Registered in the Ministry of Justice on August 23, 2016

Registration No. 43357

# Order No. 200n dated April 01, 2016 of the Ministry of Health of the Russian Federation On Approval of Rules for Good Clinical Practice

In accordance with item 18 Art. 5 of Federal Law No. 61-FZ of April 12, 2010 On Circulation of Medicines (Legislation Bulletin of the Russian Federation, 2010, No.16, art. 1815; 2012, No. 26, art. 3446; 2013, No.27, art. 3477; 2014, No. 52, art. 7540) and item 5.2.155 of Provision of the Ministry of Health of the Russian Federation approved by Resolution of the Government of the Russian Federation of June 19, 2012 No. 608 (Legislation Bulletin of the Russian Federation, 2012, No. 26, art. 3526; 2015, No. 23 art. 3333), I decree as follows:

1. To approve the attached Rules of Good Clinical Practice.

2. To establish that the Rules of Good Clinical Practice approved by this Order extend to legal relations concerning the conduct of clinical trials of a medicinal product for medical use, permission for the conduct of which has been requested in due form after this Order came into force .

3. To declare Order No. 266 of June 19, 2003 On Approval of Rules of Good Clinical Practice in the Russian Federation (registered by the Ministry of Justice of the Russian Federation on June 20, 2003, registration No. 4808) to be no longer in force.

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| Acting Minister (signed) | I.N. Kagramyan |

# Rules of Good Clinical Practice (approved by Order No. 200n of April 01, 2016 of the Ministry of Health of the Russian Federation)

# I. General Provisions

1. These Rules of Good Clinical Practice (hereafter “the Rules”) regulate the design, conduct, performance, monitoring, auditing, recording of clinical trials of a medicinal products (hereafter, respectively, “clinical trial”, “medicinal product”) with the participation of human subjects, and the analysis and reporting of clinical trial results, that provide assurance that the data and reported results are credible and accurate, and that the rights, health and confidentiality of trial subjects’ personal data are protected.

2. For the purposes of these Rules the terms and definitions which are contained in Federal Law No. 61-FZ of April 12, 2010 On Circulation of Medicines\*(1) (hereafter “the Federal Law On Circulation of Medicines”) are applied.

3. The object of the clinical trial is a pharmaceutical form of an active ingredient or a placebo being tested or used as a reference in a clinical trial, or a medicinal product with a marketing authorization when used in a way different from the approved form (in the framework of the state registration of the medicinal product), or when used for a new indication, or when used to gain further information about an approved use (hereafter “the investigational medicinal product”). Investigational medicinal products are used in accordance with a protocol that has been approved in the framework of the clinical trial approval application.

The circulation of investigational medicinal products shall be carried out in accordance with the Rules of Good Manufacturing Practice and Rules of Good Storage and Transportation Practice\*(2).

4. The clinical trial is conducted in relation to an individual (patient or healthy volunteer) who participates in a clinical trial either as a recipient of the investigational medicinal product or as a control (hereafter “clinical trial participant”).

After receiving information on the clinical trial and before the start of the clinical trial, every clinical trial participant gives voluntary consent to participate in the clinical trial by signing the patient information sheet.

Consent to participate in the clinical trial can be given by the clinical trial participant’s legally acceptable representative \*(3).

5. The clinical trial of an investigational medicinal product is conducted on the basis of the clinical trial approval issued by the Ministry of Healthcare of the Russian Federation (hereafter “the Ministry”) based on the outcome of the expert examination of clinical trial approval application dossier and ethical evaluation of the planned clinical trial according to Article 39 of Federal Law No. 61-FZ of April 12, 2010 On Circulation of Medicines.

6. Expert examination of clinical trial approval application dossier indicated in item 5 of these Rules, is carried out by the federal state budgetary institution in charge of expert examination of medicinal products \*(4), the ethical evaluation of the planned clinical trial is conducted by the Ethics Council\*(5), \*(6).

7. The clinical trial is conducted in accordance with a clinical trial protocol (hereafter “the protocol”), which includes but is not limited to the following information:

1) the protocol title, protocol identification number, and approval date. New protocol versions have a version number and date; protocol amendments have the amendment number and date;

2) name and address of the organization conducting the clinical trial and the monitoring organization (if they differ);

3) the last name, first name and patronymic (if any) and title of the person authorized to sign the protocol and the protocol amendments on behalf of the organization conducting the clinical trial;

4) the last name, first name and patronymic (if any), title, address, and telephone number of the medical expert of the clinical trial, appointed by the organization conducting the clinical trial;

5) the last name, first name and patronymic (if any) and title of the investigator responsible for conduct of the clinical trial as well as the addresses and telephone numbers of the trial sites;

6) the last name, first name and patronymic (if any), title, address, and telephone number of the physician responsible for all trial-site related medical decisions (if other than investigator);

7) names and addresses of clinical laboratories and other medical and/or technical departments and institutions involved in the clinical trial;

8) background of the clinical trial, including:

a) name and description of the investigational medicinal products (including placebo and active control);

b) summary of the results of preclinical studies and clinical trials of the investigational medicinal products (if carried out previously);

c) summary of the known and potential risks and benefits of the investigational medicinal product to the clinical trial participants;

d) description and justification for the route of administration, dosage, dosage regimen, and treatment period(s);

e) a statement that the clinical trial will be conducted in accordance with the clinical trial protocol and these Rules;

f) description of the population to be studied;

g) references to literature and data that are relevant to the clinical trial and that provide background for the clinical trial;

9) clinical trial objectives and purpose;

10) description of the clinical trial design, including:

a) a statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial;

b) description of the design type of the clinical trial (double-blind, placebo-controlled, parallel, and other types of trials) and a schematic diagram of the clinical trial design, procedures and stages;

c) description of the measures taken to minimize and avoid bias including randomization and blinding - a procedure in which one or more parties to the trial are kept unaware of the treatment assignments (single-blinding usually refers to the clinical trial participants being unaware, and double-blinding usually refers to the clinical trial participants, investigators, and, in some cases, data analysts being unaware of the treatment assignments);

d) description of the trial treatment, dosages and dosage regimen of the investigational medicinal products, description of the dosage form, packaging and labeling of the investigational medicinal products;

e) duration of participation by patients and healthy volunteers in the clinical trial, description of the sequence and duration of all trial periods including follow-up, if any;

f) description of the "stopping rules" of parts or the whole of the clinical trial, "discontinuation criteria" for individual clinical trial participants;

g) description of the accountability procedure for the investigational medicinal products, placebo and comparators;

h) description of maintenance of trial treatment randomization codes and procedures for breaking codes;

i) the identification of data to be recorded in the case report form (without prior written or electronic record of data) and to be considered to be source data;

11) clinical trial participant inclusion criteria;

12) clinical trial participant exclusion criteria;

13) withdrawal criteria for clinical trial participants (terminating investigational medicinal product administration, trial treatment);

14) information on all medicinal products to be administered in the clinical trial including their names, doses, the dosing schedules, the route and modes of administration, treatment periods, follow-up periods for each group of clinical trial participants, data on medicinal products permitted (including rescue treatment) and not permitted for use by the clinical trial participants before and (or) during the trial, procedures for monitoring clinical trial participants compliance;

15) specification of the efficacy parameters of the investigational medicinal product and methods, timing for assessing, recording and analysing of efficacy parameters of the investigational medicinal product;

16) specification of safety parameters of the investigational medicinal product and methods, timing for assessing, recording and analysing of safety parameters of the investigational medicinal product;

17) requirements for reports, recording and reporting procedure on adverse events and intercurrent illnesses;

18) the type and duration of follow-up of clinical trial participants after adverse events;

19) description of clinical trial statistical methods, including:

a) timing of interim analysis;

b) the planned number of clinical trial participants to be enrolled with sample size justification;

c) the level of significance to be used in the clinical trial;

d) criteria for the termination of the clinical trial;

e) procedure for accounting for missing, unused, and spurious data;

f) procedure for reporting any deviations from the original statistical plan (all deviations from the original statistical plan are described and justified in the protocol and (or) the final report of the clinical trial);

g) selection procedure of clinical trial participants to be included in the analyses (all randomized clinical trial participants, all dosed clinical trial participants, all eligible clinical trial participants, evaluable clinical trial participants);

20) description of quality control and quality assurance activities;

21) description of ethical aspects of the clinical trial;

22) description of data handling and record keeping;

23) description of the procedure for financing of the clinical trial and insurance of clinical trial participants;

24) indication of the possibility of publishing the clinical trial results;

8. A compilation of the nonclinical and clinical data is provided in the investigator’s brochure (hereafter “the brochure”), which includes but is not limited to the following information:

1) name of the organization that developed the medicinal product, research number, chemical, international non-proprietary, group, and trade name of the medicinal product, date of the brochure, version number of the brochure, number and date of the previous version of the brochure, and statement of confidentiality of information contained in it, indicated on the brochure title page;

2) brief summary on physical, chemical, pharmaceutical, pharmacological, toxicological pharmacokinetic, metabolic, and clinical information, that is relevant to the stage of clinical development of the investigational medicinal product, rationale for performing research with the investigational medicinal product, its expected preventive, therapeutic or diagnostic indications, general approach to be followed in evaluating of the investigational medicinal product;

3) description of physical, chemical and pharmaceutical properties, and dosage form of the investigational medicinal product, its components (including chemical and (or) structural formulae), and justification (if required) of composition of the dosage form, including excipients;

4) results of preclinical pharmacology, toxicity, pharmacokinetics, and investigational medicinal product metabolism studies, with a description, including:

a) animal species tested, their number and sex in each group;

b) unit dose, frequency and route of administration, duration of dosing;

c) systemic distribution, duration of the post-exposure follow-up;

d) nature and frequency of pharmacological or toxic effects, their severity or intensity, dose response, time to onset of effects, reversibility, duration of effects;

e) preclinical pharmacology;

f) pharmacokinetics, metabolism and disposition of the investigational medicinal product in tissues of all species studied, including data on absorption, local and systemic bioavailability of the investigational medicinal product and its metabolites as well as their relationship with data from pharmacological and toxicological trials in animals species;

g) toxicology (description of toxicological effects found in studies conducted in different animal species (if applicable) including data on single and repeated dose toxicity, carcinogenicity, special studies (local irritancy and sensitisation), reproductive toxicity, genotoxicity (mutagenicity)).

5) description of the effects of the investigational medicinal product in humans including:

a) pharmacokinetics (including metabolism, absorption, plasma proteins binding, distribution and elimination) and bioavailability of investigational medicinal product (drug interactions, meal effect and other interactions), other existing data on pharmacokinetics (results of pharmacokinetics studies performed within clinical trials on different groups);

b) data on safety, pharmacodynamics, efficacy, and dose response of effects of the investigational medicinal product (and its metabolites, if any) obtained from preceding trials (with participation of healthy volunteers and (or) patients) and interpretation of these data (summary reports of safety and efficacy of the investigational medicinal product based on the results of completed clinical trials and tabular summaries of adverse drug reactions for all clinical trials, the important differences in patterns/incidences of adverse drug reactions are described);

c) post-authorization experience of use of the investigational medicinal product with indication of the country where the investigational medicinal product has been authorized and marketed;

6) guidance for the investigator on diagnostics and treatment of possible overdose and adverse drug reactions when using the investigational medicinal product, based on previous clinical experience and pharmacological properties of investigational medicinal products, as well as summarized information on different properties of the investigational medicinal product.

9. The report on clinical trial results (hereafter “the report”) is prepared in written form by the organization that conducted the clinical trial, based on conclusions of the medical organizations that carried out the clinical trial and includes:

1) title page, containing:

а) the report title;

b) the investigational medicinal product name;

c) the studied indication for use of the investigational medicinal product;

d) a brief description of the clinical trial design, use of a comparator, duration of the clinical trial, investigational medicinal product dosage and patient population;

e) the name of the organization that conducted the clinical trial;

f) identification number of the clinical trial protocol;

g) clinical trial phase;

h) start and completion dates of the clinical trial;

i) date of the report;

j) information on the investigator, head of the medical organization, responsible representative of the organization that conducted clinical trial;

2) a brief synopsis - summary of the clinical trial with numerical data to illustrate results;

3) table of contents with a list and location of appendices and tables;

4) list of abbreviations and definitions of the terms used in the report;

5) names of medical organizations where the clinical trial was carried out, their locations, contact phones;

6) objectives and purpose(s) of the clinical trial;

7) plan of the clinical trial, including:

a) overall plan (design), plan/description of the clinical trial and schematic representation of the clinical trial stages and procedures;

b) justification of the plan/design of the clinical trial;

c) population selection criteria;

d) treatments administered, identity of investigational medicinal products, methods of assigning the clinical trial participants to treatment groups (randomization), doses and timing of investigational medicinal products administration, prior and concomitant therapy;

e) data on investigational medicinal product efficacy and safety (efficacy and safety measurements assessed and flow chart);

f) methods of quality assurance and significance of obtained data including audit information and inspection results (if performed);

g) changes made to the clinical trial protocol;

8) data on clinical trial participants and their assignment to groups;

9) information on deviations from the clinical trial protocol;

10) evaluation of efficacy of the investigational medicinal product, which includes but is not limited to:

a) data set to be analyzed during the clinical trial;

b) demographic and (or) other baseline data;

c) information on compliance by clinical trial participants with the treatment regimen;

d) results of efficacy assessment: statistical and analytical data, conclusions about efficacy;

11) information on safety of the investigational medicinal product, which includes but is not limited to:

a) adverse drug reactions (brief summary of adverse drug reactions, their analysis, lists of adverse drug reactions observed in all clinical trial participants);

b) deaths and other serious adverse events;

с) evaluation of clinical laboratory parameters;

d) vital signs, physical examination findings and other information on safety related to the examination of clinical trial participants.

12) the following information are provided in the form of appendixes for the study report:

a) tables, figures and graphs referred to , but not included in the report text;

b) protocol and protocol amendments;

c) sample case report form;

d) list of ethics committees;

e) samples of written information for patients and informed consent forms;

f) list and description of investigators and other responsible persons;

g) analytical documentation if more than one batch of the investigational medicinal product is used in the trial (listing of codes of patients receiving the investigational medicinal product from specific batches);

h) randomization scheme and codes (identification of clinical trial participants and treatment assigned);

i) information about the audit (if carried out);

j) documentation on statistical methods;

k) documentation of inter-laboratory standardisation methods and quality assurance procedures if used;

l) publications regarding the study.

# II. Independent ethics committee

10. The independent ethics committee (hereafter “the independent ethics committee”) is created at the level of the medical organization (local ethics committee), at the regional level and functions as an independent body safeguarding the rights, safety, and well-being of all clinical trial participants.

11. The independent ethics committee should consist of a sufficient number of persons having qualifications and experience for expert examination of medical and ethical aspects of the planned clinical trial; as a rule these are five persons, and at least one person should have primary area of interest in a nonscientific area.

12. The independent ethics committee acts in accordance with its approved standard operating procedures, containing requirements regarding its composition and qualification of its members, information on the institutor, the procedure for the conduct of meetings, review of documents and taking decisions on those documents.

13. The independent ethics committee deliberates and takes its decisions on the basis of the following documents:

a) the clinical trial protocol;

b) the investigator’s brochure;

c) the patient information sheet;

d) data on the investigators’ experience in the relevant specialization and their experience in clinical trials;

e) data on medical organizations where the clinical trial is intended to be conducted (full and short name, legal form of operation, legal address and address of the trial site, phone, telefax, e-mail of each medical organization);

f) information on the planned timelines of the clinical trial;

g) photocopies of the compulsory insurance concluded in accordance with standard rules for compulsory insurance, indicating the maximum number of patients participating in the clinical trial\*(7);

h) information on a composition of the investigational medicinal product.

Other clinical trial documents and materials may be submitted to the independent ethics committee, including: materials describing measures intended to recruit patients / healthy volunteers into the clinical trial; written materials to be provided to clinical trial participants; information on payments and compensations to clinical trial participants; the current version of the investigator’s curriculum vitae and (or) other materials proving his/her qualifications.

14. Following the examination of the documents indicated in item 13 of these Rules, the independent ethics committee makes one of the following decisions:

a) approves the clinical trial;

b) refuses the clinical trial;

c) recommends to make changes to the submitted documents required prior to clinical trial approval;

d) cancels or suspends the clinical trial approval, issued earlier.

15. The independent ethics committee:

a) monitors compliance with ethical norms and the rights of clinical trial participants in the course of a clinical trial;

b) considers the investigator’s qualifications for the planned clinical trial as documented by of the investigator’s curriculum vitae and other relevant documentation;

c) in the course of the clinical trial conducts continuing review of relevant documentation and evaluates progress of the clinical trial (at least once a year);

d) may request more information on the clinical trial than is outlined in the patient information sheet be given to a clinical trial participant by the clinical trial organizer, when, in the judgement of the independent ethics committee, this would increase the level of protection of the rights and safety of the clinical trial participant;

e) reviews both the amount and method of payment to clinical trial participants to assure that neither presents problems of coercion or undue influence on the clinical trial participants. Information regarding payments to clinical trial participants including the methods, amounts and schedule of payments, is set in the patient information sheet.

f) may invite people with expertise in relevant areas to assist the independent ethics committee in decision-making, who should not participate in the deliberations or in the vote by the independent ethics committee;

g) approves amendments to the clinical trial protocol;

h) performs other activities for proper execution of the independent ethics committee’s functions and responsibilities.

16. The independent ethics committee immediately notifies in writing the investigator and clinical trial organizer about its decisions concerning the clinical trial and its reasons.

17. Where the protocol indicates that obtaining consent of the patient or the patient’s legally acceptable representative before patient’s inclusion into the clinical trial is not possible, including in emergency situations, the independent ethics committee should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such clinical trials.

18. The independent ethics committee retains all relevant records related to the conduct of a clinical trial as a rule for a period of at least 3 years after completion of the clinical trial and makes them available to third parties in compliance with the legislation of the Russian Federation on personal data, commercial, state and other legally protected confidential information.

# III. The organization conducting the clinical trial

19. The clinical trial of a medicinal product can be organized by (hereafter “the clinical trial organizer”) may be:

a) the developer of the medicinal product or an entity authorized by the developer;

b) educational organizations of higher education, educational organizations of post-graduate professional education;

c) scientific and research organizations.\*(8).

20. The clinical trials of medicinal products are conducted according to a protocol developed by the clinical trial organizer or a legal entity authorized by the organizer. The organizer can amend the protocol in the written form describing the changes or official clarifications to the protocol.

21. In order to obtain an approval for the clinical trial of a medicinal product the organizer submits to the Ministry the documents listed in Part 2 Article 39 of the Federal Law On Circulation of Medicines.

22. The clinical trial organizer:

a) obtains the clinical trial approval by the Ministry before the start of the clinical trial;

b) defines and allocates the rights, duties and functions of all parties participating in the clinical trial;

c) approves documents defining procedures of the clinical trial, collection, registration and reporting of data in accordance with the protocol and these Rules (hereafter “the organizer’s standard operating procedures”);

d) reviews the brochure at least once a year and updates it, if required, provides the current brochure version to the investigator (subinvestigator), and to the independent ethics committee;

e) implements and maintains quality assurance and quality control systems in accordance with organizer’s standard operating procedures;

f) secures agreement from all parties involved in the clinical trial to ensure direct access to all medical organizations participating in the trial, all source data (or) documents, and reports obtained and composed during the clinical trial, for the purpose of monitoring and audit of clinical trial quality;

g) designate appropriately qualified personnel who will provide investigators with consultations on trial related medical questions;

h) uses an identification code assigned to each clinical trial participant by the investigator (a unique number consisting of digits and (or) letters, used instead of the last name, first name, patronymic (if any) of a clinical trial participant in reports on adverse events, adverse reactions and other data for purposes of personal data confidentiality and identification of all data for every clinical trial participant);

i) manages a case report form for each clinical trial participant (on paper or electronic document) designed to record all information in accordance with the protocol (hereafter “case report form”);

j) makes the decision to create an independent data-monitoring committee to assess the progress of the clinical trial and evaluate data on safety and efficacy of the investigational medicinal product, including (but not limited to) in order to recommend continuation or termination of the clinical trial or making changes to the protocol;

k) ensures retention of documents related to the clinical trial upon termination of clinical development of the investigational medicinal product in respect to one, several or all indications, methods of administration, dosage forms, usually for a period of two years from the time of official termination of the development;

l) reports the termination of the clinical development of the investigational medicinal product to all investigators and to the medical organizations where the clinical trial is carried out;

m) reports to the Ministry any transfer of ownership data on the investigational medicinal product;

n) selects investigators and medical organizations for conduct of the clinical trial; a coordination committee may be set up and (or) a coordinator may be selected from among investigators in case of a multicenter clinical trial;

o) engages persons with the relevant qualifications throughout all stages of the clinical trial (from designing the protocol, case report form, plan of statistical analysis, general management of the clinical trial, work with data, and data verification to statistical analysis of obtained data and preparing the final clinical trial report);

p) monitors quality and completeness of the data obtained during the clinical trial.

23. When using electronic trial data handling and/or remote electronic trial data systems, the clinical trial organizer:

a) provides and documents compliance of the electronic data processing system with requirements on data completeness, accuracy and reliability as well as consistent intended performance (hereafter “data validation”);

b) approves standard operating procedures for electronic systems;

c) ensures that electronic systems work in such a way that any changes will be documented and data that there will be no deletion of entered data;

d) provides a security system for clinical trial data, preventing unauthorized access to the data including (by not limited to) by way of establishing a list of persons authorized to access, amend and copy the data;

e) ensures that clinical trial blinding, used in the blind method, is maintained during data entry and processing in the electronic system.

24. Before entering an agreement with a medical organization to conduct a clinical trial, the clinical trial organizer provides the investigator and medical organization with the clinical trial protocol and an up-to-date brochure and provides sufficient time for acquaintance with the provided information.

25. The clinical trial organizer has to obtain from the investigator and the authorized representative of the medical organization written consent by signing of the protocol or another document:

a) to conduct the clinical trial in compliance with the protocol, these Rules and requirements of legislation of the Russian Federation on the circulation of medicines;

b) to comply with procedures for clinical trial data recording/reporting;

c) to permit monitoring and auditing;

d) to retain the clinical trial related documents until the clinical trial organizer informs the investigator and medical organization that these documents can be destroyed.

26. The clinical trial organizer should act as an insurer to insure at its own expense the risk of harm to the patient’s life and health resulting from participation in the clinical trial of a medicinal product by entering into a compulsory insurance contract\*(9). The contract conditions and the size and procedure of insurance payment are established by Order No. 714.

27. If the medical organization where the clinical trial is planned to be conducted has its own independent ethics committee, the clinical trial organizer should obtain confirmation that this independent ethics committee is organized and acts in accordance with these Rules as well as the approval by this independent ethics committee of the clinical trial.

If the independent ethics committee conditions its approval upon amendments to the clinical trial documents and data, the medical organization provides copies of all the amended documents and data to the clinical trial organizer.

If the opinion of the independent ethics committee concerning a clinical trial is changed, including withdrawal of the approval issued previously, the medical organization immediately informs the clinical trial organizer of this fact.

28. The clinical trial organizer should ensure availability of safety and efficacy data of the investigational medicinal product, substantiating its use, and update the brochure as new data regarding efficacy and safety of the investigational medicinal product becomes available in frame of the clinical trial.

29. The clinical trial organizer ensures that investigational medicinal products (including comparators and placebo) used in a clinical trial have been manufactured in accordance with Good Manufacturing Practice, met relevant quality requirements and are coded and labeled in a manner that protects the blinding, if applicable.

The primary (if technically possible) and secondary (consumer) packaging of medicinal products for clinical trials should bear the inscription “For clinical trials”\*(10).

30. In blinded clinical trials the investigational medicinal product coding system should include a mechanism that permits rapid identification of this medicinal product in case of a medical emergency, but does not permit undetectable breaks of the blinding.

31. If significant formulation changes are made in the investigational medicinal product or comparator during the clinical trial, then the results of any additional studies of the pharmaceutical form of the medicinal product (needed to assess whether these changes would significantly alter pharmacokinetics, safety and efficacy of the investigational medicinal product) should be available prior to the use of the new formulation in clinical trials. In such case the organizer is responsible for amending the protocol.

32. The clinical trial organizer is responsible for supplying the medical organization where the clinical trial is carried out with the investigational medicinal product.

The clinical trial organizer has to maintain sufficient quantities of the investigational medicinal product needed for the clinical trial and for confirmation of its compliance with the requirements of pharmacopoeia articles or (if there are no such requirements) with normative documentation or a normative document, as well as maintain records of batch sample analyses and characteristics.

The clinical trial organizer shall maintain detailed and timely records that document shipment of the investigational medicinal product to medical organizations, its return, and destruction.

The clinical trial organizer is responsible for the ongoing safety evaluation of the investigational medicinal product and notifies all investigators and medical organizations involved in the clinical trial of findings that could affect adversely the safety of clinical trial participants and (or) have an impact on the course of a clinical trial.

33. The clinical trial organizer reports to all investigators and medical organizations taking part in the clinical trial and to the Federal Service for Surveillance in Healthcare all serious and unexpected adverse drug reactions and also submits to the Federal Service on Surveillance in Healthcare periodical safety reports of the investigational medicinal product\*(11).

34. The clinical trial organizer monitors the clinical trial, including oversight of the progress of a clinical trial, collection of data and submission of results in accordance with the protocol, standard operating procedures, these Rules, and requirements of legislation of the Russian Federation on the circulation of medicines.

The clinical trial organizer appoints an individual with scientific and (or) special knowledge needed to carry out monitoring of the clinical trial.

The person appointed by the clinical trial organizer for monitoring should comply with the standard operating procedures of the clinical trial organizer.

35. The purposes of clinical trial monitoring are to verify that:

a) the rights and well-being of clinical trial participants are protected;

b) data obtained in the clinical trial are accurate, complete and verifiable from source documents;

c) the clinical trial is in compliance with the currently approved protocol version and amendments to it, requirements of these Rules and legislation of the Russian Federation on the circulation of medicines.

36. The person appointed by the clinical trial organizer for monitoring a clinical trial carries out the following activities:

a) provides interaction between the clinical trial organizer, medical organization and investigator;

b) verifies and monitors the investigator’s qualification and availability of resources of the medical organization needed for the clinical trial, including laboratories, equipment and staff;

c) verifies for the investigational medicinal product:

the storage times and conditions, and availability of sufficient supplies throughout the trial;

that the investigational medicinal product is supplied only to subjects who are eligible to receive it and at the protocol specified dose(s);

that the clinical trial participants are provided with necessary instruction on properly using, storing, and returning the investigational product;

that the receipt, use, and return and destruction of the investigational medicinal product at the medical organization are controlled and documented by investigator;

d) verifies that the investigator follows the approved protocol and its amendments, maintains documents and records data of the clinical trial in a correct, complete, accurate and timely manner;

e) verifies that written informed consent has been obtained before each clinical trial participant's inclusion in the clinical trial;

f) ensures that the investigator has the current brochure version, other documents and materials needed for the clinical trial;

g) ensures that information required for the conduct of the clinical trial is provided to investigators;

h) verifies that the investigator is enrolling only eligible clinical trial participants;

i) verifies that clinical trial data are recorded in a correct, complete and timely manner and that clinical trial documents are maintained in due order;

j) checks the accuracy and completeness of recording in the case report form of data required by the protocol, data on change of dose and (or) treatment, identified adverse events and adverse drug reactions, visits missed by a clinical trial participant, and omitted tests and examinations. All cases of exclusion and withdrawal of clinical trial participants from the clinical trial should be reported and explained in the case report form;

k) informs the investigator of any errors, omissions and illegible entries in the case report form and ensures that appropriate corrections are made, dated, explained (if required) and signed by the investigator;

l) communicates to the investigator deviations from the protocol, the organizer’s standard operating procedures, requirements of these Rules and legislation of the Russian Federation on the circulation of medicines, takes appropriate actions designed to correct and prevent recurrence of the detected deviations.

37. Written clinical trial monitoring reports are submitted to the clinical trial organizer by the person appointed to monitor the clinical trial in the manner and timeframe established by the clinical trial organizer’s standard operating procedures.

The clinical trial monitoring report should contain the date of the monitoring visit, identification of the monitored medical organization, names of the investigators, other individuals involved in the clinical trial conduct, with whom the person appointed as monitor maintained communication, a description of the review, identified shortcomings, conclusions and other relevant information regarding monitoring of the clinical trial.

38. Apart from the clinical trial monitoring the clinical trial organizer should perform an independent check of compliance of the clinical trial with the protocol, the clinical trial organizer’s standard operating procedures, these Rules and the requirements of legislation of the Russian Federation on the circulation of medicines (hereafter “the clinical trial audit”).

For the purposes of clinical trial audit the clinical trial organizer appoints individuals who are independent of all parties involved in the clinical trial conduct and have suitable qualifications, training, and experience for such an audit.

The plan and scope of the clinical trial audit are developed and approved by the clinical trial organizer taking account of the number of clinical trial participants, the type and complexity of the clinical trial, the level of risks to clinical trial participants and other circumstances.

39. If serious and (or) persistent cases of noncompliance with established requirements for the clinical trial by the investigator or medical organization are found during clinical trial monitoring or audit, the clinical trial organizer terminates participation of the investigator or medical organization in the clinical trial and amends the protocol.

40. The Ministry shall be informed by the clinical trial organizer within five working days after the date of completion, suspension or termination of the clinical trial.

41. In multicenter clinical trials the clinical trial organizer ensures:

a) that all medical organizations taking part in the multicenter clinical trial conduct the clinical trial in strict compliance with the clinical trial protocol;

b) development of case report forms that enable collection of required data from all medical organizations participating in the multicenter clinical trial;

c) that prior to the start of the clinical trial the rights and responsibilities of medical organizations and investigators have been documented and the protocol, the clinical trial organizer’s standard operating procedures and instructions on completion of case reports forms have been provided to the above mentioned participants.

# IV. The role of the investigator

42. The head of the medical organization that carries out the clinical trial appoints an investigator (hereafter “the investigator”) in charge of this clinical trial, who has a medical specialization appropriate for the clinical trial and at least three years of clinical trial experience, and, at his/her suggestion, subinvestigators out of physicians of the medical organization\*(12).

43. The investigator and subinvestigators should be aware of preclinical trial results, the current version of the brochure, protocol, other documents and data relevant for the clinical trial.

44. The investigator performs screening of clinical trial participants, ensures that adequate medical care is provided to a clinical trial participant\*(13).

45 The investigator and subinvestigators should be familiar and comply with these Rules and other requirements of legislation of the Russian Federation on the circulation of medicines. Noncompliance with these Rules and falsification of clinical trial results will lead to liability under legislation of the Russian Federation\* (14).

46. The investigator should have time and resources, including laboratories, equipment and staff, needed to conduct the clinical trial properly.

47. If an individual consented to take part in a clinical trial, the investigator notifies clinical trial participant’s primary physician about his/her participation in the clinical trial.

48. The investigator carries out the clinical trial in compliance with the protocol.

The investigator has to comply with the protocol and must not make changes to it without a decision of the Ministry and approval by the independent ethics committee, except in cases where there is a direct threat to the life and (or) health of a clinical trial participant.

Any deviation from the approved protocol is documented and promptly referred for review and approval to the independent ethics committee and the clinical trial organizer.

49. The investigator reports to the independent ethics committee:

a) deviations from, or changes of, the protocol to eliminate immediate hazards to the clinical trial participants;

b) changes affecting significantly the conduct of the clinical trial and/or increasing the risk to clinical trial participants;

c) all adverse drug reactions that are both serious and unexpected;

d) new data, which may be evidence of increased risk to clinical trial participants or may have unfavorable effect on the clinical trial.

50. The investigator has to ensure the use of investigational medicinal products by clinical trial participants in accordance with the protocol, follow the randomization method defined by the protocol (random assignment of clinical trial participants to treatment and control groups aimed to minimize bias) and ensure that the code is broken only in accordance with the protocol.

If the clinical trial is conducted using a blind method the investigator documents and explains to the clinical trial organizer any premature unblinding of the investigational medicinal product.

51. The investigator maintains records of the investigational medicinal products and comparators, including their delivery, the inventory at the medical organization, the use by each clinical trial participant, destruction and return to the clinical trial organizer.

The investigator can assign duties for the accountability of investigational medicinal products and comparators to a pharmacist or another appropriate individual who is under the supervision the investigator.

Records should include dates, quantities, batch/serial numbers, expiration dates (if applicable) and unique code numbers assigned to the investigational medicinal products and comparators and the clinical trial participants.

The investigator has to maintain records confirming that the clinical trial participants received investigational medicinal products and (or) comparators in the doses and quantities specified by the clinical trial protocol.

52. The investigator informs the clinical trial participant or his legally acceptable representative:

a) that the clinical trial is experimental, participation in the clinical trial is voluntary and the clinical trial participant may refuse to participate and withdraw from the clinical trial at any time;

b) of the purpose of the clinical trial, its duration and approximate number of clinical trial participants;

c) of treatment options during the clinical trial and probability of random assignment to one of the treatment groups;

d) of clinical trial procedures including all invasive procedures;

e) of responsibilities of the clinical trial participant;

f) of expected risks and benefits for the clinical trial participant as well as (in relevant cases) for an embryo, fetus or nursing infant;

g) of alternative procedures or treatment methods apart from those provided by the protocol, which may be available to clinical trial participant as well as their potential advantages, benefits and risks;

h) of compensation and (or) treatment available to the clinical trial participant in case of harm to health resulting from participation in the clinical trial;

i) of planned payments to the clinical trial participant for participation in the clinical trial (if any);

j) of expected expenses of the clinical trial participant resulting from his/her participation in the clinical trial (if any);

k) that by signing the patient information sheet the clinical trial participant or his legally acceptable representative gives consent to access by the person appointed for monitoring the trial, and by the auditors, independent ethics committees and competent authorities to the clinical trial participant’s medical records;

l) that records identifying the clinical trial participant will be kept confidential; their disclosure is regulated by legislation of the Russian Federation, and confidentiality of clinical trial participant data will be maintained in case of publication of the clinical trial results;

m) that the clinical trial participant or his legally acceptable representative will be immediately informed of any facts, which may affect clinical trial participant’s willingness to continue participation in the clinical trial;

n) of persons who can be contacted to obtain additional information on the clinical trial and the rights of the clinical trial participants;

o) of foreseeable circumstances and (or) reasons under which participation in the clinical trial may be terminated.

53. The use of special terms in information on the clinical trial should be minimized and the information should be understandable to the clinical trial participant or his legally acceptable representative.

54. Before voluntary informed consent may be obtained, the investigator should provide to the clinical trial participant or his legally acceptable representative an adequate time for making a decision to decide whether or not to participate in the clinical trial. The clinical trial participant or his legally acceptable representative has the right to receive full and accurate answers to all questions concerning the clinical trial.

55. Before inclusion in the clinical trial, the clinical trial participant and/or his legally acceptable representative should obtain a signed and dated copy of the patient information sheet and other materials concerning the clinical trial. The clinical trial participant is informed of all changes in the documents and clinical trial data concerning his participation during the conduct of the clinical trial.

56. Within the timeframe established by the protocol the investigator has to report to the clinical trial organizer, all serious adverse drug reactions except those, which are defined in the protocol or the brochure as not needing immediate reporting.

The investigator provides to the clinical trial organizer a detailed written report as promptly as possible upon the first reports of serious adverse reactions. The immediate and follow-up reports should identify clinical trial participants by the unique codes assigned to them.

57. For a reported death of a clinical trial participant at the request of the clinical trial organizer, independent ethics committee, Ministry and (or) Federal Service for Surveillance in Healthcare the investigator should provide any additional information concerned this case including the autopsy report and postmortem epicrisis.

58. In case of a threat to a clinical trial participant’s life or health the investigator has to notify the head of the medical organization and clinical trial organizer within 24 hours. A decision to suspend the clinical trial is made by the head of the medical organization and (or) clinical trial organizer; a decision to terminate the clinical trial is made by the authorized federal executive body on the basis of a written report from the head of the medical organization or the clinical trial organizer.

In case of early termination or suspension of the clinical trial, the investigator and (or) medical organization where the clinical trial was carried out should immediately inform the clinical trial participants, provide them with required treatment and follow-up, and inform the clinical trial organizer and independent ethics committee, providing detailed written explanation of the reason for the clinical trial suspension or termination.

59. The investigator ensures full and accurate management of clinical trial documents (including written, electronic, magnetic, and optical records, scans, X-ray images and electrocardiograms), describing the methods, organization and (or) results of the clinical trial.

60. Clinical trial documents should be retained by the medical organization in accordance with contract provisions agreed upon with the clinical trial organizer or, if this provision was not addressed in the contract, as a rule, for a period of two years after the state registration of the medicinal product in Russia or the official termination of clinical development of the investigational medicinal product.

61. Upon completion of the clinical trial the investigator notifies the head of the medical organization, prepares a report in compliance with the requirements of item 9 of these Rules and provides it to the clinical trial organizer and the independent ethics committee.

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\*(1) Bulletin of Legislation of the Russian Federation, 2010, No. 16, art. 1815; No. 31, art. 4161; No. 42, art. 5293; No. 49, art. 6409; 2011, No. 50, art. 7351; 2012, No. 26, art. 3446; No. 53, art. 7587; 2013, No. 27, art. 3477; No. 48, art. 6165; 2014, No. 11, art. 1098; No. 43, art. 5797; No. 52, art. 7540; 2015, No. 10, art. 1404; No. 27, art. 3951; No. 29, art. 4359, art. 4367, art. 4388; No. 51, art. 7245; 2016, No. 2, art. 325; No.9, art. 1268; No. 23, art. 3287.

\*(2) Item 18, Article 5, Federal Law No. 61-FZ of April 12, 2010 On Circulation of Medicines.

\*(3) Concerning the person indicated in part 2, Article 20, Federal Law No. 323-FZ of November 21, 2011 On Fundamental Healthcare Principles in the Russian Federation (Bulletin of Legislation of the Russian Federation, 2011, No. 48, art. 6724; 2013, No. 48, art. 6165).

\*(4) Order No. 750n of August 26, 2010 of the Ministry of Health and Social Development of the Russian Federation, On Approval of Rules for Medicinal Product Expert Examination and the Conclusion of an Expert Committee (registered by the Ministry of Justice of the Russian Federation on August 31, 2010, registration No. 18315) with amendments included by Orders No. 1041 of December 13, 2012 (registered by the Ministry of Justice of the Russian Federation on April 10, 2013, registration No.28082), No. 152n of April 03, 2014 (registered by the Ministry of Justice of the Russian Federation on June 10, 2014, registration No. 32648).

\*(5) Order No. 753n of August 26, 2010 of the Ministry of Health and Social Development of the Russian Federation On Approval of the Procedure for Organization and Conduct of Expert Examination of the Possibility of Conducting a Clinical Trial of a Medicinal Product and the Conclusion of an Expert Committee (registered by the Ministry of Justice of the Russian Federation on August 31, 2010, registration No. 18303).

\*(6) Order No. 986n of November 29, 2012 of the Ministry of Health and Social Development of the Russian Federation On Approval of the Resolution on an Ethics Committee (registered by the Ministry of Justice of the Russian Federation on February 07, 2013, registration No. 26897).

\*(7) Order No. 714 of September 13, 2010 of the Government of the Russian Federation On Approval of Typical Rules for Compulsory Insurance of the Life and Health of a Patient Involved in a Clinical Trial of a Medicinal Product (Bulletin of Legislation of the Russian Federation, 2010, No. 38, art. 4832; 2011, No.22, art. 3171; 2012, No. 37, art. 5002; 2014, No. 43, art. 5892) (hereafter “Order No. 714”).

\*(8) Part 3, Article 38 of Federal Law No. 61-FZ of April 12, 2010 On Circulation of Medicines.

\*(9) Taking account of Part 1, Article 44, Federal Law No. 61-FZ of April 12, 2010 On Circulation of Medicines.

\*(10) Part 8, Article 46, Federal Law No. 61-FZ of April 12, 2010 On Circulation of Medicines.

\*(11) Order No. 757n of August 26, 2010 of the Ministry of Health and Social Development of the Russian Federation On Approval of the Procedure for Monitoring of Medicinal Products, Registration of Adverse Reactions, Unforeseen Adverse Reactions in the Use of Medicinal Products (registered by the Ministry of Justice of the Russian Federation on August 31, 2010, registration No. 18324).

\*(12) Item 1, Article 40, Federal Law No. 61-FZ of April 12, 2010 On Circulation of Medicines.

\*(13) Part 2, Article 98, Federal Law No. 323-FZ of November 21, 2011 On Fundamental Healthcare Principles in the Russian Federation (Bulletin of Legislation of the Russian Federation, 2011, No. 48, art. 6724).

\*(14) Item 12, Article 40, Federal Law No. 61-FZ of April 12, 2010 On Circulation of Medicines.