thus, analytical studies should answer a number of questions:

• why is someone sick more often and someone less?

• why is somewhere sick more often, and somewhere less?

• why are sometime sick more often, and sometime less often?

The question “Why?” Implies the search for a cause with a known consequence or the determination of a consequence from a known cause: in any case, the task is to establish a cause-effect relationship between cause and effect [1].

The final result of the analytical study is the determination of the cause or probability of the existence of this cause with a known consequence [1].

Causes and effects. David Hume (1711-1776), a Scottish philosopher, defined the cause as "an event followed by another, and when after all events like the first, an event similar to the second is observed." According to this consideration, the cause always precedes the investigation, it is a necessary condition for its occurrence. However, in medicine there are cases when the action of any pathogenic factor does not always lead to the onset of the disease [4].

The causative dependence of the disease (incidence) on any factors varies. Therefore, in addition to the term “cause”, terms such as “necessary reasons”, “sufficient reasons”, “component causes”, “additional reasons” and “risk factors” (causal factors) are used [5].

Necessary consider the cause (one or more) if, in its absence, the occurrence and (or) spread of the disease is impossible. So, in the etiology of infectious diseases, pathogens are necessary. For example, without infection with the influenza virus, individual cases of influenza cannot occur. At the same time, a flu epidemic will not occur in the absence of the required number of susceptible persons [5].

Sufficient is called complex of causes and spread the disease. Occasionally, sufficient reasons are sporadic. For example, it is believed that infection with the rabies virus and the death of a sick person inevitably leads to death [13].

However, as already mentioned, the risk of the onset and spread of diseases, especially non-communicable, is most often associated with the combined influence of several factors [10].

At first glance, the complex of causes of the spread of infectious diseases is less complicated. For example, it is reliably known that the spread of anthroponosis is impossible without the presence of a reservoir (source) of infection, an appropriate method of transmission of the pathogen (transmission mechanism) and a sensitive collective. In other words, the source of infection, the transmission mechanism, and the susceptible collective are components, moreover, causes are necessary [11].

But are the necessary causes of the spread of infectious diseases at the same time sufficient reasons? There is no answer, since each necessary reason is only a potential danger [6]. For the real process of the spread of infections, it is necessary not only the presence of the three indicated necessary causes, but also their inextricable link, which in most cases is carried out due to social factors. Social factors, turning the potential danger of the necessary causes into the real one, can both sharply worsen the epidemic situation and reduce the incidence to minimum values [7].

Thus, the complex of sufficient causes of the spread of anthroponosis is not limited to the set of source of infection, transmission mechanism and susceptible staff. It necessarily includes the necessary social, sometimes climatic factors, providing an inextricable link between the necessary reasons. It is the activity of social factors in the complex of sufficient reason that determines the intensity of the distribution of anthroponoses [8].

To explain causality, several of its models have been created, that is, intentionally simplified ideas about the cause-effect relationships of factors and disease. One of these models, proposed by Rothman C.J., is shown in Fig. 4.

Rothman’s scheme clearly demonstrates that the onset and spread of any disease is associated with many factors. Moreover, some components relate to

necessary reasons, and various combinations of components form various sufficient reasons [9].

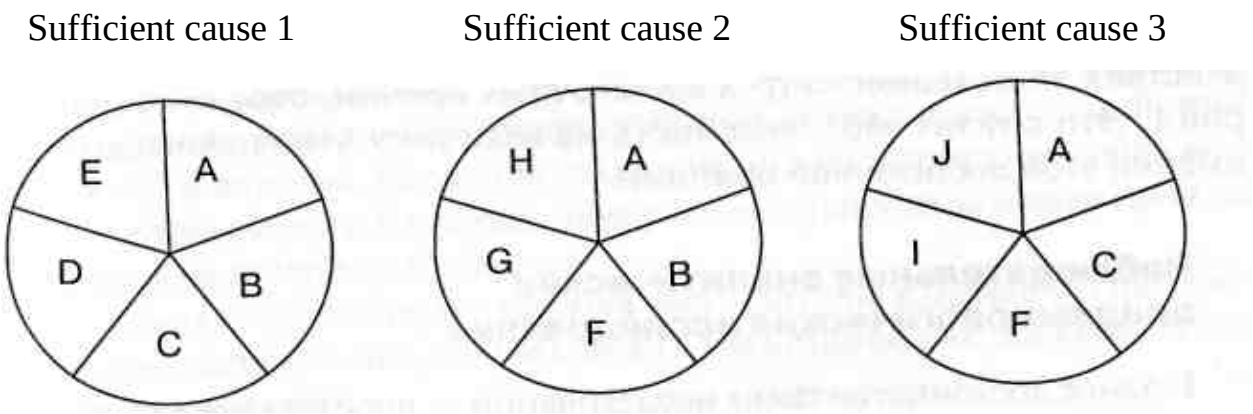


Fig. 4. The structure of the causes of a hypothetical disease

Please note that the diagram shows a hypothetical disease that occurs under the influence of three sufficient reasons indicated by circles. Each sufficient reason is formed from five component causes identified by sectors with letters, and most of the component causes in different circles are different. Only reason A occurs in every sufficient reason, therefore only it should be considered a necessary cause of this disease. The remaining components of the reasons are considered as additional. Thus, an additional reason is any component, except for the necessary reason [9].

Each cause forms the corresponding part of the incidence, which is called the etiological part (EP). The etiological part is the specific gravity (share) of those cases of the disease that could have been avoided if there was no exposure to the risk factor [2].

The scheme is very convenient for demonstrating the capabilities of medicine in the prevention of diseases. To prevent the occurrence of diseases, it is not necessary to wait for the clarification of all the components of the causes [4].

Elimination of the influence of only one component of the cause causes an effect equal to the effect of eliminating the influence of all sufficient causes that include this component [4].

So, the elimination of not only the component, but also the necessary reason A in the Rotman scheme will lead to the complete prevention of all cases of this disease.

Elimination of the additional cause E will lead to the termination of only one of the three sufficient reasons, indicated by the number 1. This will reduce the incidence by the magnitude of the EP of this particular good reason. [2].

Observational analytical epidemiological studies. The main advantage of such studies is the ease of conducting. This is due to the fact that they usually use official data on registration of diseases and their consequences and official information on possible risk factors. For example, data on the state of the external environment, information on the economic situation of various groups of the population, their individual characteristics [6].

Observational studies are characterized by a general rule - any analytical studies begin with a descriptive stage.

The identification of significant differences in the manifestations of the incidence of various population groups is the basis for developing working hypotheses about risk factors for the occurrence and spread of diseases. And only after the formation of the working hypothesis, they begin to test it in analytical studies [8].

According to the characteristics of the organization, there are three main options for observational analytical studies:

• cohort study;

• case-control research;

• transverse (simultaneous) study.

Additional analytical research options:

• environmental (correlation) research;

• retrospective epidemiological analysis [9].

In additional research options, the selection of comparison groups is most often formal in nature, therefore they cannot be fully considered as full-fledged

analytical studies, despite the fact that the results of such studies allow us to draw preliminary conclusions about the causes and spread of the studied diseases [5].

Cohort studies. The purpose of cohort studies is to determine the causes of the onset and spread of diseases. This is the most direct way to identify the etiology of diseases and quantify the risk of exposure to causal factors. The name of the study comes from the word “cohort” (a group of people) [6]. In various fields of human activity, the concept of "cohort" has its own characteristics:

• a military unit, a tenth of the legion in ancient Rome with a numerical strength of 360-600 people (one cohort, as a rule, included 3 maniples);

• figuratively - a homogeneous group of people, associates;

• in medicine - a sample of people united by common signs of a state of health in which cases of the disease are expected [5].

In any cohort study, the identification of the relationship between the causes of various consequences occurs in the direction from the alleged cause to the effect, most often from the risk factor to the disease [3].

Cohort studies can be based on three types of information:

• retrospective (archival) data (case histories, questionnaires, results of a survey of participants, etc.). Such cohort studies are called retrospective or historical;

• prospective data, which include the receipt of information during the study. Such cohort studies are called prospective (parallel) cohort studies;

• mixed data (prospective and retrospective) - combined cohort studies [2].

There are four algorithms for conducting cohort studies, depending on the number of risk factors studied and possible outcomes.

The first algorithm is the simplest [2], but less rational. In such a cohort study, the relationship between one risk factor and a specific disease is examined.

At the first stage, the population of people in relation to whom it is planned to conduct research is determined, that is, the so-called general population is distinguished. This is done taking into account signs of inclusion and exclusion from the study. For example, the aim of the study is to establish the relationship

between pregnancy and hypertension in women who gave birth in Kiev. In this situation, the general population will be represented by all residents of Kiev of childbearing age [2]. But here we are only talking about signs of inclusion. The personal characteristics of potential participants that may interfere with the proper conduct of the study (signs of exclusion) should be considered. Returning to our example, it should be pointed out that the general population is not all women of childbearing age living in Kiev, but only those who at the moment are not yet suffering from hypertension, who are not burdened with a hereditary history, etc. Thus, they determine part of the population among which participants are recruited for this cohort study. A significant condition at this stage is the inclusion of only healthy participants in the study (the absence of the disease, which is likely to appear during the study) [2].

Cohort studies are most often selective, so the next stage of the study is the formation of a statistical sample that is qualitatively and quantitatively representative. Such a sample is called a cohort [4].

A sample is qualitatively representative if its composition is as close as possible to the general population, for example, by age, gender, anthropometric indicators, socio-economic status, living conditions, etc. [3].

The quantitative representativeness of the sample is achieved by selecting the required number of participants. A fair question arises: “How many observation units are needed for a sample to be quantitatively representative?” [1].

Suppose there is a need to calculate the likelihood of an “eagle” and “tails” falling when tossing a coin. The simplicity of the experiment lies in the fact that the already known result is 50% to 50%, which will help to evaluate the correctness of the study. If the number of coin tosses (the number of observations) is ten, the ratio of the two options may differ from our expected result [1]. However, with an increase in the number of observations, the expected effect appears — the ratio of the “eagle” and “tails” becomes approximately the same. In further observations, the result will not change. That is, there is a certain number of observations, after which there is a stable pattern that we were looking for, or, in

the case of a coin, a known ratio of 50 to 50. This state of affairs describes the law of large numbers [1].

Representativeness of the sample is necessary to extrapolate the data obtained in the study to the general population. In other words, the results of a sample study should be relevant not only for the sample itself, but also for all people with similar characteristics [4].

As a result of the formation of the cohort, a group of relatively healthy people appears in the study. This constitutes an important research condition. Approximately half of the cohort participants are exposed to the risk factor; the rest of the sample is not affected by the risk factor [2].

The next stage of the study is the division of the cohort into two groups: the main and control. The main group is represented by participants affected by the risk factor (F +). Such a group is called an exposure group. The control or unexposed group is represented by individuals without a risk factor (F-). In our example, the main group consisted of women giving birth, the control group - those who did not give birth [2].

Subsequently, observations are made for both groups. The observation period is determined in advance. Most often, it is determined by the average duration of the exposure period or incubation period. During this period of time, the study participants with a specified frequency visit the medical institution, where they undergo a medical examination for the occurrence of the expected result (illness) [2].

At the end of the observation period, the study participants are divided into four groups: group a - patients who were affected by the risk factor, group b - healthy patients, on whom the risk factor also acted, group c - patients from the control group and group d - healthy people in whom the risk factor had no effect [2].

The last stage of the study is logical and statistical data processing.

The following cohort study algorithm involves the identification of one risk factor, leading to the development of several results. The difference from the

previous option is that the separation of the main (F +) and control (F-) groups into patients and healthy is carried out separately for each nosology [2].

An example of such a study is the identification of a causal relationship between smoking and diseases associated with this risk factor (stomatitis, chronic bronchitis, coronary thrombosis, lung cancer, etc.). A similar study was conducted on a cohort of English doctors, some of whom smoked, while others did not have such a bad habit [2].

The third type of cohort study algorithm involves the identification of several risk factors for one disease under investigation. In a similar study, as in the previous algorithm, the separation into comparison groups is carried out after the end of the observation period [2].

The main (F +) and control (F-) groups in this algorithm are determined several times by the number of risk factors studied, that is, each risk factor has its own pair of comparison groups. The main condition for such a study is the independent effect of the studied factors on the human body. Otherwise, it is possible to detect the specific effect of a specific risk factor on the human body [2].

The fourth method is the most universal, because such a cohort study is aimed at identifying several risk factors with several nosologies. Example: The Framingham study, begun in the USA in the city of Framingham in 1949. In order to identify risk factors for cardiovascular diseases [2].

Disadvantages of cohort studies. Cohort studies, like any other study, have strengths and weaknesses and determine the scope of these studies. There are known cases in which cohort studies cannot be used. For example, when studying diseases that occasionally occur, it is difficult to conduct a cohort study [4]. There is a need to form a large cohort, so that it becomes possible to meet cases of a rare disease. The less common the disease, the greater the physical impossibility of creating the necessary cohort. The peculiarity of the cohort study is that the researcher expects results in groups, having data on risk factors. In this situation, it is most advisable to study the effect on humans of rare risk factors, the effects of which experts know for sure. Other significant drawbacks of cohort studies are

their high cost and often long duration, for example, the Framingham study lasted 46 years [4].

The benefits of cohort studies. The possibility of obtaining reliable information about the etiology of diseases, especially in those cases when the experiment is impossible [6].

• The only way to assess the indicators of absolute, attributive, relative risk of a disease and to evaluate the EH cases associated with a perceived risk factor [2].

• The ability to identify rarely occurring causes.

• The ability to simultaneously identify several risk factors for one or more diseases [2].

• A sufficiently high reliability of the conclusions is due to the fact that in cohort studies it is much easier to avoid mistakes in the formation of the main and control groups, since they are created after detection of the studied effects (diseases, deaths, etc.) [4].

Randomized controlled trial. A clinical trial (CT) is a prospective comparative study of the effectiveness of two or more interventions (medical, prophylactic or diagnostic), which compares the results in groups that differ in the applied intervention. In this case, the hypothesis about the effectiveness of the tested method (the effect of intervention on the result) that arose prior to the study is usually checked [13].

In the presence of a control group (comparison), they speak of controlled CT, and when forming groups by randomization, they speak of a randomized controlled study (RCT, randomized controlled trial according to the classification of study types in MEDLINE) [20].

Advantages - results obtained in RCTs better reflect differences in results important for patients; systematic errors are less common; the most objective results of RCTs performed strictly according to the design of studies, which are most objective for assessing the effectiveness and verification of interventions, are most reliable [15].

Disadvantages - RCT requires a long time; they are expensive; not suitable in cases of research on rare diseases; these studies have limited generalization of the results (the possibility of transferring the results to the population). The last limitation should not be exaggerated, since other types of studies have an even worse generalization [1].

For the study, patients are selected from a large number of people with the condition under study. Then these patients are randomly divided into two groups, comparable by the main prognostic signs. One group, an experimental group or a treatment group, undergoes an intervention (e.g., taking a new drug) that is expected to be effective. The other group - the control, or comparison group, is in the same conditions as the first, except that the patients who enter it are not amenable to the intervention under study. The reliability of clinical trials depends on how much in the compared groups it was possible to ensure the same distribution of all factors determining the prognosis, except for the studied therapeutic intervention [14].

Sampling. Among the many reasons why patients with the studied disease are not included in the study, the main three reasons are [11]:

1) Patients do not meet the established inclusion criteria. This is an atypical nature of the disease, the presence of other diseases, a poor prognosis of the disease, a high probability of non-compliance with the prescribed treatment for patients. This limitation increases the likelihood of research: reduced the possibility of cases not related to the treatment itself.

2) If the patient refuses to participate in the experiment (clinical trial).

3) Patients who in the early stages of the study showed an inability to strictly follow the proposed treatment methodology are excluded. This will avoid financial and therapeutic futile efforts and reduce the reliability of the study [11].

The following structural variants of RCTs are distinguished [9].

A parallel (simultaneous) study in the groups of active intervention and control is carried out independently of each other. This is the most common research structure [2].

Cross model - a study conducted in one group of patients with a sequential change in treatment methods, separated by a period of “washout” (to eliminate the effect of the previous intervention). Similar studies are conducted in patients with stable and usually chronic pathological conditions [2].

The paired model is a way of forming groups in CI, in which each participant in the main group corresponds to a participant in the control group, usually selected according to some general characteristics [2].

A sequential model is a method of conducting research, when the decision to terminate is made when differences between the groups are achieved (usually the study is terminated at a predetermined time) [2].

Factor Protocol - the study is conducted in groups that use a combination of interventions. For example, with a 2x2 factor protocol (for two types of treatment), four groups are formed, in two of which one of the types of treatment is used, in the third - not one of them, in the fourth - both. The factor model is also used in assessing the effect of different doses of one drug and a combination of drugs [6].

An adaptive model is a set of participants in a group that receives the worst, according to accumulating estimates, treatment, decreases during the course of the study.

Zelen's design - participants distributed into the intervention intervention group are given the opportunity to refuse it and go to the control group. It is used in the study of interventions for which patients have strong advantages [6].

Compared to the parallel structure of CI, other options are relatively complicated both for execution and for understanding their results and are usually used when the parallel structure seems to be inappropriate or impossible. For the planning of studies with these types of structures, as well as for the analysis of the data obtained with this, it is necessary to consult a specialist in statistics [6].

The test performed is characterized by practical value, complexity and effectiveness. The results of treatment should be reproduced and applicable in normal clinical practice. You need to know: is the intervention studied sufficiently different from alternative therapies.

The value of the studied treatment method (drug) can be judged only by comparing its results with the effect of other therapeutic measures, that is, to compare between groups that received different treatment. Or you can compare the effect of the treatment method with the lack thereof. The latter method allows you to evaluate the overall effect of medical care, both related to the intervention being studied, and not related to it [2].

Treatment by the placebo. You can compare the effect of the study treatment (drug) with a placebo. A placebo is a dosage form that does not differ from the test drug in appearance, color, taste and smell, but does not provide a specific effect (for example, glucose tablets or injections of an isotonic solution) [13]. A placebo effect is a change in the patient's condition, which is noted by him or the attending physician, is associated with the fact of treatment, and not with the pharmacodynamic effect of the drug. The placebo effect is considered by researchers as a basal level for measuring specific therapeutic effects. It is necessary to distinguish between specific and non-specific effects of therapeutic intervention for its objective assessment [1].

A placebo in clinical trials of drugs is useful for the following purposes:

1) the distinction between the actual pharmacodynamic and psychological effects of the drug;

2) the difference between the effects of the drug from spontaneous periodic remissions and the influence of other external factors;

3) to avoid obtaining pseudo-negative results [1].

You can compare the studied treatment with conventional treatment in those cases where the effectiveness of conventional treatment has been proven.

To study the specific therapeutic effect of the intervention (drug), it is necessary to randomly assign patients to groups, that is, by randomization. Randomization is the optimal treatment choice method that avoids bias when distributing patients to groups. Randomization allows you to distribute patients into groups with approximately the same characteristics [4].

If the subjects know who receives what type of treatment, then there is a likelihood of a change in their behavior, which can cause systematic error. To reduce this effect, a blind method is used. The blind method in clinical trials can be carried out at the following levels [2]:

1) the researchers who assign patients to intervention groups do not know what treatment will be prescribed for each subsequent patient;

2) patients do not need to know what kind of treatment they are receiving;

3) doctors do not need to know what treatment (drug) is prescribed to the patient;

They use the “simple blind method” (the patient is not informed) or the “double blind method” (neither the patient nor the researcher is informed). Thus, the “double blind method” serves as a form of control to prevent the effects of bias on the results of the study [4].

There are two ways to analyze data in a randomized trial. The first method is an analysis depending on the prescribed treatment, that is, according to the groups formed by randomization; The result serves as a criterion for making clinical decisions. The second method is analysis depending on the actual treatment received; the result allows us to judge the biological mechanisms of action of the intervention [6].

It is understood that a clinical trial includes averaged patient observation data that are different from each other. In order to obtain information on a particular patient, clinicians can rely on observations from subgroups of patients or conduct tests on their own patients [4].

Perhaps treatment, effective on average for a group of patients, may be ineffective in specific patients. Although the results of a reliable clinical study provide a sufficient basis for its use in a particular patient, the experience of monitoring this patient is also important [7]. The single patient study method is an improved version of a more general informal trial and error process. The patient is sequentially assigned to one or another treatment (drug or placebo) in random order, for a short period (1-2 weeks). In this case, neither the patient nor the doctor

knows what medications are prescribed. The results are evaluated after each period and are subjected to statistical analysis. This method is necessary in cases where the course of the disease is unpredictable, the response to treatment is manifested quickly, and there is no imposition of pharmacological effects after changing drugs [5].

The results of randomized controlled trials using a blind method should be preferred over any other information on the effects of treatment. However, such tests have limitations: high cost of carrying out; there may not be a sufficient number of patients with the disease in question; experiment duration; lack of understanding of doctors and patients about the need for clinical trials, etc. When solving many clinical issues it is not always possible to practically rely on the results of RCTs, therefore other evidence is also used [1].

Thus, RCTs remain the “gold standard” of research in medicine [10]. They are characterized by the following features:

- unified selection of patients (strict selection criteria maximize the likelihood of distinguishing between effect and background fluctuations).
- randomization in the experimental and control groups (placebo or drug comparison).
- blind research; in double-blind studies, neither the patient nor the doctor (observer) knows which group the patient belongs to [10].

However, it is necessary to identify the problematic aspects of RCTs, among which [11]:

- the impossibility of generalization; stringent selection criteria lead to the fact that research results may not necessarily be applicable to other patients;
- an unrealistic clinical situation is created when patients are observed by highly motivated researchers who do not know which drug (test or placebo, control drug) is taken by patients;
- conducting truly blind studies is difficult, as observers, subjects (patients) can recognize the effect of the drug by its pharmacodynamic parameters (for example, lowering blood pressure or heart rate when taking certain classes of drugs) [11].

Clinical trials

Significant successes in elucidating the causes of the onset and spread of diseases served as the basis for the development of new methods for their diagnosis, treatment and prevention, many of them ensured a decrease in the incidence rate, primarily, infectious [13]. All this contributed to the strengthening of the empirical approach in medicine. A feature of the approach is an orientation toward the direct study of phenomena. As methods use real observation. Only this approach, according to most scientists, to a large extent guaranteed the effectiveness of the methods used for diagnosis, treatment and prevention of diseases. The prevalence of an empirical approach in medicine has led to the fact that almost until the middle of the 20th century. Judgments on the effectiveness of diagnostic methods and methods of treating patients were based mainly on personal experience, the experience of this team and authoritative opinion [16].

However, back in the XV-XVI centuries. some scientists believed that the potential effectiveness of methods of treatment and prevention of diseases, although consistent with empirical ideas, should be evaluated experimentally. An experiment (experiment) is a general scientific method for testing cause-effect hypotheses using controlled intervention in the natural course of the phenomenon under study. The purpose of epidemiological experimental studies is to assess the potential and real effectiveness and safety of prophylactic and medicinal products, methods and schemes of treatment, diagnosis and prevention of diseases [15].

Clinical trial (CT) – is a controlled experimental study where subjects receive prophylactic, diagnostic, or therapeutic agents to evaluate their effectiveness and safety [2].

The general rules for conducting CT involving people follow from the Nuremberg Code and the more detailed Helsinki Declaration of the World Medical Association. Later, in order to streamline the conduct of preclinical and clinical trials, WHO in 1974 developed Methodological Recommendations for the Evaluation of Medicines for Use in Humans. Subsequently, on the basis of this document in the United States, national rules for conducting CT were developed,

published in 1977. Under the name "Rules of Good Clinical Practice" (GCP) [2]. Then similar rules were adopted by other countries (EU, Japan, Canada, Australia). In order to harmonize them, international conferences were held (the first in 1991, www.ich.org), in which drug manufacturers played a prominent role, so the GCP does not fully comply with the requirements of the Helsinki Declaration. The language of these documents is also different. If researchers talk about research on medical interventions as research options, they are focused on assessing the effectiveness and safety of the intervention, but the more general term “research” is used in ICH documents. Since 1998, WHO has been implementing the project “Introducing International Standards into the Practice of Clinical Research in Central and Eastern Europe” [13].

Therefore, the GCP rules were designed to ensure that CT results are reliable and accurate and protect the rights, integrity and confidentiality of subjects. They cover the entire chain of clinical trials - formulation, conduct, execution, monitoring, inspection, registration, analysis and reporting of CT [12].

The clinical trial process for new drugs involves four interrelated phases.

Classification of experimental epidemiological studies [2].

A randomized clinical trial: assessing the potential efficacy and safety of immunobiological drugs and drugs.

Randomized field study: assessing the potential effectiveness and safety of immunobiological drugs.

Continuous field study: assessment of the real effectiveness and safety of immunobiological preparations and drugs.

Before the appearance on the pharmacy shelves, the drug undergoes serious research. The following practice is accepted in the world: at the beginning, these studies are carried out in the framework of the preclinical phase (preclinical phase), which implies the development of the drug in research centers and laboratories. Usually, organizations developing new drugs are called Research and Development organizations. Large pharmaceutical companies have Research and Development Departments. However, there are many small companies developing

3-4 new drugs, or even just one drug. Often the financing of such companies is provided by issuing shares in which they raise funds for research. At the end of the preclinical phase, such Research and Development companies can sell their formula to large pharmaceutical firms or start CI on their own. As a rule, they have neither the experience nor the ability to conduct a CD, then they begin cooperation with contract research organizations (Contract Research Organizations) [2].

Stage of drug development. Formula development (Development of a Compound). Research laboratories are developing a new product concept. Product characteristics should be aimed at a positive effect on undesirable pathological conditions of the patient or on slowing / preventing their development [5].

Preclinical Testing In order to prove the absence of any side effects of the product and its effectiveness in the claimed field of medicine, tests are performed on animals (mice, rats, dogs and monkeys). This is the preclinical stage of the study. The purpose of the stage is to prove that the product has no carcinogenic, mutagenic, teratogenic effects. Also, preclinical research allows you to understand the interaction of the product with the body. As soon as a pharmaceutical company proves product safety and possible efficacy in animal testing, it transfers this information to state regulatory authorities. The result of this appeal is official permission to start CI [14].

Clinical Trials / Studies in Humans. It is already being held in public. CI of the drug can last several years. More and more subjects are being drawn into each subsequent phase. Three phases of the study are distinguished. There is also a fourth, post-marketing (post-registration) phase, when the action of a product is observed after its entry into the market of medicinal (prophylactic) drugs. To ensure the safety and effectiveness of the product, the manufacturing company must analyze the results of each phase [14].

Phases of the study of immunobiological preparations [6]:

I phase. Laboratory studies of vaccines - preclinical studies on laboratory animals of toxicity and safety, physical properties, chemical composition of the

drug. The study of immunogenicity in laboratory animals. Determination of antigen concentration [6].

II phase. Limited studies on immunogenicity and safety. Determination of the correct concentration of antigen, the number of components of the vaccine, manufacturing techniques, the effect of the following doses and the main adverse reactions. The final choice of type of vaccine for the third phase of RCTs. Research is carried out only after a positive opinion of the ethics committee, the national body for the control of biomedical preparations on volunteers [6].

III phase. Large-scale vaccine studies in healthy patients (thousands of volunteers). Determining the effectiveness of the vaccine and adverse reactions; the duration of observation (usually 1 to 2 years, but not less than 6 months). The study of the effectiveness, establishing the frequency and types of adverse reactions (randomized field study) [6].

VI phase. Post-licensed vaccine quality control. Continuation of the study of the frequency and strength of adverse reactions, real effectiveness in the field experiment (continuous field study) [6].

Phases of clinical trials of drugs:

I phase. The new product is first tested in humans. The objectives of this phase of the study are related to product safety. Usually attract from 20 to 100 healthy volunteers who are hospitalized in a special center. If a study on healthy volunteers is impossible (drugs for the treatment of cancer, AIDS, etc.) or is pointless, then you can get permission to conduct the first phase of the study on patients with a certain pathological condition. Most often, volunteers are men and women 25-30 years old (women are not pregnant and do not feed) if the drug is designed for use in pediatrics, then children (non-randomized CI) can take part in later stages [4].

II phase. Evaluate the effectiveness and safety of the drug in patients with a disease for the treatment of which it was developed. Often these are placebo-controlled studies. Sometimes this phase of CI is divided into two more phases. The purpose of the first of these is to assess the short-term safety of drugs. The

second is the evidence of the clinical efficacy of drugs and the determination of the therapeutic dosage level when tested on a group of patients. The number of patients at this stage varies from 40 to 300 and depends on the size of the expected effect. If the intended effect is significant, a small number of patients is enough to prove the statistical significance of the experiment. On the other hand, if the effect is not sufficiently pronounced, much more patients are needed (randomized or non-randomized CI) [4].

III phase. Drugs are studied in large groups of patients (hundreds of people) of different ages, with various concomitant pathologies, in numerous research centers in different countries. Studies of this phase are often randomized controlled. They study all aspects of treatment, including the assessment of the risk / benefit ratio. Based on the results of CI, the State Pharmacological Center of Ukraine makes a decision on registration or refusal to register drugs [4].

VI phase. It comes after the drug has received permission to use. This phase is often called post-marketing (post-registration). The purpose of the study was to identify the differences between new drugs and other drugs in this pharmacological group, to compare its effectiveness with analogues already sold on the market, to demonstrate benefits from the point of view of the health care economy, and to identify and identify previously unknown or incorrectly defined side effects and risk factors. As a result, the safety and effectiveness of drugs can be periodically reviewed in accordance with new clinical data on its use (continuous / randomized clinical / field study) [4].

Inclusion and exclusion criteria.

Inclusion criteria of patients (examined), necessary to describe the population (general population), which corresponds to the patients included in the study.

Exclusion criteria. Necessary to create a homogeneous sample, that is, less variability of the variables in the initial state and in assessing the magnitude of the intervention effect. Persons with severe concomitant diseases, life-threatening conditions or interfering with the fulfillment of the experimental conditions (for

example, with dementia) are excluded from the CT participants. Thus, the statistical sensitivity of the experiment grows [11].

Participant consent. Ideally, all patients who meet the inclusion criteria should participate in the study. In practice, not all patients agree. Some may prefer one of the proven treatment methods and do not wish to expose themselves to the test method. Others, in principle, do not want to be the object of research or choose another method of treatment. Such patients are not included in the study. It is necessary that the response rate, that is, the proportion of people who responded to a request to participate in the study, be sufficiently high, at least 80%. Patients will follow the recommendations depending on the acceptability of the study. The results of treatment of such patients are higher regardless of treatment. Subjects actively choose a method of treatment, are treated more diligently, more correctly perform the appointment. This property of people is called accuracy or thoroughness, but more often - compliance [6].

Planning the number of participants. The number of patients included in the experiment (sample size) should be justified, while proceeding from:

- estimated level of effectiveness;
- research structure;
- a predetermined threshold of statistical significance of revealing the effect;
- prevalence of the disease.

When planning a study, it is calculated that the number of patients is sufficient to identify the intended effect. The calculations are quite complex, they are performed using statistical programs [6].

Randomization – random distribution of patients into groups. Its purpose is minimal differences between groups; by all indications they are random rather than intentional. From the principle of random grouping, we obtain a methodology for statistical data analysis: the differences in groups are random by definition [4].

Randomization is carried out in various ways: using random number tables, computer programs. Randomization is sometimes replaced by pseudo-randomization (distribution into groups by the first letter of the name, date of birth,

medical number, day of the week of admission to the clinic, etc.). Its application may affect the correctness of the formation of the sample and, accordingly, the evaluation of the results. The worst adverse consequence of pseudo-randomization is that each patient will be known to belong to a specific group (main or control). Thus, the main condition for randomization will not be fulfilled - hiding its results; its most important function will not be realized - ensuring the blind nature of research. In studies where measures to conceal the results of randomization or concealment were taken were insufficient, the assessment of the effectiveness of the intervention was overestimated by about 25%. Reliable technical measures are taken to ensure concealment (for example, after registering a patient who agreed to participate in the study, information about him is entered into the database of the research organizer) [6].

Placebo. When evaluating the effectiveness of a new drug, the question arises of its effectiveness, that is, the ability to reduce the likelihood of adverse outcomes compared with the lack of intervention. In the control group, the absence of intervention may be psychologically unacceptable for patients, leading to their failure to follow the study regimen. Patients left without treatment go on self-medication. That is why patients in the control group are given a substance (procedure) that does not differ from active intervention. Usually, a placebo is a dosage form devoid of the active component, for example, a tablet form identical to the active in color and form, but containing only an indifferent substance - kaolin or starch, for injection forms - an isotonic sodium chloride solution [1]. The use of a placebo is not always possible, and sometimes unethical, for example, when patients are unacceptably deprived of effective treatment. Then the control group is prescribed standard treatment and a placebo, and the main group is given standard treatment and the study drug. The efficacy of a new drug is easier to show in comparison with a placebo; when comparing with an existing drug, it is necessary to prove a greater or the same effect of the new drug [6].

It is believed that the use of placebo gives a positive effect, the "placebo effect." The beneficial effect of placebo is associated with its psychological effect

on the patient. Placebo has a negligible effect only on the results reflecting the subjective condition of the patient (sleep quality, pain intensity). Placebo is not affected by clinically important results (life expectancy, duration of remission, functional defect, etc.) [1].

Difficulties in prescribing the drug. Regardless of the nature of the intervention (medical, diagnostic, preventive), it should be clearly described and standardized.

When prescribing certain interventions, dose selection does not cause difficulties: parenteral administration of the drug according to the scheme ensures the intake of a certain amount of active substance into the body. The use of oral forms of drugs already leads to difficulties in dosage. Depending on the compliance, patients may not take the dose, but with pronounced side effects, they can be completely reduced. There are interventions that are difficult to dose. These include surgical interventions, manual therapy, acupuncture [4].

During CT, treatment previously prescribed to the patient is usually discontinued. The period after the termination of the previous treatment and before the start of CT is set so that the concentration of the active substance decreases. If patients of the main group take additional drugs (co-intervention), then a bias in the results may occur towards higher efficiency. If patients in the control group use the same drugs as in the main group (contamination, contamination), then the result may be biased towards the ineffectiveness of the drug [6].

The study takes measures to prevent pollution and co-intervention and to increase the compliance of patients and staff in the implementation of the actions proposed by the protocol. One way is to conduct an introductory stage to the study. At this stage, patients who do not follow the regimen are detected, for example, by determining in the urine the substances introduced into the drug as a label. Then, only executive patients are included in the studies. Co-intervention and contamination are almost inevitable, they must be taken into account when analyzing data [4].

Results ("target" signs) – events that will evaluate the effectiveness of treatment or other interventions. kinds of results:

• clinically important results (mortality, life expectancy, frequency of exacerbations, maintenance);

• intermediate;

• indirect;

• surrogate results [2].

The quality of life. When evaluating the effectiveness of an intervention, one should not forget about assessing the quality of life. To assess the quality of life, complex scales are used, the final rating of which is obtained by summing up various information (about the intensity of pain, mood, breathing, the ability to wash independently, serve yourself, etc.) [3].

Study termination. Duration of CT is planned based on the number of participants, the expected frequency of cases and differences between interventions (effect size), and the planned statistical significance of the results. Conducting research until the moment when its result becomes statistically significant is incorrect, since sooner or later, statistically significant differences can be achieved. That is why the duration of CT is set in advance [11]

In lengthy trials, the rules for terminating CT are established in connection with the need to observe the safety of participants and with the possible obtaining of convincing results in favor of one of the investigated interventions [2].

Tests with data analysis depending on the prescribed or received treatment. The results of controlled randomized trials can be analyzed and presented in two ways: either on the basis of the fact of prescribing a particular treatment during randomization, or on the basis of the treatment actually received by the patient. The correct presentation of the results depends on the formulation of the question [6].

• If the question is which treatment tactics are best for making a clinical decision, then an analysis should be applied based on the treatment prescribed during randomization, regardless of whether all patients actually received this

treatment. This approach is called the analysis to the treatment prescribed (intention to treat analysis) [4]. Advantages of this approach: the question posed corresponds to the one that usually interests the clinician when prescribing treatment, and the compared patients are really randomly assigned to groups. Disadvantage: if many patients did not receive the proposed treatment, then the differences between the experimental and control groups disappear, the probability of a negative study result increases. In this case, the absence of differences between the groups can be interpreted in different ways: the experimental intervention is actually ineffective, or it simply has not been applied [3].

• If we are interested in whether the experimental treatment is really better than the control one, then in this case the analysis coming from the received treatment is more suitable for the answer, that is, an assessment of the effect of the treatment that each patient really received and regardless of what treatment he was prescribed for randomization. In this case, the mechanism of the investigated effect is clarified. The disadvantage of this approach: if most patients did not receive the proposed treatment, the test ceases to be randomized and becomes a regular cohort study [6]. This means that all differences between groups, excluding the method of treatment, must be somehow leveled (by introducing restrictions, pairing, subgrouping or standardization) to achieve full compatibility, as is the case with non-experimental studies [4].

International requirements. The basis of the CT is a document of the international organization “International Conference on Harmonization” (ICH). This document is called the “Guideline for Good Clinical Practice (GCP)” (“Description of the GCP Standard,” GCP is often translated as “Good Clinical Practice”) [11].

CT must be carried out in accordance with the basic ethical principles of the Helsinki Declaration, the GCP standard and current regulatory requirements. By the beginning of CT, it is necessary to assess the ratio of possible risk with the expected benefit for the subject and society. At the forefront is the principle of the priority of the rights, safety and health of the subject over the interests of science

and society. The subject may be included in the study only on the basis of voluntary informed consent obtained after a detailed review of the study materials. This consent is confirmed by the signature of the patient (authorized person) [10].

CT should be scientifically substantiated, detailed and clearly described in the study protocol. Assessment of the risk-benefit ratio, as well as consideration and approval of the research protocol and other documentation related to the conduct of CT, are the responsibility of the Independent Ethical Commission (NEC). After obtaining approval from the NEC, it is possible to proceed with CT [10].

Drug development and their CT - the procedures are very expensive. Some companies seeking to reduce the cost of testing, conduct them first in countries where the requirements and cost are much lower than in the country of the developer. So, many vaccines were first tested in India, China and other third world countries. The charity supplies of vaccines to the countries of Africa and Southeast Asia were also used as the II – III stage of CT [11].

Principles of good clinical trials. In Ukraine, clinical trials are regulated by orders of the Ministry of Health of Ukraine No. 690 of September 23, 2009 “On approval of the Procedure for conducting clinical trials of medicines and examination of clinical trial materials and the standard provision on ethical commissions”, No. 944 of December 14, 2009 “On approval of the Procedure for conducting preclinical studies medicines ”, No. 1169 dated September 26, 2017“ Medicines. Good Clinical Practice 42-7.0: 2008 ”. The standards in these orders are identical to the Consolidated GCP of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICH, which prepared by the Association of International Pharmaceutical Manufacturers, the International Confederation of Consumer Societies. Good clinical practice: an international ethical and scientific standard for planning and conducting research involving a person as a subject, as well as documenting and presenting the results of such studies [7].

Compliance with this standard serves as a guarantee for society that the rights, safety and well-being of subjects of research are protected, consistent with the

principles laid down by the Helsinki Declaration of the World Medical Association, and the CT data are reliable [10].

The purpose of this national standard is to establish uniform rules with the countries of the European Union, the USA and Japan that facilitate mutual recognition of CT data by the authorized bodies of these countries [11].

The principles of quality CT (GCP) [14].

• CT must be carried out in accordance with the basic ethical principles of the Helsinki Declaration, GCP rules and applicable regulatory requirements.

• Before starting CT, an assessment of the relationship between the perceived risk and the expected benefit to the patient and society should be carried out. CT can be started and continued only if the expected benefits prevail over the risk.

• Rights, safety and health of the subject are more important than the interests of science and society.

• The justification for the planned CT should be based on data from preclinical and clinical studies of the study drug.

• CT should be scientifically based, detailed and clearly described in the study protocol.

• CT are brought into line with a protocol previously approved / approved by the Independent Ethics Commission.

• Responsibility for providing medical care to a patient can only be assumed by a qualified doctor.

• All persons involved in conducting CT must have professional education and experience appropriate to the tasks set.

• A test subject may be included in the study only on the basis of voluntary informed consent obtained after a detailed review of the study materials.

• The collection, processing and storage of information obtained during CT should ensure accurate and correct presentation, explanation and confirmation of data.

• Documents to identify the subject must be kept secret from unauthorized persons.

• Production and storage of the test drug, as well as its handling, is carried out in accordance with the Rules for the Organization of Production and Quality Control of Medicines, or Good Manufacturing Practice (GMP). The drug is used in accordance with the approved research protocol [14].

Documents required for a randomized clinical trial [10]:

• study protocol and amendments to it;

• the written informed consent form, its subsequent revisions;

• materials for attracting subjects to the study (for example, advertisements);

• researcher brochure;

• information on the safety of the study drug;

• information on bills and compensation to subjects;

• CV (curriculum vitae) of the researcher at the moment and / or other materials confirming his qualifications;

• any other documents that may be required by the Independent Ethical Commission to fulfill its duties [10].

Regulation on the Independent Ethical Commission. The main objective of the IEC is to protect the rights and health of subjects, as well as guarantee their safety. The IEC receives for consideration the documents indicated above (documents necessary for conducting the RCT) [4].

The IEC considers the issue of conducting CT on time and gives a written opinion indicating the name of the study, the documents reviewed and the date of one of the following possible solutions:

• permission to conduct research;

• a requirement to amend the submitted documentation to obtain permission to conduct research;

• denial of permission to conduct research;

• cancellation / suspension of previously granted research permits [4].

The IEC evaluates the qualifications of the researcher based on his current CV and / or other necessary documentation obtained at the request of the IEC [4].

In the course of the study, the IEC considers the documentation with a frequency that depends on the degree of risk of the subjects, but at least once a year.

If the protocol indicates the impossibility of obtaining the consent of the test person or his legal representative before being included in the study (for example, in the treatment of emergency conditions), the IEC must ensure that the ethical aspects of this study are fully reflected in this protocol and / or other documentation [4] .

To avoid undue interest or coercion of subjects, the NEC considers the procedure and amount of payments to subjects.

The IEC includes a sufficient number of persons with the necessary experience and qualifications for the expert assessment of the scientific, medical and ethical aspects of the planned study [5].

The composition of the IEC recommended the inclusion of:

• at least five members; among them:

• at least one member - not a scientist;

• at least one member - not an employee of the medical institution / research center in which the tests are carried out [5].

Only members of the IEC who are not employees of the researcher or sponsor may vote on the permission / approval of the study. The IEC draws up a list of its members indicating their qualifications. The IEC acts in accordance with the approved standard procedures, maintains the necessary documentation and keeps a record of the meeting. Its activities must comply with the GCP Rules and applicable regulatory requirements [4]. At official meetings, the IEC makes decisions if there is a quorum determined by the relevant regulation. Only members of the IEC, directly involved in the review of documentation for the study and its discussion, can vote and give recommendations on obtaining permission to conduct the test. The researcher provides information to the IEC on any aspects of the study, but does not participate in debates or in voting on the issue of permission to conduct research [5].

Informed consent. The doctrine of informed consent means that the doctor, before asking the patient for consent to conduct a course of treatment or a separate procedure, associated with risk and having alternatives, must provide the patient with the following information [4]:

• The essence of the proposed treatment (procedure);

• risks and benefits of the recommended measures, the degree of danger of the most adverse consequences (death or severe disability);

• alternative treatment methods (procedures), risks, danger of adverse consequences;

• consequences of delayed or non-delivered treatment;

• the likelihood of a successful result, a manifestation of this success;

• possible problems and the length of the rehabilitation period and the patient's return to the normal volume of activity for him;

• other related information in the form of answers to questions, a statement of similar cases from my own experience, etc. [4].

Information should be provided in a form accessible to the patient, in a language that he understands. The question of the competence of the decision often arises with the patient's apparent incapacity (children, persons recognized incompetent due to mental disorders, etc.). Here decisions are made according to the same schemes, with the participation of guardians or trustees. For homeless people, decisions are made by specially authorized social workers. If there is no consensus in the family or in the guardianship authorities, the court shall decide on the guardian. Voluntaryism - the absence of any external pressure (threat, bribery, enslaving financial conditions) on the patient when making a decision, especially when signing written consent or refusals [2].

Clinical guidelines. Diagnostic and treatment protocols

In many countries, national programs for the development of clinical guidelines and protocols for diagnosis and treatment are supported by a detailed methodology for their development, and in 2002, a methodology for the development of clinical guidelines was prepared by the World Health Organization. Moreover, in 2002, the International Network of Clinical Guidelines and Protocol Developers was formed - Guidelines International Network (GIN), which included developers from 56 countries [12].

Currently, in the framework of the implementation of the Decree of the Government of Ukraine of February 16, 2004 “On standardization in the field of health care”, the authorized body in the field of health represented by the Ministry of Health of Ukraine (hereinafter referred to as the authorized body) is actively developing and introducing into medical practice CG and Diagnostic and treatment protocols (DTP) [13].

One of the main criteria necessary for the development of CG and DTP that meet modern quality requirements in healthcare is the widespread use of evidence-based medicine methods and principles — the use of the results of correctly performed modern scientific research as the main foundation for a critical assessment of clinical information. The introduction of evidence-based medicine principles in healthcare practice provides for the optimization of the quality of medical care in terms of safety, efficacy and cost. Modern evidence-based medical practice requires the doctor to diagnose diseases, prescribe effective treatment, and minimize the negative effects of interventions based only on the most reliable information [15].

To date, several techniques have been developed in the world that ensure reliability and high quality when creating protocols and manuals. For example, the “necessary elements of benign CT” proposed by the American Institute of Medicine (US Institute of Medicine) special guidelines for the creation of CG (developed by SIGN, NZGG, WHO and others) the international AGREE

questionnaire, which unifies the assessment and preparation of clinical guidelines [15].

Thus, the methodology for the development of DTP and CG, carried out from the perspective of evidence-based medicine, should be based, first of all, on the search and systematic synthesis of reliable and modern scientific evidence. This makes it possible, taking into account the latest and reliable information, to optimize or level out the influence on the doctor's decision of such largely subjective factors as intuition, qualification, opinions of authoritative colleagues, recommendations of popular manuals and reference books [8].

Modern requirements for the development of the CGand DTP [3]:

1) Development of CG and DTP is carried out to ensure the best clinical results in the treatment and prevention of diseases that are most common and socially significant for society.

2) The process of formation of CG and DTP is based primarily on taking into account the interests and needs of consumers of clinical services.

3) CG and DTP should be compiled taking into account the latest scientific data, ensuring a high degree of evidence of each recommendation.

4) The structure of the created CG and DTP should be simple, understandable, easy to reproduce in print and electronic formats.

5) In the development, implementation and monitoring of CG and DTP, it is necessary to take into account the real economic, clinical, administrative and other conditions of the existing health care system, within which the CG and DTP will operate in order to ensure their maximum viability.

6) When using CG and DTP should easily adapt to the characteristics of an individual patient.

7) After the introduction of CG and DTP into clinical practice, it is necessary to continuously monitor their effectiveness and evaluate their impact on the practice of public health.

8) For existing CG and DTP, regular periodic reviews and updates are necessary, taking into account new scientific evidence [3].

The process of creating CG and DTP should be thought out and systematized and include the development of the entire package of supporting documents, using the country's existing experience and foreign developments in this area, using a standard generally accepted and scientifically based approach, and clear evolutionary algorithms for the development process [3].

The formalized (standardized) development process of the CG and DTP has a positive effect on their quality, allowing to significantly reduce the time and financial costs of their creation. In addition, a single approach provides transparency in the process of compiling benefits [4].

Organization of the development of the CG and DTP. Creation of CG and DTP is a complex process that requires a long time. The terms of their development can vary depending on: the volume of the literature studied, which should be critically evaluated, the number of consultations, the duration of the examination of the CG and DTP, as well as the time required for approval by the authorized body, and most importantly, the workload of the members of the working group (Table 3) [4].

Table 3. Estimated Development Time CG and DTP

Formation of a working group, topic selection	Search for existing CG and DTP, their generalization and development of projects of their own CG and DTP		Approbation	Clinical refinement and assessment	Examination and approval
	For CG	For DTP			
1 month	6 month	3 month	6 month	1 month	1 month

In addition, the initial preparatory and conciliation work should be carried out before the start of the process of development of the CG and DTP, defined, for example, by the order of the authorized body on the creation of the CG and DTP. The step-by-step stages of the process should be thought out, the main participants to be involved at one or another stage of the work should be identified, the necessary resources and funds that will be needed for the process of creating and

implementing specific CG and DTP are calculated. Active action is required by representatives of the main parties involved, and, first of all, the high interest of the authorized health authority that regulates these issues [4].

To create comprehensive manuals and protocols that meet most of the requirements of modern healthcare, it is necessary to involve a variety of structures: from the Ministry of Health to nongovernmental associations of patients, clinical practitioners in various fields, including leading specialists from research institutes and medical universities, chief doctors of clinics, as well as experienced doctors of primary health care and paramedical personnel [3].

Coordination of the creation of protocols and guidelines should be carried out by a certain leading organization, which, as a rule, is determined by the authorized body in the field of health (hereinafter - the authorized body) on a competitive basis, or by a special department in the structure of the authorized body or other responsible organization. As part of its work, the availability of sufficient financial and material resources, highly qualified personnel and well-developed infrastructure should be provided. Also, this organization should have sufficient authority and support from the Ministry of Health and other interested organizations, including representations of international medical programs and local drug associations [2].

All protocols and guidelines created must be examined and adopted by the Expert Council for Standardization in Health Care (hereinafter referred to as the Expert Council) before being put into practice. Otherwise, it will not be possible to achieve uniformity of application of the created protocols and guidelines throughout the country, and the efforts of specialists may be wasted [4].

Also, the leading organization that carries out the main work on the creation and implementation of the CG and DTP, first prepares the necessary package of documents that support this process, approves them in authorized structures, and also conducts a detailed analysis of the existing legislative framework, which covers, one way or another, the development and application of CG and DTP [3].

The definition of the theme of the CG and DTP is determined by their relevance and relevance for practical health care. The topics of CG and DTP should cover those areas of medicine where they can really improve the quality of medical care. The list of nosologies for the development of CG and DTP is determined by the expert council of the authorized body according to the following main parameters: prevalence / incidence, high level of complications and mortality, social significance (high level of disability, disability), economic cost, mutual conflict of existing approaches, etc. [2]

The list of CG and DTP should be based on existing international classifiers and catalogers of diseases, such as ICD, SNOMED, RCC, etc. From objective methods for selecting current nosologies for which protocols and guidelines will be developed, it is currently convenient to use a selection according to the frequency analysis of the occurrence of a disease, high cost or social significance [12].

To select the most important topics for which the CG and DTP will be developed, it is also advisable to use the following criteria [11]:

• lack of a unified view of the diagnosis, prevention and treatment of diseases, as evidenced by differences in approaches to treatment and its results;

• the availability of proven effective treatment methods that can lead to a decrease in mortality and the incidence of complications,

• the presence of interventions associated with an increased risk of iatrogenic complications;

• at the time of making recommendations, on this topic in Ukraine there is no CR and MPL based on DM [11].

Prior to the development of CG and DTP, their purpose, the range of issues to be considered, and also the requirements for the final product by its customers should be characterized.

As a rule, for many nosologies at one time or another, clinical guidelines and protocols have already been created, both by organizations of state subordination and by foreign institutions. They can be taken as basic documents and adapted to local conditions.

Examples of practical application of EBM

Consider applying the principles of evidence-based medicine as an example of cardiovascular disease (CVD). Among the causes of death in European countries, CVD comes first. This leads to the activation of early diagnosis, treatment of diseases and identification of risk factors - to develop individual tactics for the prevention of cardiovascular catastrophes [17].

Adverse CVD risk factors include smoking, hypercholesterolemia, insulin resistance and diabetes mellitus, and arterial hypertension. Almost all risk factors are modifiable, that is, it is possible to influence them, contributing to their disappearance or reduction of their adverse effects [18].

The main conditions for the prevention of adverse effects of risk factors on the development and progression of CVD defined in the European recommendations for the prevention of CVD are as follows [21]:

- cessation of smoking;
- adherence to a special diet;
- increased physical activity;
- body mass index should not exceed 25 kg / m2;
- blood pressure (BP) should not exceed 140/90 mm Hg;
- total cholesterol - not more than 5 mmol / l;
- low density lipoprotein cholesterol should not exceed 3 mmol / l;
- blood glucose should not exceed 6 mmol / l [21].

An important prerequisite for successful prevention is the assessment and stratification of CVD risk. Assessment of the overall risk is carried out using the SCORE (Systematic Coronary Risk Estimation) scale, which is based on the results of large European studies and allows to predict the risk of death from atherosclerosis over the next 10 years. To assess risk, the following risk factors are analyzed: gender, age, smoking, systolic blood pressure, total cholesterol, or high density lipoprotein cholesterol / cholesterol ratio (fig. 5). A high risk criterion is the probability of death from cardiovascular complications ≥ 5% [16].

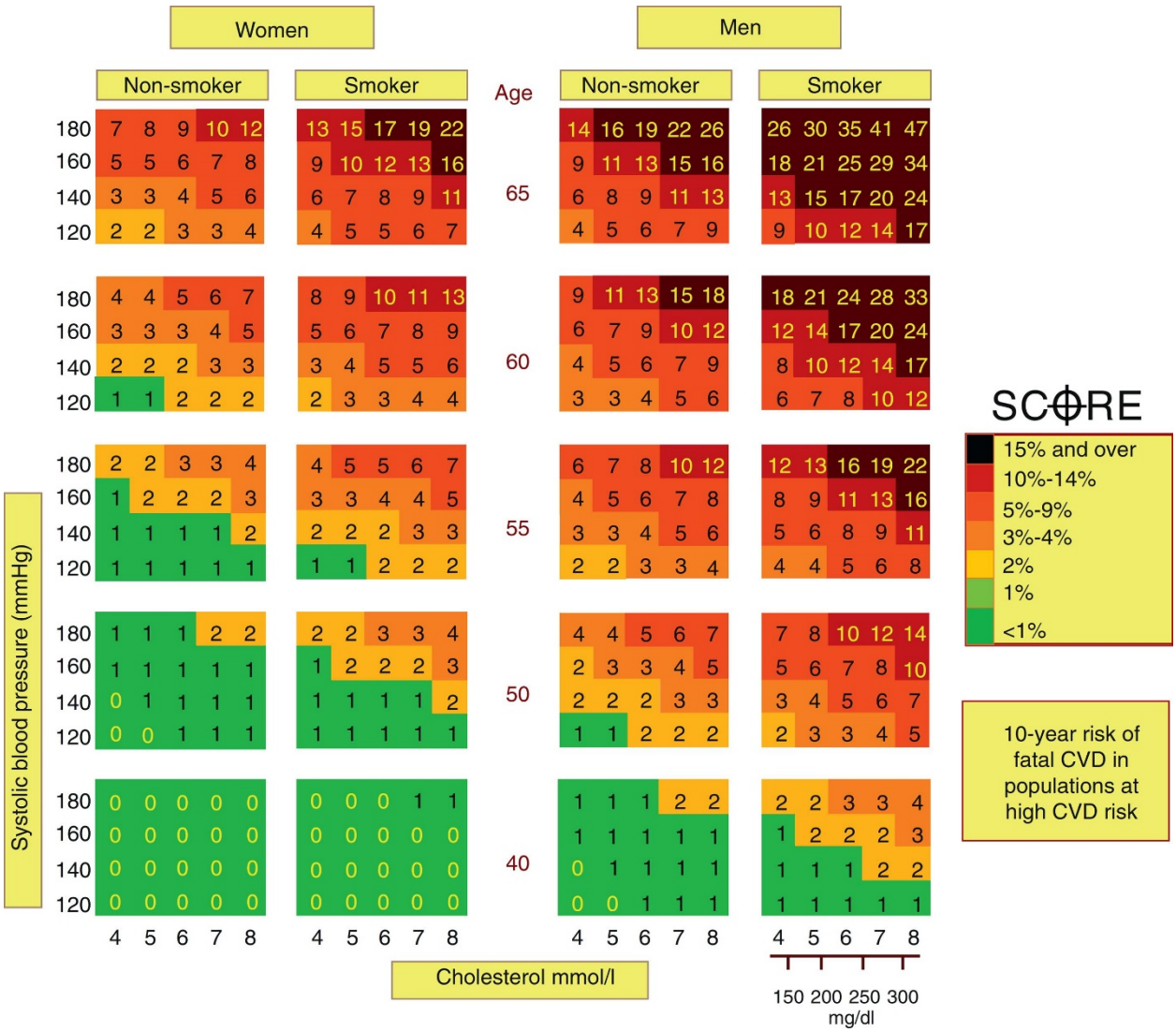


Fig. 5. Ten-year mortality rate from cardiovascular diseases in Europe

Use the scale as follows [16]:

1. To assess the total 10-year risk of death from cardiovascular events, on the scale it is necessary to find a cell (taking into account gender, smoking and age) that corresponds to the level of systolic pressure (mmHg) and total cholesterol (mmol / l or mg%).

2. To assess the relative risk, you should compare the risk category with patients who do not smoke, of the same age and gender, with a blood pressure level below 140/90 mm Hg. and total cholesterol less than 5 mmol / l.

3. The scale helps to evaluate the results of the transition from one category to another. For example, if a patient quits smoking or reduces the level of influence of other risk factors.

4. Patients with low risk should be encouraged to maintain it at the same level.

5. Maximum attention should be paid to people whose probability of death within 10 years is ≥ 5% or reaches this level in middle age [16].

Another clinical example is atrial fibrillation (AF), which is the most common chronic heart rhythm disorder in the general population and is associated with a high risk of adverse cardiovascular events, in particular stroke [18].

The identification of the clinical risk factors for stroke has led to the development of various risk assessment schemes for its development. In most cases, patients were artificially assigned to high, medium, and low risk groups. The simplest method is the CHADS2 index [CH, AH, age, diabetes, stroke (risk doubling)] (Table 4), which was proposed based on the results of the SPAF study. When calculating the CHADS2 index, stroke and TIA patients are assigned 2 points, and at the age of ≥ 75 years, in the presence of hypertension, diabetes or heart failure - 1 point [18]. The CHADS2 index can be used for a quick initial assessment of the risk of stroke. If the CHADS2 index is ≥ 2, continuous anticoagulant therapy with vitamin K antagonists is indicated (target INR 2.5, therapeutic range 2.0-3.0) in the absence of contraindications.

Table 4. Index $CHADS_2$ and heart rate

Index $CHADS_2$	Patients number (n=1733)	Stroke rate, % per year (95% confidence interval)
0	120	1,9 (1,2-3,0)
1	463	2,8 (2,0-3,8)
2	523	4,0 (3,1-5,1)
3	337	5,9 (4,6-7,3)
4	220	8,5 (6,3-11,1)
5	65	12,5 (8,2-17,5)
6	5	18,2 (10,5-27,4)

A similar approach can improve outcomes in AF patients in routine clinical practice. As can be seen from the table. 7, there is a clear relationship between the

CHADS2 index and stroke rate. The risk of stroke is considered low, medium, and high if the CHADS2 index is 0, 1-2, and> 2, respectively [18].

The corrected stroke rate was calculated based on multivariate analysis (it was assumed that patients did not receive ASA) in hospitalized patients with AF. The low number of patients with the CHADS2 index of 5-6 does not allow an accurate assessment of the risk of stroke in such patients. The stroke rate in the population is gradually decreasing; therefore, the actual risk of stroke in outpatients may differ from the calculated indicators [18].

The Stroke in AF team compared 12 published risk assessment schemes in patients with non-valve AF. It was concluded that the existing schemes have significant and clinically significant differences from each other. Most of them were characterized by moderate accuracy in the prognosis of stroke (an indicator of about 0.6). In addition, the percentage of patients who were assigned to different risk groups using different schemes varied widely. Based on the CHADS2 index, most patients were assigned to the medium risk category, and in the entire cohort the indicator was 0.58 [15].

The authors of these recommendations suggest abandoning the use of the categories low, medium and high risk and consider it appropriate to consider risk as a continuum. We recommend a more detailed analysis of stroke risk factors and resolve the issue of antithrombotic therapy based on their presence (or absence). This approach is justified by the results of published studies in which oral anticoagulants had an advantage over ASA even in patients with an average risk (index CHADS2 = 1, that is, in the presence of one risk factor) and rarely caused large bleeding. It is important to emphasize that the use of antiplatelet drugs was not accompanied by a reduction in the risk of adverse events. In addition, the CHADS2 index does not include many risk factors for stroke, and a comprehensive assessment of the likelihood of its development should take into account other risk-modifying factors (Table 5) [18].

Table 5. Index CHA_2DS_2VASc and stroke rate

(a) Risk factors for stroke and thromboembolism in patients with non-valve AF	
Major risk factors	**Clinically Significant Non-Principal Risk Factors**
History of stroke, TIA or systemic embolism, age ≥75 years	HF or moderate / severe LV systolic dysfunction (ejection fraction ≤40%), hypertension, diabetes, female gender, age 65-74 years, heart disease

(b) Calculation of the risk index in points (CHA_2DS_2VASc)	
Risk factor	Points
Heart failure / left ventricular dysfunction	1
Arterial hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke / TIA / Thromboembolism	2
Vascular disease[a]	1
Age 65-74 years	1
Female	1
Maximum value	9

(c) Index CHA_2DS_s-VASc and stroke rate		
Index CHA_2DS_s-VASc	Patient number (n=7329)	Stroke rate, % per year
0	1	0%
1	422	1,3%
2	1230	2,2%
3	1730	3,2%
4	1718	4,0%
5	1159	6,7%
6	679	9,8%
7	294	9,6%
8	82	6,7%
9	14	15,2%

Before starting anticoagulation, it is necessary to assess the risk of bleeding. Despite anticoagulation in elderly patients, the frequency of intracranial bleeding is significantly lower than in the past, and ranges from 0.1 to 0.6%. This may reflect reduced anticoagulation intensity, more careful dose selection, or improved hypertension control. The frequency of intracranial bleeding increases with INR> 3.5–4.0, while with INR 2.0–3.0 their risk is further increased compared to that at lower INR values [19].

Various indices have been developed to assess the risk of bleeding in patients receiving anticoagulant therapy. All of them suggest the allocation of groups of

low, medium and high risk (usually large bleeding). It can be assumed that the risk of major bleeding in the treatment of ASA and vitamin K antagonists is comparable, especially in older people [18]. The danger of falls is probably exaggerated, because the patient needs to fall more than 300 times a year so that the risk of intracranial bleeding exceeds the benefit of PAA in the prevention of stroke [19].

Based on a survey of a cohort of 3978 Europeans with AF who participated in EuroHeart Survey, a new simple bleeding risk index was developed - HAS-BLED (hypertension, impaired renal / hepatic function, stroke, history of bleeding or a tendency to bleeding, labile INR, age> 65 years, medication / alcohol intake) (Table 6) [19].

Table 6. HAS-BLED Bleeding Risk Index

Letter*	Clinical characteristics	Number of points
H	Hypertension	1
A	Impaired liver or kidney function (1 point for each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Label INR	1
E	Age >65 years	1
D	Medicines or alcohol (1 point for each)	1 or 2
	Total	Max 9 points

This index should be used to assess the risk of bleeding in patients with AF. An index value of ≥ 3 indicates a high risk. However, caution must be exercised and regular monitoring of the condition of patients who receive antithrombotic drugs (vitamin K antagonists or ASA) [19].

Control tasks

1. Controlled trial is:

A. retrospective

B. prospective

C. transversal

D. perpendicular

2. «Golden standard» of medical studies are:

A. cross-sectional trial

B. single blind trials

C. randomized controlled trials

D. paired comparative trials

3. A method in which neither the patient nor the doctor who is watching him knows which treatment method was used

A. double blind

B. triple blind

C. single blind

D. placebo controlled

4. A safe inactive substance, offered under the guise of drugs, which does not differ from the medicine in appearance, taste, smell, texture, is called

A. bioadditive

B. study drug analogue

C. homeopathic drug

D. placebo

5. A study in which the patient does not know and the doctor knows what treatment the patient receives is called

A. placebo controlled

B. double blind
C. triple blind
D. simple blind

6. How to create conditions so that in a randomized controlled trial, patients receiving placebo were not deceived:
A. the attending physician receives the patient’s oral consent to conduct the study
B. the patient signs an “Informed Consent” (where his consent to use a placebo is provided)
C. placebo does not have a harmful effect on the body, so its use does not require consent
D. patient signs consent to hospitalization

7. A study with a randomly selected control group and the presence of influence from the researcher is called
A. randomized controlled clinical trial
B. non-randomized trial
C. observational study
D. retrospective study

8. The concept of the "gold standard" includes
A. double-blind, placebo-controlled, randomized trial
B. simple non-randomized research
C. triple blind research
D. double blind non-randomized study

9. Conscious, clear and impartial use of the best evidence available when deciding on care for specific patients is one of the definitions:
A. biometry
B. evidence-based medicine

C. clinical epidemiology
D. medical statistics

10. By the method of selecting patients, studies are divided into
A. random and complex
B. equally probable and impossible
C. randomized and non-randomized
D. primary and tertiary

11. Random selection of observations is called
A. randomization
B. median
C. moda
D. probability

12. According to the degree of openness of the data, the study may be
A. opened and blind
B. closed and blind
C. opened and randomized
D. randomized or multicenter

13. From the perspective of evidence-based medicine, the doctor must decide on the choice of treatment method based on
A. information from the internet
B. peer experience
C. articles from a peer-reviewed journal with a high citation index
D. articles from an unknown source

14. The indicators characterizing the reliability of the information provided in the scientific journal are

A. reliability index

B. confidence index

C. significance index

D. citation index

15. One of the prerequisites for the emergence of evidence-based medicine is

A. limited financial resources for public health

B. the appearance of new medical specialties

C. improvement of research methods

D. development of mathematical statistics

Test answers:

1-B; 2-C; 3-A; 4-D; 5-D; 6-B; 7-A; 8-A; 9-B; 10-C; 11-A; 12-A; 13-C;14-D;15-A.

Glossary

Absolute risk – the absolute difference between the frequency of development of an undesirable effect when using a drug and the frequency of development of the same effect without using it

Analytical study – devoted to identifying the causes of the onset and spread of disease

Relative risk – the ratio of the frequency of development of an undesirable effect among people exposed to the factor being studied, with the frequency of development of a similar effect in the group of people not exposed to this factor

Odds ratio – an indicator that is used in medical statistics to quantify the connection density between traits in a population

Sample – this is a specially selected part of the population

Selective research – study based on data from a study of the incidence of a relatively small part of the population - samples

Secondary endpoint – characterizes the improvement in the quality of life of the patient either due to a decrease in the incidence of non-lethal forms of complications, or through the relief of clinical signs of the disease

Evidence based medicine – evidence-based clinical medicine section

Case Control Study – analytical retrospective study, the purpose of which is to identify the studied risk factor for the disease

Dynamic research – provides for a systematic study of information on incidence among the same population

Experimental study – involves a controlled intervention in the natural course of the disease in order to identify its causes

The final clinical result – a phenomenon that is important for changing health indicators (recovery, disability, mortality, life expectancy) and / or quality of life

Clinical study – an experiment conducted in a clinic to assess the potential effectiveness of drugs, diagnostic methods, treatment regimens for patients

Clinical epidemiology – methodological basis of evidence-based medicine, which studies the patterns of the spread of diseases

Cochrane Collaboration – an international non-profit organization that studies the effectiveness of medical devices and methods through randomized controlled trials

Meta analysis – the scientific method of summarizing (integrating) the quantitative results of homogeneous studies conducted at different times by different authors of the same medical technology in order to obtain the total statistical indicators of these studies

Observational study – does not include interference in the natural process of the onset and spread of diseases

Scientific research – organized to receive (confirm) new data

Indirect Performance Criteria – laboratory indicator or symptom, the dynamics of which directly characterizes the patient's condition and is reflected in the final clinical result

Instant study – it can be both descriptive and analytical. The main goal is to obtain information about the incidence of a population of a disease for a limited period of time, if necessary, such studies can be repeated.

Descriptive study – provides for descriptive epidemiological data, i.e. incidence data

Primary endpoint – a leading indicator that indicates a possible extension of the patient's life (reduction in overall mortality, mortality from the disease)

Field study – conducted outside health facilities

Population – this is a large group of people living in a certain geographical region and reproducing themselves in a generation

Prospective study – involves the study of information as new (fresh) cases of the disease do not exist before the start of the study

Randomization – random distribution of patients into groups

Retrospective study – based on the study of information on cases of the disease that occurred at any time in the past

Routine research – does not provide for the receipt of new scientific data, is carried out in the framework of the currently existing scientific ideas about the causes of the onset and spread of the disease

Systematic review – scientific research of a series of published separate homogeneous original studies with the aim of their critical analysis and evaluation

Surrogate endpoints – disease parameters that provide for a direct or long-term result of the factor

Continuous research – this study, conducted in the volume of the general population, which in epidemiology is more often referred to as the term population

Tertiary endpoint – this is an indicator that is not related to improving the quality of life or prolonging it, but may indicate the ability to prevent diseases by eliminating risk factors

GCP (Good Clinical Practice) – international standard of ethical standards and quality of scientific clinical research

GIN (Guidelines International Network) – international network of developers of clinical guidelines and protocols

GLP (Good Laboratory Practice) – a system of norms, rules and guidelines aimed at ensuring the reliability of laboratory research results

GMP (Good Manufacturing Practice) – rules for the organization of production and quality control of drugs

ICH (International Conference on Harmonization) – international conference on the harmonization of technical requirements for the registration of drugs used by humans

MEDLINE – The largest bibliographic database of articles in the field of medical science created by the US National Library of Medicine

SCORE (Systematic Coronary Risk Estimation) – cardiovascular risk rating scale

CHA2DS2-VASc – stroke risk index

HAS-BLED – bleeding risk index

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