

Branch Standard
The Standardization System in the Russian Federation Health Care System
Clinico-Economic Studies
General Provisions
91500.14.0001-2002-07-29
(Approved by the RF Ministry of Health on June 29, 2002)

I. Scope

The Branch Standard "Clinico-Economic Studies. General Provisions" is applicable to the health care system of the Russian Federation.

OST 91500.14.0001-2002 is an open system whose elements can be corrected or amended under conditions of the rapid development and improvement of methodological approaches to clinico-economic studies.

This standard is applicable to clinico-economic studies where results are intended for submission to regulatory authorities, and its requirements can be extended to other types of clinico-economic studies.

II. General Statements

OST 91500.14.0001-2002 is the code of rules that govern the conduct of clinico-economic studies and uses of their results, as well as documentation and reporting of the results. Observance of these rules guarantees the validity of results obtained in clinico-economic studies, protection of their subjects' rights and health, and protection of investigators' rights.

OST 91500.14.0001-2002 was designed to provide a regulatory basis to realization of Basic Legislation of the Russian Federation on Health Care (Vedomosti S'ezda Narodnykh Deputatov and Verkhovnogo Soveta Rossiiskoi Federatsii, 1993, No. 33, Art. 1318), the Law of the Russian Federation "On Medicines" No. 86-FZ of June 22, 1998 (Sobranie Zakonodatel'stva Rossiiskoi Federatsii, 1998, No. 26, Art. 3006); the Law of the Russian Federation "On Medical Insurance of Citizens in the Russian Federation" No. 1449-1 of June 28, 1991 (Vedomosti S'ezda Narodnykh Deputatov and Verkhovnogo Soveta Rossiiskoi Sovetskoi Federativnoi Sotsialisticheskoi Respubliki, 1991, No. 27, Art. 920), Resolution of the Government of the Russian Federation No. 1387 of November 5, 1997 "On measures for Stabilization and Development of Health Care System and Medical Science in the Russian Federation (Sobranie Zakonodatel'stva Rossiiskoi Federatsii, 1997, No.46, Art. 5312), and Resolution of the Government of the Russian Federation No. 1096 of September 11, 1998 "On the Program of State Guarantees of Provision of Free Medical Care to Citizens of the Russian Federation" (Sobranie Zakonodatel'stva Rossiiskoi Federatsii, 1999, No.44, Art. 5322).

OST 91500.14.0001-2002 was designed to ensure the following:

- unified approach to the conduct of clinico-economic studies and uses of their results;

- protection of the rights and health of subjects who participate in clinico-economic studies;
- protection of investigators' rights;
- substantiation of the choice of medicines and medical technologies for the development of regulations that would result in their rational uses;
- unification of newly developed basic programs of mandatory medical insurance;
- formulation of consistent clinical and economic requirements to the efficacy, safety, compatibility, and interchangeability of medical interventions, as well as their evaluation criteria;
- scientific substantiation of the development of a unified system of interrelated criteria for evaluation of clinical and economic parameters of the effectiveness of medical services, and establishing evidence-based requirements to their list and scope;
- economic substantiation of amendments to regulations in the standardization system of subjects of the Russian Federation, health care organizations, and medical institutions.

III. Conduct of This Regulation

This branch standard shall be conducted by the I.M. Sechenov Moscow Medical Academy of the RF Ministry of Health. The conduct procedure involves interaction of the I.M. Sechenov Moscow Medical Academy of the RF Ministry of Health with all interested organizations and persons, collection of information on results of the conduct, coordination of submission of suggestions for the improvement, amendment, and updating of this branch standard.

IV Clinico-Economic Analysis

4.1 Types of Clinico-Economic Analyses

Clinico-economic analysis is a methodology used for comparing the qualities of two or more methods of prevention, diagnosis, or pharmacological/nonpharmacological therapies based on comprehensive accounting of the results and costs of the medical intervention. The methodology of clinico-economic analysis is applicable to all medical interventions, e.g., pharmacological (pharmacoeconomics) and nonpharmacological therapies, diagnosis, prevention, and rehabilitation, in order to determine their economic expediency. There are several methods of clinico-economic analysis proper and supplementary methods that help obtaining trustworthy and practically significant results.

The major methods of clinico-economic analysis are as follows.

Cost-effectiveness analysis is a type of clinico-economic analysis that compares the results and costs of two or more interventions where the efficacy differs but the results are measured in the same units (mm Hg, hemoglobin concentration, number of complications prevented, years of life saved, etc.).

Cost-minimization analysis is the special case of cost-effectiveness analysis whereby two or more interventions characterized by identical effectiveness and safety but different

costs are compared. This analysis is recommended for comparative evaluation of different forms or conditions of the use of the same medicine or medical technology.

Cost-utility analysis is the special case of cost-effectiveness analysis where results of an intervention are measured in "utility" units from a medical services consumer perspective (such as quality of life). The most often used integral index is life-years or quality-adjusted life years (QALYs) gained.

Cost-benefit analysis is a type of clinico-economic analysis where the costs and results are measured in monetary units. This allows comparing the economic effectiveness of interventions whose results are expressed in various units (for example, an influenza vaccination program and a neonatal intensive care system for neonates with low birth weight).

Supplementary techniques of clinico-economic analysis include:

Cost of disease analysis takes into account all costs incurred by management of patients with a specified disease, both at the given time (interval) and any stage of health care, as well as disability and premature death rates. This analysis does not involve comparison of health care interventions and can be used for studying typical patient management practices for the specific disease. This approach is used for special purposes, such as costs planning, setting tariffs for multipart payment systems used by health care organizations and medical insurance providers, etc.

Modeling is a method of study of various objects, processes, and events based on mathematical or logical models that provide a simplified formal description of the object under study (patient, disease, or epidemic situation) and its changes caused by health care interventions.

Clinico-economic study is the study of practical application of methods in diagnosis, prevention, pharmacological and nonpharmacological therapies, and rehabilitation, which is performed for evaluating the cost-result relationships.

Sensitivity analysis is that aimed at determining the extent to which results of the study would change with changing its input parameters (variation in drug prices and changed parameters of efficacy, side effects, etc.).

Discounting introduces a correction factor for time in cost calculation: future costs are less important than current costs; conversely, immediate benefits are more valuable than future benefits.

Results of cost-effectiveness and cost-utility analyses are reported as appropriate indices of cost/effect ratio and/or incremental cost ratio (additional cost of achieving an additional result). Results of cost-minimization analysis are reported as absolute differences in costs related to the intervention examined in comparison to alternatives. Results of cost-benefit analysis are reported as the absolute difference between costs and benefits in monetary units or the costs-to-effect (both in monetary units) ratio.

It is recommended that the study report be accompanied by separate statements on costs and results of all interventions used.

4.2 Structure and Methodology of Clinico-Economic Analysis

Clinico-economic analysis includes the following steps:

- a) Development of the design and protocol of analysis, including:
 - formulation of goals and purposes of analysis;
 - choice of an alternative (reference) intervention;
 - choice of efficacy and safety outcomes for the medical interventions examined;
 - designing (when necessary) the protocol of an additional clinico-economic study and informed consent form.
- b) Evaluation of evidence for the efficacy and safety of health care interventions.
- c) Choice of the method of the clinico-economic analysis proper.
- d) Cost accounting for the purpose of this analysis.
- e) Economic calculation.
- f) Sensitivity analysis.
- g) Conclusions and suggestions, with account taken of the weaknesses of analysis that would limit the applicability of its results.

4.2.1 Formulation of the Goals and Purposes of Analysis

The investigator or sponsor of the study is responsible for formulation of its goals and purposes. In the Goals and Purposes section, there should be clear statement of the study perspective, that is, the subjects, groups, or organizations whose interests will be primarily reflected by the study design. Clinico-economic analyses can use various perspectives:

- societal perspective (including not only the health care system but also social services and other spheres involved);
- perspective of the federal health care system;
- perspective of the health care system of a subject of the Russian Federation;
- institutional perspective (that of a health care provider or health care regulatory body, including medical institutions, medical insurers, etc.), or private practice perspective;
- patient's and his/her family perspective;
- perspective of medical insurers, mandatory medical insurance foundations, and other institution and persons (should be specified).

4.2.2. Choice of a Reference Intervention

The intervention examined in a clinico-economic analysis can be compared to the following.

- An intervention most often used on similar indications (the typical management practice for the disease); an analysis of typical management practice is based on

examination of medical cards of hospitalized or ambulatory patients, as well as questionnaires filled by expert in specific fields of medicine or patients).

- An intervention considered the best (most effective) among several interventions currently used for similar indications. The optimal and most effective interventions are determined in research performed in accordance with current principles of clinical epidemiology.
- The least expensive intervention among several alternatives used for similar indications.
- An intervention recommended by a standard or other regulation.
- With no-intervention condition, provided that this can occur in clinical practice.

The choice of a reference intervention depends on the study perspective, goals, and purposes, and must be substantiated by the investigator.

4.2.3. Evaluation of the Efficacy and Safety of Medical Interventions: Outcomes

The following efficacy outcomes can be used in studies of medical interventions.

- a) Changes in health indices in the group treated with a drug or nonpharmacological medical technology (mortality, survival, life span, disability-adjusted live years, etc.).
- b) Changes in health-related life quality such as quality-adjusted life years saved (QALY)
- c) Indirect clinical effects (decreased complication or readmission rates, etc.).
- d) Direct clinical effects, such as shifts in physiological or biochemical parameters at which the pharmacological or nonpharmacological treatment was targeted (for example, blood pressure decrease, increased Hb levels, symptomatic relief or worsening, and functional deterioration or recovery).

Outcomes grouped under (a) and (b) in this list (definitive or strict criteria) are preferred. However, groups (c) and (d) criteria (intermediate or surrogate criteria) can be used when detailed data are not available.

4.2.4. Evaluation of the Efficacy and Safety of Medical Interventions: Evidence

The essential condition of clinico-economic analysis is evaluation of data on the efficacy and safety of the medical intervention, including the use of medicines. The validity of these results depends on the type of the study and ranges from high to low in the following order:

- evidence obtained from systematic survey;
- evidence obtained from prospective randomized studies;
- evidence obtained from large-scale prospective comparative nonrandomized studies;
- evidence obtained from retrospective comparative studies of large populations;

- evidence obtained from noncomparative studies or examination of a limited group of patients;
- evidence obtained from occasional observations;
- formalized expert opinion (e.g., that obtained by the Delphi method).

A clinico-economic study can be based on lower-rank evidence only if more valuable higher-rank evidence is not available.

Data on the efficacy and safety of medical technologies obtained from the authors' own clinico-economic study must be compared with results of other studies. When substantial discrepancies are found, a sensitivity analysis must be performed to estimate the variability of efficacy outcomes.

4.2.5. Choice of a Method for Economic Study

The specific choice of methodology for a clinico-economic analysis depends on the study goal, perspective, sponsor, medical technology examined, and clinical outcomes of this technology.

The choice of methodology for clinico-economic analysis must be substantiated by the investigator.

4.2.6. Cost Accounting

Investigators must account all costs as completely as possible over the whole period covered by clinico-economic analysis. It should be taken into account that the period of cost accounting can be several times longer than the period of direct treatment if the medical intervention studied causes long-term effects. The choice of the time period for cost accounting must be substantiated in the study report.

Evaluation of drug and services cost structures employ ABC analysis (classes A, B, and C include 80%, 15%, and 5% costs, respectively), VEM (Vital, Essential and Nonessential) analysis, and frequency analyses of the use of medical interventions.

4.2.7. Types of Costs

Medical intervention costs include the following groups.

a) Direct medical costs (all expenses of the health care system), such as:

- costs of diagnostic, therapeutic, rehabilitative, and preventive medical services; manipulations and procedures, including those performed at home (including medical personnel hourly rates);
- drug acquisition costs;
- inpatient hospital care costs;
- costs related to transportation of the patient by medical transport;

- costs of the use of medical equipment, rooms, and resources (distribution of fixed costs from budget items), etc.
- b) Direct nonmedical costs:
 - cash (minor) expenses of the patients, such as payments for additional services provided by medical institutions;
 - costs of nonmedical services (e.g., social services) delivered to a patient at home;
 - patient transportation expenses by personal or community (nonmedical) transport, etc.
- c) Indirect (alternative) costs (missed opportunity costs):
 - costs incurred by the absence of the patient at work due to disease or disability, including sick list payments, disability compensations, and other social compensations adopted by current legislation;
 - "cost" of the absence from work of family members or other caregivers related to the patient's condition;
 - economic losses due to decreased productivity at work;
 - economic losses due to premature death.
- d) Intangible losses are those related to pain and discomfort suffered by the patient in the course of treatment; currently, these costs are often left beyond the scope of analysis because it is difficult to provide their quantitative (monetary) estimates.

4.2.8. Sources of Information on Monetary Equivalents of Direct Costs

Determination of the monetary equivalent of direct medical costs is based on the following:

- medical services tariffs adopted in the regional Mandatory Medical Insurance (MMI) system;
- budget allocations for medical services offered by specific health care providers;
- tariffs of commercial medical services, including those covered by voluntary medical insurance or other commercial sources;
- averaged tariffs of several health care institutions (not less than 3-5, with substantiation of the choice);
- investigators' own economic calculations on the costs of medical services (the methodology of calculations must be specified).

Determination of direct drug acquisition costs (in monetary units) is based on the following:

- retail prices of medicines (for an analysis of ambulatory treatment costs and in the case where medicines are purchased directly by the patient);
- distributors bulk prices (for an analysis of in-hospital treatment costs) (not less than 3-5 bulk suppliers, with substantiation of the choice).

The preferred sources are averaged price estimates. Sources of pricing information on drugs and medical services must be specified in the report.

4.2.9. Cost Calculation

Cost calculation (estimation of expenses) in an economic analysis goes through four stages:

- Identification and description of resources consumed (list of diagnostic and therapeutic techniques; medicines administered; time spent by medical, management, and supplementary personnel; bed-days spent in specialized hospital departments; etc.).
- quantitative estimates of these resources in physical units (bed-days, number of surgical procedures, number of physician's visits or specialist consultations, number of instrumental and laboratory tests, number of nursing procedures, etc.).
- evaluation of each resource consumed in monetary units (costs of each bed-day, personnel, and each laboratory/instrumental test).
- correction for uncertainty and time (discounting). The recommended discount rate (without inflation) is 5% per year. A complete listing of costs taken into account in the economic study must be given in the report and accompanied by references to pricing information sources. A recommended practice is to provide an appendix with a list of prices for services and drugs used by investigators for the purposes of economic analysis.

4.3. Clinico-Economic Study

Clinico-economic studies are needed to obtain information on the actual efficacy and safety of medical interventions, as well as their costs. Clinico-economic studies can be performed as:

a) part of a clinical study of the efficacy and safety of medicines or nonpharmacological medical interventions;

b) self-contained study:

- retrospective survey, that is, examination of medical records related to the intervention;
- prospective survey in the form of examination of the efficacy and safety of a medical technology without the investigator's interference with patient management practices used by physicians;
- prospective study in the form of examination of the efficacy and safety of a medical intervention with parallel economic analysis.

c) Clinico-economic modeling analysis.

All clinico-economic studies must be performed by specialists whose education, professional training, and qualifications allow them to be responsible for appropriate conduct of the study. It is recommended that physicians, economists, clinical

pharmacologists, programmers, and specialists in data processing be involved in the study.

4.3.1. Principal Investigator

The Principal Investigator must be a specialist in an area of clinical medicine (such as clinical pharmacology or clinical epidemiology) who is aware of and works in accordance with current regulations applicable to qualitative clinical studies.

The Principal Investigator should gather a sufficient team of qualified investigators whose professional education and experience are consistent with the study goals.

The study personnel should work in settings that provide suitable working environment and ensure safety of the patients for the whole term of the study.

Each member of the study team must know the protocol, be informed on the test drug or medical technology, and know his or her duties and responsibilities in the study.

4.3.2. Information Obtained from the Study

Methods of collection, processing, and storage of information obtained from the study must ensure accurate and adequate representation, explanation, and confirmation of data, and these procedures must comply with requirements of this Branch Standard.

4.4. Clinico-Economic Study Performed as Part of a Clinical Study

Clinico-economic studies performed as part of clinical study must be in accordance with directives laid down in the Helsinki Declaration, standards and rules of Good Clinical Practice, this Branch Standard, and other applicable regulations. Data on a clinico-economic study planned as part of a clinical study must be included in the study protocol and submitted to Health Care Ethics Committee (hereinafter called Ethics Committee) together with the informed consent form and other documents in accordance with current regulations.

Data collected and recorded in a clinico-economic study can be entered in the main extended Case Report Form or a separate form developed with special consideration of goals and purposes of the study. The extended or additional Case Report Form must be submitted for approval in accordance with current regulations.

4.4.1. Study Subjects

Human subjects who receive the study or reference drug (medical intervention) can participate in the study only on a voluntary basis, after receiving detailed information on the study procedures and signing an informed consent form. The information that a clinico-economic study would be part of the clinical study must be included in the informed consent form. Informed consent must be obtained with observance of current regulations and ethical principles laid down in the Helsinki Declaration, and the subject's identity must be kept confidential.

4.4.2. Clinico-Economic Study Results

Results of a clinico-economic study performed as part of a clinical study must be presented in a separate report submitted simultaneously with the clinical study report and include detailed description of the study methodology (including the randomization procedure if applicable, placebo control, blinding, patients inclusion/exclusion criteria, sample sizes, and characterization of groups), evaluation of the efficacy of the study drug or medical technology, rates of side effects observed, patients withdrawal from the study, deviations from the protocol, and the study suspension or termination. The recommended clinico-economic study report form is given in Appendix 1.

4.5. Clinico-Economic Observation (retrospective or prospective)

Retrospective or prospective clinico-economic observation does not presume any active intervention involving human subject. Attending physicians prescribe therapies independently of investigators, and information is collected by copying appropriate data from medical records or polling (by means of questionnaires or interviews) of patients, their relatives, medical personnel, or other subjects in accordance with the study goals.

In order to protect the rights of subjects that provide information for further analysis, the study protocol must be submitted to the Ethics Review Board at the study site before the actual beginning of the study. If no Ethics Review Board is available at the study site or several institutions are involved simultaneously, the study protocol must be submitted for approval to the Ethics Committee.

Only medical specialists are allowed access to medical records. The study protocol must guarantee the nondistribution and nondisclosure of any information derived from medical records to third parties. In this context, the third parties are defined as persons not involved directly in providing medical care to the patient. The Principal Investigator is responsible for observance of the Protocol. Data presented for analytical and reporting purposes must be blinded as to the identity of the study subject. The Principal Investigator must inform the subjects that data on their health conditions would be copied from their medical records.

4.5.1. Collection of Information by Means of Questionnaires and Interviews

The subject who answers questions presented in a questionnaire or interview has the right to withdraw himself or herself from the study at any time. Information on the number of subjects who refused to continue participation in the study is entered in report without disclosure of these subjects' identity.

Refusal to continue the subject's participation in the study must not influence the scope or extent of medical care available to the subject.

The investigator must explain the goals and purposes of the study to the subjects and provide comprehensible information, avoiding special terminology where possible. The study protocol must guarantee nondistribution and nondisclosure of information to third

parties. Data presented for analytical and reporting purposes must be blinded as to the identity of the study subject. Study data sheets must not contain the subject's personal identification data.

4.6. Prospective Clinico-Economic Study

Clinico-economic study presumes active interference of the investigator with therapeutic and diagnostic procedures in the form of changes/additions to the general therapeutic procedure, including that prescribed by the patients management protocol). This definition applies to all studies where protocols presume the participation of the investigator in the planning of medical interventions.

Treatment performed in a clinico-economic study must be strictly consistent with the study protocol. Deviation from the protocol caused by the patient's health conditions or other considerations results in exclusion of this patient from the study. Clinico-economic study must comply with general ethical principles of the Helsinki Declaration and current regulations of the Russian Federation applicable to studies involving human subjects.

Medicines used in clinico-economic studies must be registered in the Russian Federation in accordance with current regulations and only for the approved indications. If the clinico-economic study test drug is not registered in the Russian Federation or registered but used for other than approved indications, this study must be regarded as a clinical study and performed in accordance with applicable current regulations.

Two procedures of clinico-economic study are essential for protection the study subjects' rights and safety, as well as protection of the investigators' professional interests and rights.

- approval by the Ethics Committee;
- informed consent of study subjects.

Documents are submitted to the Ethics Committee in accordance with Standard Operating Procedures (SOP).

The Ethics Committee review procedure is determined by current regulations, SOPs, or the Statute of the Ethics Committee. Principal Investigator must obtain all the information on the Ethics Committee review procedures and schedule and the list of documents to be submitted. Principal Investigator is responsible for interacting with the Ethics Committee, submitting information on the study, and obtaining the appropriately documented approval.

Definitions of inclusion and exclusion criteria must minimize the risk of health hazards.

During the participation of the subject in the study and after completion of the study, the investigator or medical institution must provide all the necessary medical care for any adverse events that may appear during the study, including clinically significant deviations of laboratory test results.

Information obtained during the study must not be distributed or disclosed to any third party (persons not involved directly in providing medical care to the patient). Data presented for analytical and reporting purposes must be blinded as to the identity of the study subject.

4.6.1. Voluntary Informed Consent

The voluntary informed consent form is the statement whereby the subject agrees to participate in the clinico-economic study after obtaining all relevant information.

Candidates for participation in prospective clinico-economic studies or their legal representatives must sign a written informed consent form. In the procedure of obtaining and signing the informed consent, the investigator must abide to current regulations and the main ethical principles of the Helsinki Declaration. Information presented to potential participants consists of two blocks:

- information on the planned study (including information on the investigational drug);
- information on the patient's rights.

The potential participant receives the main information at the stage of recruitment for the study. This information is presented in a document that consists of two parts: Subject's Information Sheet and Informed Consent Form, which the volunteer must sign before entering the study.

Independent Ethics Committees must determine whether this document is consistent with current regulations.

During the study, each participant must be informed an any additions to or changes in the study protocol or new information on the effects of the investigational drug to an extent that may influence the subject's decision to continue his or her participation in the study. The Ethical Review Board (Committee) must encourage the provision of appropriate information to subjects and approve new (amended) versions of the informed consent form.

The study participants must be provided with information under the following conditions:

- information sheet and informed consent form must be presented in writing to potential participants only after approval of these documents by the Ethical Review Board (Committee);
- the potential participant or his/her legal representative must be given sufficient time to analyze this information and make a decision;
- participants must receive reliable and relevant information; the text should avoid poorly intelligible scientific terms or these terms must be explained;
- whenever new information on the investigational drug or the course of the study becomes available, this information should be presented to study subjects in writing (in a new informed consent form or supplement to it) after approval of these documents (amendments) by the Ethical Review Board (Committee);
- neither the study physician nor his/her colleagues must exert pressure on potential participants in order to obtain the consent; the study physician must present all the information to participants at any time of the study;
- the study participant's information sheet and informed consent form must be presented in a single document, preferably with common pagination, and each page must

indicate the page number and total number of pages (e.g., page 1 of 5, 2 of 5, etc.); the participant must sign a form acknowledging the receipt of one copy of this document signed by study physician.

The information sheet presented to each potential participant must contain the following information:

- study title and protocol No.;
- sponsor (if exists);
- study goals and purposes with substantiation of the necessity of the study;
- study type and duration for each participant (it is desirable to specify how many participants are involved in this study in Russia and other countries), and the probability for each participant to be assigned to any study group ;
- characterization of the study and reference drugs (treatment schedules);
- study procedures, including invasive ones;
- possible benefits, risks, and discomfort experienced by the participant; the participant must be informed if the study has no therapeutic purposes;
- actions the participant must undertake in the case of unpredicted changes in his or her health conditions: contact persons and terms of referral, as well as alternative treatment available;
- the subject's expenses, if any, related to participation in the study; procedures and amount of reimbursement if any will be provided;
- study participant responsibilities;
- compensation that the participant will be provided if his or her health conditions deteriorate during the study;
- information on the confidentiality of participants, as well as the possibility and extent of disclosure of data to selected persons (study auditors, monitors, etc.);
- the study physician's statement that the participant will be notified whenever important new information becomes available that may be relevant to the subject's consent;
- information on approval of the protocol by an Ethics Review Board;
- contact for obtaining additional information;
- possible circumstances and/or causes of withdrawal from the study;

Information contained in the subject information sheet must be:

- complete, reliable (objective), and trustworthy;
- topical, which is achieved by issuing interim information sheets;
- comprehensible to laypersons;
- written correctly, and the translation must be thoroughly edited and adapted (errors and stylistic flaws may give impression of poor literacy or disrespect for potential participants);

- given in a delicate form.

The document must be reviewed by an Ethics Committee.

Ethics Committees that review information documents intended for study participants must pay special attention to objectivity and privacy. Objectivity means observing a balance between the rights and interests of participants and study physicians. Privacy of study participants is ensured by observing confidentiality rules, documentation procedures, and restricted access to medical records.

Thus, the significance of the study participant's informed consent is as follows:

- it serves as evidence of the facts that information was provided and the patient gives his/her consent;
- it formulates the content of information communicated to the patient;
- it formulates the agreement between the investigator and patient;
- it clearly formulates the patient's health risks and the study physician's risk of professional liability, and minimizes the circumstances dependent on the physician and patient that may cause adverse events;
- it protects the patient's rights and protects the physician from undue claims.

The informed consent form must be signed and dated by the patient if he or she is able to do so. If the study subjects can be included only with permission of their legal representatives (e.g., minors or severely demented persons), the informed consent form must be signed by their legal representatives. If informed consent cannot be obtained from the patient because his or her current condition needs urgent medical aid, informed consent can be obtained from the patient's relatives.

4.7. Clinico-Economic Modeling

Modeling is performed when actual data required for clinico-economic calculations cannot be obtained from a study or observation.

Modeling can be used:

- when a clinical study did not record indirect or long-term results of treatment, and results of clinical studies are supplemented with data obtained from other sources (nonrandomized studies, observational studies, expert opinions, etc.);
- when results of studies performed in other countries are used for substantiation of clinical or management decisions made in Russia;
- when conclusion on the expedience of administration of medicines, schedules, and therapies must be made in relation to patient groups not included in previous studies (e.g., patients with complicated disease);
- when differences in resource consumption between investigational and actual settings must be accounted for.

The most frequently used modeling approaches are:

- decision tree;

- Markov model.

When other models are used in the study, the report must contain detailed description of their methodology and data processing.

When representing results of model-based clinico-economic calculations, investigators must substantiate the choice of a specific method of analysis, formulate all conditions of modeling (tolerance, hypotheses, etc.), describe and substantiate their choice of the source literature from which data were taken to provide the basis for analysis.

Results of model-based economic analysis are regarded as preliminary ones. However, they can be used for substantiation of economic expediency of the use of medicines, treatment schedules, and therapies where study or observation results are not available.

V. Use of This Regulation

OST 91500.14.0001-2002 must be used as the regulatory basis for clinico-economic studies in all organizations and institutions of the health care system.

5.1. Interpretation of Results of Clinico-Economic Studies for Determination of the Expediency of Inclusion of Medicines or Nonpharmacological Therapies in Appropriate Regulatory Documents for the Health Care Standardization System

Clinico-economic substantiation of the expediency of uses of medicines or nonpharmacological therapies must be taken into account in the development of:

- patient management protocols;
- list of vitally important and essential medicines;
- formulary lists and schedules;
- other regulations on the scope and structure of public health care.

It is also recommended to provide clinico-economic substantiation for the use of medical interventions in methodological guidelines, manuals, reference materials, and textbooks that describe approaches to diagnosis, treatment, and prevention of diseases, as well as patients rehabilitation. The validity and practical significance of results of clinico-economic studies are evaluated by experts involved in the development of appropriate regulations.

The following points must receive special consideration in determining the validity of results of clinico-economic analyses:

- clear definition of study goals and purposes;
- formulation of the study perspective and its compliance with the goals of persons who make decisions on the expedience of the medical intervention studied;
- substantiation of the choice of the reference medical intervention, and compliance of this alternative with the goals of persons who make decisions on the expedience of the medical intervention studied;
- clear definitions of the efficacy and safety outcomes used and their evaluation (clinical and social significance of the outcome, the significance level of data on the presence and magnitude of the effect);

- availability of the essential data on cost accounting methodology (list of resources accounted and sources of pricing information);
- substantiation of the clinico-economic analytical methodology used;
- use of additional analyses, such as modeling, discounting, and sensitivity analysis, that increase the validity of the study results;
- the level of correspondence of methods used and conclusions made.

The minimum list of questions that should have positive answers in critical analysis of clinico-economic study results is given in Appendix 2.

APPENDIX 1
to Branch Standard
Clinico-Economic Studies
General Provisions
91500.14.0001-2002

Recommended Structure for a Clinico-Economic Study Report

1. Principal Investigator: full name, affiliation, position, research degree, and title.
2. Contact information of investigators: full names, affiliation, position, work phone number, fax number, and e-mail.
3. Study goals and purposes.
4. Study site.
5. Brief description of the study intervention (for medicines: international nonproprietary name, trade name, manufacturer, pharmaceutical properties, pharmacological group, indications, dosage and administration, efficacy for indications similar to those examined in the study, safety (side effects), reference to clinical study results, and data on registration in the Russian Federation; for nonpharmacological interventions: name of the method, mechanism of action, indications, method and frequency of administration, efficacy for indications similar to those examined in the study, safety (side effects), reference to clinical study results, data on approval in the Russian Federation).
6. Reference intervention used for comparison of the efficacy and economic expediency of the use of the test drug with substantiation of the choice (except for analyses of the cost of a disease):
 - 6.1. a medicine most often used for similar indications (typical practice);
 - 6.2. the most suitable medicine currently available for similar indications;
 - 6.3. the least expensive medicine used for similar indications;
 - 6.4. placebo;
 - 6.5. no-treatment condition
 - 6.6. other (please indicate);
 - 6.7. substantiation of choice;
 - 6.8. description of the reference medicine or medical intervention (see Section 4).
7. Study perspective (please specify whether the economic expediency was studied from the societal perspective or the perspective of the health care system of subjects of the Russian Federation, institutional, or patient's perspective).
8. Method of economic analysis with substantiation of choice:
 - 8.1. cost-minimization analysis;

8.2. cost-effectiveness analysis;

8.3. cost-utility analysis;

8.4. cost-benefit analysis.

9. Method of evaluation of the efficacy of the intervention studied:

9.1. data from the literature (indicate the type of the study, its title, authors, and reference to publication):

9.1.1. results of systematic survey;

9.1.2. randomized controlled study;

9.1.3. prospective comparative study;

9.1.4. retrospective comparative studies;

9.1.5. prospective noncomparative study;

9.1.6. other study type (please indicate);

9.2. investigators; own results (indicate what type of study was performed):

9.2.1. systematic survey;

9.2.2. randomized controlled study;

9.2.3. prospective comparative study;

9.2.4. retrospective comparative studies;

9.2.5. prospective noncomparative study;

9.2.6. other study type (please indicate).

10. Brief description of the study: sample size, characterization of patients, description of interventions examined, terms of observation, results and their statistical significance, use of methods that decrease the probability of error (blinding, placebo control, etc.).

11. If the efficacy was evaluated by using the results of the investigators' own study, please indicate whether these results were consistent with other similar studies.

12. Efficacy outcomes used for the test drug:

12.1. medico-biological (such as blood biochemistry and blood pressure), please indicate;

12.2. medico-social (e.g., number of complications prevented, life span, or number of life years saved) please indicate;

12.3. quality of life (please specify the method);

12.4. other (please indicate).

13. Costs accounted in the study:

13.1. direct medical costs;

13.1.1. drug medication costs;

13.1.2. costs of medical services;

- 13.1.3. other (please indicate).
- 13.2. indirect medical costs (please indicate);
- 13.3. nonmedical costs (please indicate).
14. Source of pricing information used in calculations:
 - 14.1. drugs prices;
 - 14.2. medical services prices;
 - 14.3. other prices.
15. Method of discounting, if applicable.
16. Results (cost-effectiveness, cost-utility, or cost-benefit ratio, incremental or cost ratio; method of calculation).
17. Methods and results of sensitivity analysis, if one was performed.
18. Conclusions.

APPENDIX 2
to Branch Standard
Clinico-Economic Studies
General Provisions
91500.14.0001-2002

**Recommended Questions for Estimating the Validity and Practical Significance of
Results of a Clinico-Economic Analysis.**

1. Were the study goals and purposes clearly formulated ?
2. Was the study perspective specified? Is it consistent with the problem for whose solution the study results were intended to be used?
3. Is this a comparative study?
4. Is there sufficient information on the study intervention and reference (alternative) intervention?
5. Does the report contain substantiation of the choice of a reference intervention used for comparison of the efficacy and economic expediency of the investigational drug (except for the cases where the cost of disease was analyzed)? Is this choice consistent with the problem for whose solution the study results were intended to be used?
6. Is there any detailed and comprehensible description of the method of the clinico-economic study?
7. Were data on the efficacy of each study intervention presented? Are they reliable?
8. If the efficacy was evaluated by using the results of the investigators' own study, then are these results consistent with other similar studies?
9. Are the efficacy outcomes chosen for this study consistent with the problem for whose solution the study results were intended to be used?
10. Was information on final (strict) efficacy outcomes for study interventions (life years saved and quality of life) provided?
11. Were all considerable costs related to study intervention accounted (from the study perspective)?
12. Were sources of pricing information used for cost calculation specified?
13. Was cost discounting performed in a study of more than one year duration ?
14. Was sensitivity analysis performed?
15. Are conclusions consistent with methodology used ?