

Ministry of Health of Ukraine

#### ORDER

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|  |  | 23.09.2009 № 690 |

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| Registered at the Ministry  of Justice of Ukraine on  29.10.2009  under № 1010/17026 |

**About Approval of Procedure for Conducting Clinical Trials of Medicinal Products and Expert Evaluation of Materials Pertinent to Clinical Trials and Model Regulations of the Ethics Committees**

(amended by MoH Ukraine Orders

№523 as of 12.07.2012

№304 as of 06.05.2014

[№ 966 as of 18.12.2014](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran2#n2)

[№ 639 as of 01.10.2015](http://zakon0.rada.gov.ua/laws/show/z1520-15/paran5#n5))

According to articles 7, 8 of the Law of Ukraine “On Medicines”, Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, as amended, and with the purpose of harmonization with international rules of conducting clinical trials of medicinal products I order:

1. To approve Procedure for Conducting Clinical Trials of Medicinal Products and Expert Evaluation of Materials Pertinent to Clinical Trials (attached).

2. To approve Model Regulations of the Ethics Committees.

3. To consider as void the MoH Ukraine Order as of 13.02.2006 № 66 “About Approval of Procedure for Conducting Clinical Trials of Medicinal Products and Expert Evaluation of Materials Pertinent to Clinical Trials and Model Regulations of the Ethics Committee” registered at the Ministry of Justice of Ukraine on 10.03.2006 under № 252/12126, the MoH Ukraine Order as of 17.05.2007 № 245 “About Approval of the Procedure for Assigning Specialized Health Care Settings Where Clinical Trials May Be Conducted” registered at the Ministry of Justice of Ukraine on 17.08.2007 under № 950/14217, and the MoH Ukraine Order as of 11.08.2006 № 560 “About Approval of a List of Health Care Settings Where Clinical Trials May Be Conducted”.

4. That Yu. B. Konstantinov, Director, Board for Regulatory Policy in Circulation of Medicines and Healthcare Products provides the state registration of the present order at the Ministry of Justice of Ukraine according to the established procedure.

5. I hereby authorize Z.M. Mytnyk, Deputy Minister, to supervise execution of this order.

6. The order shall take effect from the date of its publication.

**V. M. Kniazevych**

Minister

APPROVED

MoH Ukraine Order

as of 23.09.2009 № 690

(in wording of the MoH Ukraine Order

as of 12.07.2012 № 523)

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# PROCEDURE

**for Conducting Clinical Trials of Medicinal Products**

**and Expert Evaluation of Materials Pertinent to Clinical Trials**

**I. General**

1.1. This Procedure has been compiled in accordance with articles 3, 44 of the Essential Principles of the health legislation of Ukraine, articles 7, 8 of the Law of Ukraine "On Medicines", Law of Ukraine "On Personal Data Protection" and with due consideration of requirements of Directives 2001/20/EC of the European Parliament and of the Council of 4 April 2001, 2001/83/EC of November 06, 2001, Regulations of the European Parliament and of the Council 1901/2006 of December, 2006 and 1902/2006 of December, 2006, ICH GCP, international ethical principles for biomedical research involving human subjects and Ethical Code of Doctor.

1.2. This Procedure specifies main requirements to clinical trials of medicinal products, which may be conducted on patients (volunteers) along full or shortened program, including the bioavailability/bioequivalence studies, as well as the multicenter clinical trials.

1.3. This Procedure shall cover all types of clinical trials of medicinal products except for non-interventional studies and clinical trials of medicinal products which are conducted without participation of pharmaceutical companies within research activity.

This Procedure shall not cover all types of clinical trials of tissue and cell transplants, including stem cells of cord blood.

4. The State Expert Center of the Ministry of Health of Ukraine (hereinafter – the Center) shall be responsible for an expert evaluation of materials of clinical trials as well as for clinical audit of the clinical trial of medicinal products.

**II. Definition of Terms**

2.1. The terms in this Procedure are used in the following meaning:

Multi-center clinical trial – the trial of a medicinal product which is conducted according to a single protocol of a clinical trial conducted at more than one trial site;

Bioavailability– the rate and extent to which an active substance or its active moiety is absorbed from a pharmaceutical form and becomes available at the site of action;

Bioequivalence– two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutically alternative and if their bioavailability after administration in the same molar dose is similar to a degree that their effects, with respect to both efficacy and safety, will be essentially the same;

Close relatives – physical persons the natural relation between whom is based on a descent one from another or from common ancestors and has legal significance in cases envisaged by the legislation. The close relatives are husband/wife, parents, children, sibs;

Investigator’s brochure – a compilation of the clinical and pre-clinical data on the investigational medicinal product which are relevant to its study in humans;

Manufacturer of medicinal product – a legal entity that performs at least one stage of manufacture of a medicinal product, including packaging;

Subject (trial subject) – a patient (healthy volunteer) who participates in a clinical trial according to the current procedure;

Investigational medicinal product - a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a registration certificate, but used or manufactured (formulated or packaged) in a way different from the registered pharmaceutical form, or when used for an unregistered indication, or when used to gain further information about the registered form of the medicinal product;

Investigator/co-investigator – a doctor with a sufficient proficiency and the experience in patient care, knows rules of good clinical practice and relevant regulatory documents. The investigator is responsible for the conduct of the clinical trial of medicinal product at trial site. If the trial is conducted by a team of individuals at a trial site, one of investigators is nominated as responsible study team leader and may be called the principal investigator.

Investigational medicinal product’s dossier – an information about the quality of any investigational medicinal product including a reference product and a placebo as well as data of pre-clinical study and information about the previous clinical trials or the clinical use of the investigational medicinal product.

Expert evaluation of materials of clinical trial – averification, analysis and assessment of materials of clinical trial of a medicinal product in order to prepare motivated conclusions on the conduct of a clinical trial/substantial amendment.

Health facility (health care setting) (hereinafter – HCS) – a legal entity of any type of property and organization and legal form or its separate subdivision, the main task of which is to provide medical care based on an appropriate license and professional activity of medical (pharmaceutical) staff;

Legal representatives– parents, adoptive parents, parent tutors, tutors, trustees, representatives of tutorial and custodial authorities.

Applicant for clinical trial – a natural person or a legal entity (e.g., sponsor, contract research organization), who submits to the Center an application for obtaining conclusion on the conduct of a clinical trial/substantial amendment. If not a sponsor, an applicant may submit the application only if sponsor's power of attorney with clearly defined granted powers is available.

Clinical study report – results of a clinical study and their analysis in writing.

Subject identification code/number - a unique identifier assigned to each trial subject by the investigator to protect the subject's identity and used in lieu of the subject's name in the clinical trial materials.

Case Report Form (hereinafter - CRF) – a printed, electronic or optical document designed to record all of the trial protocol-required information on trial subject to be provided to a sponsor.

Informed consent – a decision, which must be in writing, dated and signed, to take part in the clinical trial, taken freely after having been duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, by his or her legal representative (close relative); If the individual is unable to write/read, his/her oral informed consent in the presence of at least one witness who confirms the trial subject’s consent in written form may be given in exceptional cases;

Clinical trial (study) of medicinal product – a research work aimed at any investigation in humans as trial subjects intended to discover or verify clinical, pharmacokinetic, pharmacodynamic and/or other effects including to study absorption, distribution, metabolism and excretion of one or more investigational medicinal products and/or to detect adverse reactions to one or several investigational medicinal products with the purpose to assess its (their) safety and/or efficacy.

Clinical audit of clinical study – a procedure of an official check by the Center of materials (documents), facilities, equipment and instruments, records, systems, which assure safety and quality, and of other resources related to a clinical trial and which may be available in a health care setting, laboratories, premises of the sponsor or the contract research organizations, etc.

Ethics committee at a health care setting(hereinafter – ethics committee) - an independent body at a health facility (a health care setting) where clinical trials are conducted and which includes medical and scientific professionals and non-medical members, community members whose responsibility is to protect the rights, safety and well-being of trial patients (healthy volunteers), ethical and legal principles of conducting clinical trial.

Based on the assessment of ethical and legal principles the ethics committee at health facility (health care setting) endorses the conduct of clinical trial at place of its conduct located at HCS at which this committee has been formed and is functioning.

Contract research organization – a natural person or a legal entity which according to the contract concluded with the sponsor performs one or more of its functions (powers) in the clinical trial and acts on the basis of the power of attorney with clearly defined granted powers from the sponsor.

Medicinal products - substances or their mixtures, of natural, synthetic, or biotechnological nature used for prevention of pregnancy, for prophylaxis, diagnosis, and treatment of human diseases, or intended to change the organism's physiological state and functions.

Site of trial (hereinafter - trial site) – a particular site where the main activities pertinent to a clinical trial (patients’ inclusion, treatment, observations etc.) are carried out in a health care setting.

Monitor – a person assigned by the sponsor or the contract research organization who controls the performance of a clinical trial in compliance with the protocol of clinical trial.

Non-interventional trial - a study where the medicinal products are prescribed in the usual manner in accordance with the approved Instructions for Medical Use. The assignment of the patient to a particular therapeutic group is not foreseen in advance by a trial protocol, but the prescription of the medicinal product falls within current practice and is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients, and the epidemiological methods shall be used for the analysis of collected data.

Unexpected Adverse Reaction- an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for a non-registered product or Instructions for Medical Use/summary of product characteristics for a registered product).

Patient (healthy volunteer) **-** an individual who may be involved as a trial subject in a clinical trial of medicinal product.

Source documents – original documents, data and records (e.g., hospital records, ambulatory medical records, laboratory notes, memos, subjects’ diaries or evaluation checklists, medicines dispensing records, printouts from automated instruments, verified and attested copies or transcripts of sound track, microfiches, photographic negatives, microfilms or magnetic carriers, x-rays, administrative materials, records kept at pharmacy, laboratory and instrumental diagnostics department of subjects involved in a trial, etc.);

Adverse reaction – in context of clinical trial of a medicinal product (original/generic) or study of its new indication, particularly if therapeutic doses of the medicinal product are not defined, adverse reactions include any negative and unexpected responses to any dose of the medicinal product. The term “response to the administration of a medicinal product” means the presence of at least admissible possibility of causality between the medicinal product and adverse reaction, i.e. the relationship should not be ruled out.

For the registered medicinal products this term means any negative or unexpected reactions associated with the use of medicinal product in normal doses for the prevention, diagnosis or therapy of disease, rehabilitation, correction and modification of physiological function;

Adverse event - any untoward medical event in a subject which does not necessarily have a causal relationship with the use of medicinal product. Any untoward and unexpected event (including changes in laboratory findings), symptom or disease temporally associated with the use of (an investigational) medicinal product, etc. regardless of the association with use of a (investigational) medicinal product.

Amendment to protocol of clinical trial **-** a written description of changes to or formal clarification of the clinical trial protocol.

Protocol of clinical trial – a document that describes the objectives, methodology, procedures, statistical considerations and organization of a clinical trial, as well as data obtained previously on the investigational medicinal product and the verification of a trial.

Serious adverse reaction or serious adverse event – any untoward medical occurrence that at any dose of the medicinal product results in death; is life-threatening; requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity; congenital anomaly or birth defect.

Sponsor – a legal entity or a natural person who takes responsibility for the initiation and organization, and/or financing of a clinical trial of the medicinal product.

Substantial amendment to protocol of clinical trial - amendment to the protocol of clinical trial is considered as significant if it is likely to have a significant impact on the safety or physical or mental integrity of the patient (healthy volunteer) involved in the clinical trial, or have effect upon a scientific value of the trail;

Qualified person (of a manufacturer) – a natural person assigned by a manufacturer who is responsible for ensuring that all batches of a medicinal product are manufactured in compliance with main principles of good manufacturing practice, checked for compliance with a product specification and permits to sale or use in a clinical trial for each batch of a medicinal product.

2.2. Other terms in this Procedure are used in the meaning given in the Essential Principles of the health legislation of Ukraine, the Law of Ukraine "On Medicines", the Family Code of Ukraine and other regulatory documents.

**III. General principles of conducting clinical trials**

3.1. All clinical trials shall be conducted according to international ethical principles with an assurance of protection of the subjects’ rights, safety and well-being. A clinical trial should be conducted only if the anticipated benefit justifies the risk.

3.2. Clinical trials of medicinal products shall be conducted to establish or prove the efficacy and safety of medicinal product. They may be conducted at HCSs as determined by the central executive body (hereinafter - CEB), which develops and ensures implementation of state policy for health care, if there is a CEB’s decision about conducting clinical trials (hereinafter – the CEB’s decision), which is taken based on positive conclusion of the expert evaluation of materials pertinent to clinical trial, issued by the Center (hereinafter – the Conclusion).

*{Item 3.2, section III in wording of the MoH Ukraine Order* [*№ 966 as of 18.12.2014*](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran15#n15)*}*

3.3. All persons attracted to the performance of clinical trial should have appropriate education, proficiency and experience to perform functions and discharge obligations pertinent to the clinical trial.

3.4. Sponsor is entrusted with a choice of investigators and health care settings. Requirements to investigators and health care settings are stated in Section V of this Procedure.

The sponsor may delegate some or all of his powers to a contract research organization. Even so the sponsor remains to be responsible for conducting clinical trial and the data obtained from a clinical trial.

3.5. All clinical trials shall be commenced after the CEB’s decision is taken and protocol(s) of Ethics Committee at HCS, where the clinical trials is to be conducted, pertinent to approval of this clinical trial is received. That is the basis for its commencement, and conclusion of the contract insuring life and health of patient (volunteer) in established order.

*{Item 3.5, section III in wording of the MoH Ukraine Order* [*№ 966 as of 18.12.2014*](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran15#n15)*}*

3.6. Ensuring confidentiality of documents which might identify subject's personality is a compulsory requirement for protecting his rights.

3.7. Planning, conducting and reporting of all clinical trials including the bioavailability/bioequivalence studies, should be performed according to Good Clinical Practice (GCP) rules.

Each clinical trial of medicinal product shall be entered in the list of clinical trials published on the official site of CEB before the first trial subject is involved. Entering the clinical trial in the list is for information only and shall not interfere with its conducting.

*{item 3.7, section III amended by a new paragraph according to MoH Ukraine Order* [*№ 639 as of 01.10.2015*](http://zakon0.rada.gov.ua/laws/show/z1520-15/paran15#n15)*}*

3.8. If the investigational medicinal product is a narcotic product, psychotropic substance or precursor, its clinical trial shall be conducted in compliance with requirements of the legislation related to narcotic products, psychotropic substances or precursors.

3.9. System of specific procedures should be in place to ensure quality of all aspects of clinical trial.

3.10. The clinical trial information should be recorded, processed, and stored in a way that allows its accurate reporting, interpretation and verification.

The main documents of a clinical trial which are to be stored at the HCS/clinical trial site and with the sponsor are listed in Annex 1 to this Procedure, these documents should be stored in the archives for at least 15 years after termination of clinical trial.

3.11. Manufacture, storage and handling of the investigational medicinal product shall be performed in due course in compliance with Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP).

Main requirements to labeling of the investigational medicinal product are stated in Section VI of this Procedure. The investigational medicinal product shall be used only in accordance with the approved protocol of the trial.

3.12. At any stage of clinical trial or after its completion the Center may conduct clinical audit of clinical trial on compliance with GCP as per section XIII of this Procedure.

*{item 3.12, section III in wording of MoH Ukraine Order* [*№ 639 as of 01.10.2015*](http://zakon0.rada.gov.ua/laws/show/z1520-15/paran15#n15)*}*

**IV. Main requirements to protection of subjects**

**1. General provisions on protection of subjects**

1.1. The subject's protection should be ensured prior to any clinical trial through risk/benefit assessment, including the results of previous studies, as well as during its conduct through screening by the Center and ethics committees at HCSs.

1.2. Patients who are incapable to give informed consent for participation in clinical trials on their own should be given special protection. Such patients may not be included in clinical trials if the same results can be obtained using persons capable of giving informed consent.

Patients who are incapable to give informed consent should be included in clinical trials only when there are grounds for expecting that the use of the investigational product would be of direct benefit to the patient, thereby outweighing the risks.

In cases where the clinical trial involves patients incapable of giving their informed consent on their own because of their clinical condition, it is necessary to get the informed consent of the patient’s legal representative, and in case of his/her absence – of close relatives. The protocol of clinical trial or the amendment to it should include a description of the procedure for obtaining patient’s informed consent as soon as his/her capability to give informed consent on his/her own is restored.

1.3. A clinical trial may be undertaken if:

1.3.1 The foreseeable risk and inconveniences have been weighed against the anticipated benefit for subjects (patients/healthy volunteers);

1.3.2 The trial subject or, when he/she is not able on his/her own to give informed consent, his/her legal representative, and in case of no legal representative of patients who are in critical and urgent condition – close relative – has had the opportunity, in a prior interview with the principal investigator/investigator in charge of obtaining informed consent, to understand the objectives, risk and inconveniences of the clinical trial, and the conditions under which it is to be conducted;

1.3.3. The rights of the subject to physical and mental integrity, to privacy and to the protection of the personal data are safeguarded in accordance with the legislation;

1.3.4 If the individual is unable to write/read, oral informed consent in the presence of at least one witness who confirms the patient’s consent in written form may be given in exceptional cases;

1.3.5 Where there is a will the subject (legal representative/close relative who signed the informed consent) may withdraw from the clinical trial at any time and without any harm for himself (the subject);

*(subitem 1.3.6., item 1.3, chapter 1, section IV is excluded based on MoH Ukraine Order № 304 as of 06.05.2014)*

1.4. If any adverse reaction occurs that may be considered as an insured accident the principal investigator/investigator should inform the sponsor immediately but not later than within two days.

1.5. The sponsor should send an appropriate notification to the insurance company within 7 calendar days of first knowledge by him.

*(item 1.5, chapter 1, section IV amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

1.6. The subject or legal representative/close relatives may independently (this should be indicated in the informed consent) inform within 9 days an appropriate insurance company on the fact of adverse reaction to estimate it as an insured accident.

**2. Provision of information on clinical trial to patients (healthy volunteers) and obtaining their informed consent**

2.1. Patients (healthy volunteers) to be involved in clinical trials shall receive sufficient information on purpose and essence of a clinical trial. The principal investigator/investigator in charge of obtaining informed consent should inform the patient (healthy volunteer), but if the latter is incapable to provide informed consent, the subject’s legal representative/close relative about all aspects of the trial.

2.2. The decision of patient (healthy volunteer) or his legal representative/close relative to participate or continue participation in a clinical trial should be taken on his own and without force or unduly influence.

2.3. None of the written and oral information concerning the clinical trial should contain any language that causes the patient (healthy volunteer) and his legal representative/close relative to waive their legal rights to release the investigator, the sponsor of clinical trial from liability for injuring.

2.4. The written and oral information about the clinical trial should not contain any special terminology and should be understandable to the patient (healthy volunteer) or his legal representative.

2.5. The investigator should provide the patient (healthy volunteer) or his legal representative (close relative) ample time to take a decision whether to participate in a clinical trial or not. All questions about the trial should be answered to the satisfaction of the patient (healthy volunteer) or his legal representative/close relative.

2.6. The requirements to written and oral information to be given to the patient (healthy patient) or his legal representative/close relative are provided in annex 2 of this Procedure.

*(paragraph 1, item 2.6, chapter 2, section IV in wording of MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran12#n12)*)*

The subject’s information should be kept secret and processed within the framework of clinical trial in depersonalized format.

2.7. Prior to the participation in the clinical trial a patient (healthy volunteer) or his legal representative/close relative as well as the principal investigator/investigator responsible for obtaining informed consent shall sign and personally date the informed consent forms in duplicate, one to be left with the principal investigator/investigator, another – with the subject. It must be indicated that informed consent was given freely by the subject (legal representative/close relative) after receiving the full information about the clinical trial.

2.8. When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of their parents/legal representative/close relative (e.g., children age under 14, minors, or incapacitated persons), these subjects should be informed about the trial to the extent compatible with their understanding and, the minors should sign and personally date the written informed consent.

2.9. One copy of the informed consent signed and dated should be kept with the principal investigator/investigator (in the archives) within, at least, 15 years after its termination.

2.10. If the patient find himself in critical or emergency situations, when his informed consent to participate in the clinical trial cannot be obtained, the informed consent should be requested from the subject's legal representative/close relative.

When the informed consent of the patient to participate cannot be obtained and the subject’s legal representative/close relative is not available, enrolment of such patients is inadmissible, they should be given medical assistance according to procedure established.

2.11. Informed consent should include consent of the patient’s (healthy volunteer’s) or his legal representative/close relative for processing his personal data, particularly, pertinent to:

purpose of processing personal data;

composition and content of personal data;

owner of patient’s personal data;

access to personal data of third party

2.12. All information in the informed consent should be understandable to the patient/healthy volunteer/legal representative/close relative.

2.13. The Center, the ethics committee at HCS, and the sponsor may check the procedure for providing the patient/healthy volunteer/legal representative/close relative with the information on the clinical trial and for obtaining the trial subject’s informed consent.

2.14. In case of the violation of the trial subject’s rights during the trial the subject (legal representative/close relative) may apply to the sponsor, the Center, the ethics committee at HCS, CEB or the Court in compliance with the procedure established by the legislation.

2.15. The interests of the subjects (patients/healthy volunteer) always prevail over those of science and society.

**3. Clinical trials on children under age 14 and minors**

3.1. A clinical trial on children under age 14 and minors (from 14 to 18 years old) may be undertaken only if:

a) the informed consent of both parents has been obtained;

b) the children under age 14 and minors must be given a written or oral information about the clinical trial according to their capacity of understanding and, if the child under age 14 is capable he should give his oral consent to participate in the clinical trial;

The minor patient should personally sign and date the informed consent.

The principal investigator/investigator in charge of obtaining informed consent should consider the explicit wish of a child under under 14 or a minor to participate or refuse participation or to be withdrawn from the clinical trial at any time;

c) No incentives or inducements are given except compensation in the event of a clinical trial-related injury;

d) Children under age 14 and minors shall get direct benefit from the clinical trial if:

a clinical trial is essential to validate data obtained in other clinical trials on adults or by other research methods;

a clinical trial relates directly to a clinical condition from which children under age 14 and minors suffer;

a clinical trial is of such a nature that it can only be carried out on children under age 14 and minors.

e) Clinical trials have been designed to minimise pain, discomfort, fear and risk. Both the risk threshold and the degree of distress, pain should be specially defined and constantly monitored;

3.2. Information on involvement in clinical trials of children under age 14 and minors may be presented in optional form, but full name and age of a child, full name of parents, place of child’s residence, availability of informed consent, summary of clinical trial content must be indicated and marked as confidential. This information should be sent by the principal investigator/investigator to tutorial and custodial authorities in place of child’s residence within 24 hours of obtaining informed consent to participate in clinical trial according to subitems “a”, “b” of item 3.1 of this chapter.

3.3. Clinical trials of medicinal products on a child under age 14 or a minor devoid of parental custody, an adopted child or an orphan shall be prohibited.

3.4. The interests of children under age 14 and minors should always prevail over those of science and society.

**4. Clinical trials on incapacitated subjects not able to give**

**informed consent on their own**

4.1. Clinical trials of incapacitated patients shall be allowed only if:

The informed consent of the legal representative/close relative has been obtained (consent may be revoked at any time, without detriment to the subject);

The incapacitated patient shall receive information regarding the trial, its risks and benefits according to his/her capacity of understanding;

The principal investigator/investigator in charge of obtaining informed consent takes into account the wish of an incapacitated patient to participate or refuse participation or to be withdrawn from the clinical trial at any time;

No incentives or inducements are given except compensation in the event of a clinical trial-related injury;

Clinical trial is essential to validate data obtained in other clinical trials or by other research methods;

A clinical trial should relate directly to a clinical condition from which a subject suffers;

Clinical trials have been designed to minimise pain, discomfort, fear and risk. Both the risk threshold and the degree of distress, pain should be clearly defined and constantly monitored;

There are grounds for expecting that administering the investigational medicinal product will produce a benefit to the subject outweighing the risks or produce no risk at all;

4.2. The interests of incapacitated subject always prevail over those of science and society.

**V. Requirements to investigators and HCS/clinical trial site**

5.1. Investigators to be involved in a clinical trial should:

Have a sufficient proficiency, experience in treating patients of respective type;

Have knowledge of international requirements related to good clinical practice and regulatory documents on clinical trials in Ukraine, and participate in workshops organised by the Center;

Work in HCS where the clinical trial to be conducted (if the principal investigator/investigator is a worker of a department of an institute of higher medical education the contract on cooperation between the institute of higher medical education and HCS is required);

Investigators to be involved in clinical trials of phase I and of bioequivalence of medicinal products in addition to the main skills should have an expertise in clinical trials supported by information given in curriculum vitae.

5.2. HCS may be involved in a clinical trial if:

Ethics committee is established and functions at HCS;

There are sufficient resources to provide the subjects with an emergency medical aid in case of complications occurred during clinical trials (for hospitals – availability of intensive care unit or resuscitation department or intensive care ward (s)/intensive care bed(s);

According to the procedure envisaged by the legislation metrological control of measuring equipment is performed in time in HCS units (laboratory, functional diagnostics department) which may be involved in clinical trials;

There are conditions and resources for storing investigational medicinal products (according to storage conditions indicated on the labelling of medicinal products or in the clinical trial protocols) and documentation related to a clinical trial;

There is a possibility to involve an appropriate number of subjects according to the clinical trial protocol;

Primary medical documents (hospital records/ambulatory medical records) are recorded according to requirements of the current legislation and there are conditions for their archiving (in the archives) for at least 15 years after the termination of a clinical trial.

5.3. HCS may be involved in a clinical trial of phase I and of bioequivalence of medicinal products if HCS meets the requirements stated in item 5.2 of this section, and has:

Separate wards for subjects (healthy volunteers) and conditions necessary for a 24-hour vigilance over their condition;

Separate medical treatment/manipulation room, dining-room and sanitary room for subjects;

Storage conditions for biosamples during clinical trials.

5.4. The laboratory for conducting pharmacokinetic studies to be involved in clinical trials should comply with requirements of Good Laboratory Practice (GLP).

5.5. The health-care setting, which conducts clinical trials of bioequivalence of medicinal products, submits to the Center accreditation certificate issued by CEB (if available).

*{Section V is amended by a new item according to MoH Ukraine Order* [*№ 639 as of 01.10.2015*](http://zakon0.rada.gov.ua/laws/show/z1520-15/paran19#n19)*}*

**VI. The main requirements to labeling of investigational medicinal product**

6.1. The labeling of investigational medicinal product shall be such as to enable identification of the product and trial.

6.2. The relevant information shall be provided in Ukrainian or in officially recognized language of international communication.

The following should be included in labelling:

а) Name of legal entity/full name of natural person, location of legal entity/residence of natural person and contact phone number of sponsor/contract research organization or principal investigator/investigator (details of contact person for emergency unblinding of medicinal product).

b) Pharmaceutical form, route of administration, quantity of dosage units (in the case of open clinical trials – the name/identifier and strength/potency);

c) The batch number and/or code to identify the contents and packaging operation;

d) Trial reference number (code) allowing its identification: clinical trial site, principal investigator/investigator and sponsor if not given elsewhere;

e) The trial subject identification number/subject treatment number and where relevant, the visit number;

f) Full name of principal investigator/investigator, if not included in subitems “a” or “d” of this item;

g) Directions for use (references may be made to package-insert, instructions for medical use or to other document intended for the trial subject or person administering the investigational medicinal product);

h) “For clinical trial use only” or similar wording;

i) Storage conditions;

j) Period of use (“use-by date”, expiry date, or re-test date as applicable), in “month/year” format and in manner that avoids any ambiguity;

k) “Keep out of reach of children” (except for cases when the product is for use in clinical trials where it is not taken home by subjects).

Location/residence phone number of key person to contact for information on the investigational medicinal product, clinical trial and emergency unblinding shall not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times.

If there is no outer packaging, any relevant information shall be provided on the immediate packaging.

6.3. The outer packaging should carry the particulars listed in item 6.2 of this section when the investigational medicinal product is to be provided to the trial subject or the person administering the medication within an immediate container together with outer packaging (that is intended to remain together).

The following information shall be included on the labelling of the immediate container (or any sealed dosing devise that contains the immediate container):

а) Name of legal entity/full name of natural person of sponsor/manufacturer/full name of principal investigator/investigator;

b) Pharmaceutical form, route of administration (may be excluded for solid pharmaceutical forms for internal use), quantity of dosage units and in case of open label trial – name/identifier and strength/potency;

c) Batch or code number of the investigational medicinal product to identify the contents and packaging operation;

d) Clinical trial reference code allowing identification of trial, clinical trial site, investigator and sponsor if not given elsewhere;

e) Trial subject identification number/treatment number and where relevant, the visit number.

6.4. If the immediate container takes the form of blister packs or small units (e.g., ampoules and other) on which the particulars required in item 6.2 of this section cannot be displayed, outer packaging should be provided bearing a label with those particulars. The immediate container should nevertheless contain the following brief information:

а) Name of legal entity/full name of natural person of sponsor/applicant/full name of investigator;

b) Method of administration (may be excluded for solid pharmaceutical forms for internal use) and strength/potency;

c) Batch or code number of the investigational medicinal product to identify the contents and packaging operation;

d) Clinical trial reference code allowing identification of the trial, site, principal investigator/investigator and sponsor, if not given elsewhere;

e) Trial subject identification number/ treatment number and where relevant, the visit number.

6.5. Symbols or pictograms may be used to clarify certain information mentioned above. Additional information, warnings and/or handling instructions may be displayed.

6.6. Simplified labeling for investigational medicinal products is allowed if they are intended for clinical trials with the following characteristics:

Planning of the trial does not require particular manufacturing or packaging processes;

The clinical trial is conducted with the medicinal products registered in Ukraine according to the established procedure;

The investigational medicinal products have the same characteristics as those covered by the indications for use, according to which the medicinal product has been registered in Ukraine.

In this case the following particulars shall be added to the labeling of the original container (but shall not obscure the original labeling):

а) Name of legal entity/full name of natural person of sponsor/manufacturer/full name of principal investigator/investigator;

b) Clinical trial reference code allowing identification of the trial, trial site, investigator and sponsor.

6.7. If it becomes necessary to change the use-by date, an additional label indicating a new use-by date and a batch number should be affixed. It may be superimposed on the old use-by date, but not on the original batch number. When appropriate, this operation may be performed by an investigator under a supervision of the clinical trial monitor who should be appropriately trained. This additional labeling should be properly documented in the clinical trial documentation.

**VII. Expert evaluation of materials related to clinical trial of medicinal product**

{title of section VII in wording of the MoH Ukraine Order [№ 966 as of 18.12.2014](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran15#n15)}

7.1. To conduct clinical trials of medicinal products the applicant shall submit to the CEB documents (materials) of clinical trial specified in subitems 7.1.1 and 7.1.2 of this item; to the Center – in subitems 7.1.3 -7.1.21 of this item inclusive. Documents (materials) of clinical trial include:

*{Paragraph 1, item 7.1, section VII in wording of the MoH Ukraine Order* [*№ 966 від 18.12.2014*](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran23#n23)*}*

7.1.1 Cover letter (see Annex 3 to this procedure).

*(subitem 7.1.1, item 7.1, section VII amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran16#n16)*)*

7.1.2. Application for conducting clinical trial of medicinal product/approval of the Ethics Committee at HCS pertinent to conducting clinical trial of medicinal product using the template (see Annex 4 to this Procedure).

*(subitem 7.1.2, item 7.1, section VII* *amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran16#n16); *in wording of the MoH Ukraine Order* [*№ 966 as of 18.12.2014*](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran15#n15)*)*

7.1.3. Protocol of the clinical trial of the medicinal product with all amendments to it that should include the information stated in Section 6 of Good Clinical Practice (GLP).

7.1.4. A brief summary (synopsis) of the protocol in Ukrainian.

7.1.5. Case report form (except for international clinical trials).

7.1.6. Investigator’s Brochure that should include an information stated in section 7 of Good Clinical Practice (GCP).

7.1.7. An investigational medicinal product’s dossier.

The full dossier of investigational medicinal product shall be submitted in a format given in Annex 5 to this Procedure if the investigational medicinal product hasn’t been registered in Ukraine.

*(paragraph 2, subitem 7.1.7, item 7.1, section VII amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran16#n16)*)*

The simplified dossier shall be submitted if the full dossier has previously been submitted to the Center by the same applicant together with an application for obtaining a conclusion for conducting clinical trial of the medicinal product concerned.

If a medicinal product has already been registered in Ukraine the sponsor may submit a summary product characteristics as an investigational medicinal product dossier.

For comparators and placebo the simplified dossier or summary product characteristics shall be submitted.

7.1.8. Certificate for a batch of an investigational medicinal product to be used for a clinical trial. Certificate for a batch (certificate of analysis, quality certificate) of an investigational medicinal product – a document issued by a manufacturer to accompany any batch of a medicinal product to verify its quality (according to the specification).

If during a clinical trial another batch of an investigational medicinal product to be imported in Ukraine is used the applicant of the clinical trial shall submit to the Center a certificate for the batch concerned together with a cover letter within 10 days after termination of the investigational medicinal product customs clearance.

7.1.9. During the clinical trials of medicinal products only in Ukraine (with the purpose of their further registration in Ukraine) the conclusion of the Center’s accredited laboratory for pharmaceutical analysis regarding quality of each batch to be used for clinical trials shall be attached.

In case of the objective impossibility to conduct certain studies at this laboratory the conclusion of another accredited laboratory assigned by the Center where such study can be made.

For testing methods of analysis an appropriate number of samples of medicinal products shall be submitted to this laboratory.

7.1.10. Results of the previous expert evaluations and/or the Center’s conclusions concerning a pre-clinical study and clinical trial of a medicinal product (if any).

7.1.11. List of authorized competent authorities of other countries where applications for the clinical trial are also submitted, and detailed information on their decision taken (if any).

7.1.12. A letter of authorization from the sponsor with clearly specified granted powers if a clinical trial applicant differs from a sponsor.

7.1.13. The draft informed consent and other written information to be provided to a patient (healthy volunteer) (in Ukrainian or in officially recognized language of international communication). The draft should envisage a patient’s consent to use his personal data for processing the study results.

7.1.14. Brief data on all ongoing clinical trials conducted with the use of the investigational medicinal product concerned (if any).

7.1.15. Expert evaluation of the clinical trial issued before (if any).

7.1.16. Application from the principal investigator according to form given in Annex 6 to this Procedure.

*(subitem 7.1.16, item 7.1, section VII amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran16#n16)*)*

7.1.17. Information on HCS and a clinical trial site (see Annex 7 to this Procedure) by the time of submission of documents (materials).

*(subitem 7.1.17, item 7.1, section VII amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran16#n16)*)*

7.1.18. Information on principal investigator/investigator (*Curriculum vitae,* hereinafter - CV*)*) should contain the following details: full name, year of birth, education, place of employment, position, record of service, degree, scientific works, previous participation in clinical trials (specify).

Co-investigators’ CVs should be submitted if doctors of different disciplines are to be involved.

7.1.19. A confirmation shall be issued for the investigational medicinal product that operations at a manufacturing site or site involved in the manufacture of the medicinal product concerned are performed in compliance with good manufacturing practice providing a GMP certificate or a written official declaration of the Qualified person (of a manufacturer), or a copy of document issued by the State Administration of Ukraine on Medicinal Products that confirms the compliance of the manufacturing conditions with the Good Manufacturing Practice (GMP) requirements (for domestic manufacturers – copy of valid license to manufacture medicinal products).

If the above documents have been entered to the EudraGMP database, the applicant shall refer to this database. In addition, the applicant shall certify a copy of document with annexes (if any).

*{Subitem 7.1.19, item 7.1, section VII amended by new paragraph according to MoH Ukraine Order* [*№ 966 as of 18.12.2014*](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran27#n27)*}*

7.1.20. A sample labeling of an investigational medicinal product in Ukrainian or officially recognized language of international communication.

7.1.21. Additional information on an investigational medicinal product (if applicable): viral safety studies; relevant documents for studies or medicinal products with specific properties (if any), a declaration on compliance of biological active substance with GMP requirements.

*(subitem 7.1.22, item 7.1, section VII is excluded based on MoH Ukraine Order № 304 as of 06.05.2014)*

*(subitem 7.1.23, item 7.1, section VII is excluded based on MoH Ukraine Order № 304 as of 06.05.2014)*

*(subitem 7.1.24, item 7.1, section VII is excluded based on MoH Ukraine Order № 304 as of 06.05.2014)*

7.2. Based on results of review of application about conducting clinical trial of medicinal product, the CEB sends a letter of referral with this application to the Center within three calendar days and informs the applicant accordingly.

Within 30 days of receipt at the Center of the CEB’s letter of referral the applicant submits documents (materials) of clinical trial specified in subitems 7.1.3 -7.1.21, item 7.1 of this section to the Center in triplicate (the Center may request additional copy(ies), if necessary).

*{item 7.2, section VII in wording of the MoH Ukraine Order* [*№ 966 as of 18.12.2014*](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran15#n15)*}*

7.3. A contract for conducting expert evaluation shall be concluded between the Center and the applicant. The expert evaluation of clinical trial materials is subject to payment (not considering a number of trial sites and amendments to the protocol which accompany an application).

7.4. Clinical trial documents (materials) are subject to expert evaluation at the Center with obligatory consideration of ethical, moral, and legal aspects of the clinical trial after their submission in corpore to the Center according to item 7.1 of this section. The Center shall conduct expert evaluation within 47 calendar days.

{*item 7.4, section VII in wording of the MoH Ukraine Order* [*№ 966 as of 18.12.2014*](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran15#n15)}

7.5. During the expert evaluation of the clinical trial materials the Center, based on experts’ remarks and comments, may singly request (in writing) the applicant to submit additional materials.

The time necessary for their preparation shall not be added to the time period for conducting the expert evaluation. If the applicant fails to submit the requested additional materials or a letter with substantiated timeframe necessary for their preparation within 60 calendar days, the clinical trial materials shall be withdrawn from further consideration.

The Center shall inform the applicant about the decision taken in writing with no cost of expert evaluation to be reimbursed to the applicant. Further on, at applicant’s request, the materials shall be submitted in due course to obtain the Center’s conclusion.

7.6. Based on results of expert evaluation, the Center shall provide the CEB with positive or negative conclusion. Based on the Center’s conclusion the CEB shall take a decision about conducting/refusing to conduct clinical trial substantiating the reasons in case of refusal to conduct clinical trial. The CEB shall take a decision within 5 working days.

The title of clinical trial, its code, version and date of protocol, sponsor, applicant and/or legal or physical person who acts under the power of attorney issued by the sponsor or applicant for importing investigational medicinal products or auxiliary consumables, principal investigator, trial site, list of investigational medicinal products, comparators and auxiliary consumables are approved by the decision on conducting clinical trial.

*{paragraph 2, item 7.6, section VII in wording of MoH Ukraine Order* [*№ 639 as of 01.10.2015*](http://zakon0.rada.gov.ua/laws/show/z1520-15/paran21#n21)*}*

{*item 7.6, section VII in wording of the MoH Ukraine Order* [*№ 966 as of 18.12.2014*](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran15#n15)}

7.7. If the applicant doesn’t agree with the CEB decision about refusal of clinical trial, he may apply within 30 calendar days of receipt of this decision to CEB for its revision with additional materials submitted substantiating such revision. The above application shall be considered within 30 calendar days, after its receipt, until final decision is taken. The final decision with appropriate substantiation shall be sent to the applicant in writing.

To defend his rights the Applicant may appeal to the Court in established order.

{*item 7.7, section VII in wording of the MoH Ukraine Order* [*№ 966 as of 18.12.2014*](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran15#n15)}

**VIII. Assessment of ethical, moral, and legal aspects of the clinical trial**

8.1. Assessment of ethical, moral, and legal aspects of the clinical trial shall be performed by ethics committees at health care settings where clinical trials are conducted.

8.2. Positive opinion of the ethics committee being an endorsement of the clinical trial at a specific health care setting where clinical trial site (s) is/are located shall be legalized by an appropriate protocol of its meeting.

8.3. Ethics committees shall ensure compliance with ethical standards during clinical trials in specific HCS.

8.4. To obtain the results of assessment of ethical aspects of the clinical trial the applicant shall submit the following documents to the ethics committee at HCS:

8.4.1. Cover letter (see Annex 3 to this Procedure).

*(subitem 8.4.1, item 8.4, section VIII amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

8.4.2. Application for getting conclusion of the State Expert Center MoH Ukraine/endorsement of the ethics committee at HCS pertinent to conducting clinical trial of medicinal product (see Annex 4 to this Procedure).

*(subitem 8.4.2, item 8.4, section VIII amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

8.4.3. The protocol of clinical trial of medicinal product with all available amendments which are to contain information given in section 6 of GCP in source language and summary (synopsis) of clinical trial protocol in Ukrainian.

*{subitem 8.4.3 item 8.4 section VIII in wording of MoH Ukraine Order* [*№ 639 as of 01.10.2015*](http://zakon0.rada.gov.ua/laws/show/z1520-15/paran24#n24)*}*

8.4.4. Investigator’s Brochure that should include information given in section 7 of Good Clinical Practice (GCP).

8.4.5. A copy of the Center’s conclusion approved by CEB (if any).

8.4.6. A letter of authorization from the sponsor with clearly specified granted powers if a clinical trial applicant differs from a sponsor.

8.4.7. The draft informed consent and other written information to be provided to a patient (healthy volunteer) in Ukrainian or in officially recognized language of international communication).

8.4.8. Information on subject recruitment procedures (information and promotional materials to be used for subject recruitment to a clinical trial (if any)).

8.4.9. Brief data on all ongoing clinical trials conducted with the use of the given investigational medicinal product (if any).

8.4.10. An application from a principal investigator according to form given in Annex 6 to this Procedure, it should be submitted at HCS where the ethics committee is located.

*(subitem 8.4.10, item 8.4, section VIII amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

8.4.11. Information on HCS and clinical trial site (see Annex 7 to this Procedure) valid at the time of submission of documents (materials).

*(subitem 8.4.11, item 8.4, section VIII amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

8.4.12. Information on principal investigator/investigator (CV) should contain the following details: full name, year of birth, education, place of employment, position, record of service, degree, scientific works, participation in clinical trials in the past (specify).

Co-investigators’ CV should be submitted if doctors of different disciplines are involved in the clinical trial.

8.4.13. Information which defines the terms of inducements or compensations provided to subjects for participation in a clinical trial (if envisaged by a clinical trial protocol), which may be submitted in a cover letter with reference to the relevant document foreseeing this.

8.4.14. Sponsor’s/applicant’s instructions to principal investigator/investigator concerning actions to be undertaken in the event which can be considered as an insured accident during the clinical trial in case of harm to subjects’ health and life.

8.4.15. Copy of certificate to the patient’s (volunteer’s) life and health insurance contract.

*{item 8.4 section VIII amended by a new subitem according to the MoH Ukraine Order* [*№ 639 as of 01.10.2015*](http://zakon0.rada.gov.ua/laws/show/z1520-15/paran26#n26)*}*

8.5. Clinical trial materials (one copy) shall be submitted to the ethics committee. An application fully completed according to form given in Annex 4 to this Procedure shall be submitted in e-format.

*(item 8.5, section VIII amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

8.6. After obtaining a full set of documents the ethics committee shall perform an assessment of ethical, moral, and legal aspects of clinical trial materials, and then shall issue an endorsement for conducting a clinical trial at a specific HCS or a substantiated refusal.

8.7. During the assessment of ethical, moral and legal aspects of the clinical trial materials the ethics committee may singly request (in writing) the applicant to submit additional materials and/or invite the applicant to the committee’s meeting for giving additional clarification. The time necessary for submitting additional materials/clarification shall not exeed 30 calendar days.

The time necessary for assessing ethical, moral and legal aspects shall not exceed 30 calendar days of getting an application by the committee (not including time necessary for preparation of the requested materials/clarification).

8.8. The ethics committee shall inform the applicant about the decision taken in writing.

8.9. In case of negative results of assessment of ethical, moral and legal aspects of the clinical trial the applicant may again submit within 30 calendar days after getting the decision the materials with grounds for their revision which to be reviewed within 30 calendar days with giving the final assessment of ethical, moral and legal aspects of this clinical trial.

**IX. Conducting a clinical trial**

9.1 Clinical trial may be commenced in each particular trial site provided there is a CEB’s positive decision, an extract from the protocol of ethics committee at HCS pertinent to approval of this clinical trial and if contractual relations are executed between all legal and physical persons involved in clinical trial and after concluding the patient’s (volunteer’s) life and health insurance contract in due order.

*{paragraph 1, item 9.1, section IX in wording of the MoH Ukraine Order* [*№ 966 as of 18.12.2014*](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran15#n15)*,* [*№ 639 as of 01.10.2015*](http://zakon0.rada.gov.ua/laws/show/z1520-15/paran29#n29) *}*

Sponsor (contract research organization on behalf of the sponsor) shall conclude with HCS contracts for conducting clinical trials of medicinal products according to the legislation.

If research institution or higher medical school not having their own clinical trial site takes part in the clinical trial, the conclusion of tripartite contract of the sponsor (contract research organization on behalf of the sponsor), HCS, and research institution or higher medical school should be envisaged.

The sponsor or contract research organization (on behalf of the sponsor) shall cover the cost of extra work/ services rendered by principal investigator/investigators not pertinent to their functions at HCS, or the research institution, or higher medical school/college of accreditation levels III-IV based on the separate contract concluded with the principal investigator/investigator (co-investigator, if applicable) according to the legislation.

This contract shall envisage an exact delimitation of the HCS and principal investigator/investigator/co-investigator functions which are performed by them in their free time and, as a rule, pertinent to intellectual work (analytical, information, expert and advisory, preparation of clinical trial reports, etc.). If while performing this work/rendering services the principal investigator/investigator/co-investigator use material and technical base (facilities and equipment) the appropriate HCS expenses may be covered by the sponsor (contract research organization on behalf of the sponsor) according to the contract concluded with the HCS which, in particular, should include a provision regarding such obligation of the sponsor (contract research organization on behalf of the sponsor) or principal investigator/investigator/co-investigator according to the separate contract concluded between him and HCS.

Importation of investigational medicinal products and auxiliary consumables may be conducted by the sponsor, applicant and/or legal or physical person who acts under the power of attorney issued by the sponsor or applicant for importing investigational (registered or non-registered) medicinal products and auxiliary consumables (medical devices, medical equipment, etc.) intended for use within the framework of this clinical trial.

*{Item 9.1, section IX amended by a new paragraph according to a MoH Ukraine Order* [*№ 639 as of 01.10.2015*](http://zakon0.rada.gov.ua/laws/show/z1520-15/paran31#n31)*}*

9.2. Import/export in/from the territory of Ukraine, accounting and storage of an investigational medicinal product and auxiliary consumables intended for clinical trial, biosamples for laboratory analyses shall be carried out according to the procedure established by legislation.

If the investigational medicinal product is a narcotic product, psychotropic substance or precursor the export-import operations are possible after obtaining appropriate permit of the State Service of Ukraine on Drugs Control.

9.3. After the start of clinical trial (the informed consent signed by the first patient (healthy volunteer)) according to the clinical trial protocol the sponsor or his authorized representative shall inform thereof the Center within 10 calendar days using the form presented in Annex 8 to this Procedure.

*(paragraph 1, item 9.3, section IX amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

*(paragraph 2, item 9.3, section IX excluded based on MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

In case of the investigator/clinical trial site exclusion agreed by the Center and approved by the CEB the sponsor or his authorized person shall inform the Center and the ethics committee by a letter (format optional) concerning the decision taken within 30 calendar days of the latter.

9.4. If applicable, during a clinical trial and after its termination the Center and the ethics committee may request (in writing) the investigator/the sponsor to submit additional materials on clinical trials.

9.5. The principal investigator/investigator shall conduct clinical trial according to a clinical trial protocol. The principal investigator/investigator may deviate from a clinical trial protocol only in case of elimination of immediate hazards to subjects without the preliminary approval of the Center. Such a deviation from a clinical trial protocol shall be documented by the investigator. A description of the deviation made, its reasons and (if applicable) suggestions concerning amendments to a clinical trial protocol shall be submitted to the sponsor.

9.6. The ethics committees at HCS shall supervise rights protection, safety, well-being of patients (healthy volunteers), subjects, and compliance with ethical, moral and legal principles of clinical trials.

**X. Changes and additions during clinical trial**

**Chapter 1. Introduction of amendments during clinical trial**

1.1. During clinical trials changes and additions may be introduced in materials of the clinical trial. Such changes and additions shall be considered as amendments. Such changes and amendments can be substantial or non-substantial.

1.2. Amendments to materials of the clinical trial are considered as substantial if they are likely to have an impact on safety or physical or mental well-being of the trial subject; a scientific value of clinical trial; conduct or management of the clinical trial; quality and safety of an investigational medicinal product used in the clinical trial, and propose a substitution of the principal investigator or additional involvement in the clinical trial of new investigator/clinical trial site in Ukraine according to form given in Annex 9 to this Procedure.

*(item 1.2, chapter 1, section X amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

1.3. If the amendments are substantial the sponsor shall inform the Center and the ethics committee on reasons and contents of the amendments.

1.4. For approving substantial amendment the applicant shall submit to the CEB a cover letter (in form given in Annex 10 of this Procedure), an application for substantial amendment/approval of substantial amendment by ethics committee at HCS (in form given in Annex 11 of this Procedure), and shall submit to the Center the materials of substantial amendment, extracts from the documents containing previous and new wording or new version of amended documents which can be identified by its new number and date; additional information including summary (if any), updated general assessment of risk and benefit (if available), possible consequences for subjects involved in clinical trial, possible consequences for assessing the results of clinical trial.

*(item 1.4, chapter 1, section X amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*; in wording of the MoH Ukraine Order* [*№ 966 as of 18.12.2014*](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran15#n15)*,* [*№ 639 від 01.10.2015*](http://zakon0.rada.gov.ua/laws/show/z1520-15/paran34#n34)*)*

1.5. If the substantial amendment concerns more than one protocol of a clinical trial concerning the investigational medicinal product the sponsor may submit a single notification to the Center provided a cover letter and application contains a list of all protocols of clinical trials which this amendment concerns.

1.6. If the amendments are non-substantial (e.g., change of a contact phone number, name of applicant or investigator in any country except for Ukraine, etc.) regarding the aspects indicated in Annex 9 to this Procedure and if they have no direct relation to a clinical trial in Ukraine, such changes aren’t subject to an expert evaluation at the Center. In this case the applicant shall inform in writing the Center on non-substantial amendments made in the clinical trial materials.

*(item 1.6, chapter 1, section X amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

1.7. The investigator shall continue clinical trial in compliance with substantial amendment(s) made to the clinical trial protocol, only if the CEB takes a decision concerning substantial amendment(s) and there are no objections from the Ethics Committee (concerning a specific clinical trial site).

Based on results of review of application, the CEB shall send to the Center a letter of referral with the materials specified in item 1.4 of this chapter within 3 calendar days.

*{item 1.7, chapter 1, section Х in wording of the MoH Ukraine Order* [*№ 966 as of 18.12.2014*](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran15#n15)*)*

1.8. If during the clinical trial the event relating to the conduct of the clinical trial or the development of the investigational medicinal product occurs and it is likely to affect the safety of the subjects, the sponsor and/or the investigator shall take appropriate urgent safety measures to protect the subjects. The sponsor shall forthwith inform the Center and the ethics committee of the event occurred and the measures taken to eliminate it.

**2. Expert evaluation of substantial amendments at the Center**

2.1. The Center shall give a conclusion on substantial amendments based on their expert evaluation.

2.2. The Center shall conduct the expert evaluation of the submitted materials with the purpose to make a substantiated conclusion concerning the possibility to conduct the clinical trial in compliance with the amendments to the clinical trial materials.

A contract for conducting expert evaluation of amendments shall be concluded between the Center and the applicant. The expert evaluation of amendments to the clinical trial materials attached to the application shall be paid for. The term of the expert evaluation by the Center is within 27 calendar days.

*{paragraph 2, item 2.2, chapter 2, section Х amended by MoH Ukraine Order* [*№ 966 as of 18.12.2014*](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran15#n15)*}*

2.3. During the expert evaluation of the amendments in order to make a conclusion on substantial amendment the Center shall singly request (in writing) the applicant to submit additional materials. The time necessary for their preparation shall not be added to the time period for conducting the expert evaluation.

If the applicant fails to submit the requested additional materials or a letter with substantiated timeframe necessary for their preparation within 30 calendar days, the amendments shall be withdrawn from further consideration. The Center shall inform the applicant about the decision taken in writing with no cost of expert evaluation to be reimbursed to the applicant. The applicant may submit again materials to receive the Center’s conclusion.

2.4. Based on results of expert evaluation, the Center shall issue to the CEB a positive or negative conclusion concerning substantial amendment. Based on the conclusion the CEB shall take a decision about approval of substantial amendment or about its refusal substantiating the reasons in case of refusal. The CEB shall take a decision within 5 working days.

*(item 2.4, section 2, section Х in wording of the MoH Ukraine Order* [*№ 966 as of 18.12.2014*](http://zakon3.rada.gov.ua/laws/show/z0062-15/paran15#n15)*)*

2.5. If the applicant doesn’t agree with the Center’s decision on withdrawal of the substantial amendment from the consideration or with the conclusion on the substantial amendment he may submit a substantiated application to a head of the Center or CEB. The applicant shall present to the Center the application properly substantiated within 30 calendar days of receipt of the relevant decision. The application shall be reviewed within 30 calendar days after its receipt in order to take a final decision. The final decision with appropriate grounds shall be sent to the applicant in writing. If the applicant considers his rights as violated he may appeal to the Court in compliance with the procedure established by legislation

**3. Assessment of substantial amendments by the ethics committee at HCS**

3.1. The principal investigator/investigator shall inform the ethics committee on reasons and content of substantial amendments.

3.2. The ethics committee shall approve only those substantial amendments that concern the specific clinical trial site (s) and principal investigator (s) of the specific HCS at which this committee functions.

3.3. For endorsing the substantial amendments the principal investigator shall submit to the ethics committee an application and information in compliance with item 1.4 of chapter 1 of this section.

Ethics committee at HCS shall review substantial amendments within 15 calendar days of receipt of full set of documents. The ethics committee at HCS shall inform in writing the principal investigator about decision taken.

*{paragraph 2, item 3.3, section X in wording of MoH Ukraine Order* [*№ 639 as of 01.10.2015*](http://zakon0.rada.gov.ua/laws/show/z1520-15/paran36#n36)*}*

3.4. If the principal investigator/investigator doesn’t agree with the ethics committee’s decision he may take a substantiated application. The principal investigator/investigator shall submit the application properly substantiated within 10 calendar days of receipt of the relevant decision. The application shall be reviewed by the ethics committee within 10 calendar days after its receipt in order to take a final decision. The final decision with appropriate grounds shall be sent to the applicant in writing.

**XI. Termination of clinical trial**

11.1. The Sponsor shall inform the Center and the ethics committee about termination of the clinical trial (date of last visit of the last subject) in Ukraine within 90 days of its end using the form given in Annex 12 to this Procedure.

*(item 11.1, section XI amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

11.2. In case of international multicenter clinical trials the sponsor shall additionally, within 90 calendar days, inform the Center and the ethics committee about the complete termination of the clinical trial in other countries.

11.3. In case of pre-term termination of the clinical trial the sponsor shall inform the Center and the ethics committee (s) within 15 days of the termination indicating the reasons for pre-term termination of the trial.

11.4. The sponsor shall inform the Center in writing on a regular basis (at least once a year after the commencement of the clinical trial or more frequently, upon request) and in case of termination of the clinical trial about the status of the conduct of clinical trial in Ukraine using the form given in Annex 13 to this Procedure.

The principal investigator/investigator shall inform the ethics committee in writing on a regular basis (at least once a year after the commencement of the clinical trial or more frequently, upon request) about the status of the conduct of clinical trial in the appropriate trial site using the same form.

*(item 11.4, section XI amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

11.5. The investigational medicinal products not used during clinical trial shall be destroyed according to the legislation or shall be given back to the sponsor.

11.6. The sponsor shall ensure preparation of a final report on the conducted clinical trial of the medicinal product using the form given in Annex 14 to this Procedure.

The sponsor shall provide to the Center a concise information about the clinical trial within one year after complete termination of the clinical trial (in international clinical trials – after the end of the trial in all countries).

The principal investigator/investigator shall provide to the ethics committee a concise information about the clinical trial within one year after complete termination of the clinical trial (in international clinical trials – after the end of the trial in all countries).

*(item 11.6, section XI amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

**XII. Notification of adverse events and reactions**

**1. Notifications to be made by the principal investigator/investigator**

1.1. While conducting clinical trial the principal investigator/investigator shall report all serious adverse events to the sponsor except for those that the protocol or investigator’s brochure identifies as such not requiring immediate reporting. The initial and follow-up reports shall identify subjects by unique code numbers assigned to them for the study.

1.2. The principal investigator/investigator shall also report the sponsor any adverse events and/or laboratory abnormalities identified in the clinical trial protocol as critical to safety evaluations according to the requirements and within the time periods specified by the sponsor in the protocol.

1.3. The principal investigator/investigator shall record immediately and within 7 calendar days after learning about this case all suspected unexpected serious adverse reactions associated with the investigational medicinal product which resulted in death or were life-threatening, to the ethics committee. The follow-up information on this case shall be given to the ethics committee within subsequent 8 calendar days. Requirements to the notification on a suspected unexpected serious adverse reaction are listed in Annex 15 to this Procedure.

*(item 1.3, chapter 1, section XII amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

1.4. The principal investigator/investigator shall inform the ethics committee about all other suspected unexpected serious adverse reactions associated with the investigational medicinal product which become known to him within 15 calendar days.

1.5. In case of subject’s death the principal investigator/investigator shall provide to the sponsor, the Center and the ethics committee any additional information requested by them.

**2. Notifications to be made by the sponsor**

2.1. Reporting the suspected unexpected serious adverse reactions to the Center (reporting period) begins from the date of approval by CEB of the Center’s conclusion on clinical trial and terminates with the end of clinical trial in Ukraine.

2.2. The sponsor shall record immediately and within 7 calendar days after learning about such case report all suspected unexpected serious adverse reactions associated with the investigational medicinal product which resulted in death or were life-threatening to the Center. Relevant follow-up information on this case shall be given to the Center within subsequent 8 calendar days. Requirements to the notification on a suspected unexpected serious adverse reaction are listed in Annex 15 to this Procedure.

*(item 2.2, chapter 2, section XII amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

2.3. The sponsor shall report to the Center all other serious unexpected adverse reactions associated with the investigational medicinal product which become known to him within 15 calendar days.

2.4. The sponsor shall inform all principal investigators/investigators who take part in the clinical trial of this investigational medicinal product concerned on all detected events capable of affecting subjects' safety.

2.5. The sponsor shall keep documentation related to all adverse events the principal investigators/investigators report to him.

2.6. During long-term clinical trials the sponsor shall provide the Center a written report on the safety of the investigational medicinal product under development in paper and electronic format at least once a year, within 60 calendar days after preparation of the report according to the requirements stated in Annex 16 to this Procedure.

While writing the report the sponsor shall consider the following points: relation of the adverse reaction with the investigational medicinal product’s dose, duration of the treatment; reversibility of the subject’s condition after withdrawal or suspension of the treatment; evidence of previous toxicity in the trial subjects; increased frequency of toxicity of the investigational medicinal product; overdose of the investigational medicinal product and its consequences, further treatment; drug interactions or other associated risks; any specific safety issues related to special populations of the patients (the elderly, children or any other risk groups); positive or negative experiences during pregnancy or lactation; abuse (if any); risks which might be associated with the investigation or diagnostic procedures; risks which might be associated with insufficient quality of the investigational medicinal product; safety and efficacy data on the investigational medicinal product obtained during the non-clinical studies.

In case of the substantiated suspicion on the increased risk for the subjects the Center may oblige the sponsor to submit safety report on the investigational medicinal product under development more frequently.

*(item 2.6, chapter 2, section XII amended by MoH Ukraine Order* [*№ 304 as of 06.05.2014*](http://zakon3.rada.gov.ua/laws/show/z0739-14/paran10#n10)*)*

2.7. In case of conducting several clinical trials of the same investigational medicinal product, the sponsor shall provide to the Center a single generalized report on the safety of investigational medicinal product. In a cover letter attached to the report the sponsor shall provide a listing of all clinical trials conducted in Ukraine or with Ukraine’s participation which are associated with this report. In this case the term of annual reporting begins from the date of receipt of the Center’s conclusion on the conduct of the first listed clinical trial.

**3. Recording and analysis of notifications about suspected unexpected serious adverse reactions by the Center**

3.1. The Center shall record all cases of unexpected serious adverse reactions which become known to it and examine them.

3.2. If there is a suspicion of an increased risk to subjects the Center may request the sponsor an additional information on safety of the suspected medicinal product which shall be provided within 7 calendar days of the receipt of the request.

If during this period the sponsor does not provide such information or a letter with substantiated timeframe necessary for their preparation, the Center may take a decision on temporary suspension or full stoppage of the clinical trial concerned, informing the sponsor and investigators about this in writing.

**XIII. Clinical audit of clinical trials of medicinal products**

13.1. The Center may conduct clinical audit of clinical trials of medicinal products. The clinical audit of a clinical trial shall be conducted free of charge.

Subject to the clinical audit by the Center shall be documents, records, facilities, equipment and instruments, quality assurance system and other resources which can be kept at HCS, laboratories (including the pharmacokinetics laboratories), in the offices of the sponsor and/or the contract research organization or in other sites related to the clinical trial of the investigational medicinal product.

13.2. The quarterly plan of the clinical audits and their results shall be published on the official web-site of the Center.

13.3. The clinical audit of the clinical trial shall be conducted not earlier than 14 calendar days after submission of the preliminary notification and agreement with the applicant of the clinical trial and the principal investigator/investigator on its start date.

Where the Center has objective grounds for considering that the conditions described in the application for the Center’s conclusion are no longer met or has information raising doubts about safety of the subjects or scientific validity of the clinical trial, or the data evidencing adulteration the period between the preliminary notification and the audit of the clinical trial may be shortened.

13.4. The clinical audit of the clinical trial shall be carried out by the Center’s specialists with knowledge and experience in arranging and conducting clinical trials and who do not take part in their conduct as well as are independent from the sponsor and investigators.

13.5. If applicable, other specialists (depending on the peculiarities of trial protocol and purpose of the clinical audit of clinical trial) may be involved in the audit of the clinical trial.

13.6. According to the current legislation persons who conduct the clinical audit of the clinical trial shall not disclose confidential data they obtain during its conduct.

13.7. During the clinical audit of the clinical trial the principal investigator/investigator (or a person carrying out his functions) should be present at the clinical trial site. Also present may be the sponsor’s representatives.

13.8. During the clinical audit critical, essential or non-essential remarks may be made.

13.8.1. The critical remarks are related with the revealed shortcomings/violations affecting subjects’ rights, safety or health and/or affect the quality and integrity of the clinical trial data. The critical remarks include: data non-compliance, data adulteration, lack of primary medical documents and numerous essential remarks. Critical violations may be the reason for temporary suspension or full stoppage of the clinical trial. The Center shall inform the applicant and the investigator about the decision taken and grounds for suspension or full stoppage of the clinical trial in writing.

13.8.2. The essential remarks include those made in case of revealing shortcomings which may affect the subjects’ rights, safety and health, and/or may affect the integrity of the clinical trial data. Essential shortcomings include deviations from the clinical trial protocol and/or numerous non-essential remarks. Essential shortcomings require their timely correction within the timelines established based on the clinical audit’s results with the notification on their elimination (in writing) to the Center.

13.8.3. The non-essential remarks include those made in case of revealing shortcomings which do not affect the subjects’ rights, safety and health and/or cannot affect quality and integrity of the clinical trial data and which should be corrected and taken into account in the future activity.

13.9. Based on the results of clinical trial audit prepared shall be the report and a document confirming the fact of the clinical audit, including the remarks made during the clinical trial (if any) and specifying the timelines to eliminate the revealed violations (shortcomings). The Center shall send the document/statement confirming the fact of the clinical trial audit to the applicant and/or the principal investigator of the clinical trial within 30 calendar after the full termination of the clinical trial audit.

13.10. In case of the shortcomings, revealed during the clinical trial audit, which do not require suspension or full stoppage of the clinical trial, the principal investigator/investigator and/or the sponsor shall eliminate them in the timelines specified by the Center. The principal investigator/investigator and/or the applicant shall send information about elimination of shortcomings to the Center.

If the revealed shortcomings aren’t eliminated (beside those for the valid reasons and force majeur) within the timelines specified the Center may fully stop the clinical trial.

**XIV. Suspension or full stoppage of a clinical trial**

14.1. A clinical trial may be temporarily or fully stopped by the sponsor, the principal investigator/investigator or the Center.

14.2. The sponsor may suspend or fully stop the clinical trial, and shall inform the principal investigator/investigator, HCS, the ethics committee and the Center accordingly.

In case of full stoppage the principal investigator/investigator according to the sponsor’s decision shall stop the recruitment of new patients, and those involved before in the clinical trial shall go to phase of their condition control and follow-up, and standard medical care, if necessary. The sponsor shall provide instructions on further administration of the investigational medicinal product to the patients. The sponsor must inform the ethics committee and the Center about the reasons for temporary suspension, the period for which the clinical trial has been suspended, measures taken to ensure the protection of rights, safety and well-being of patients. The sponsor may resume the clinical trial after the elimination of reasons for the temporary suspension of the clinical trial and the notification of the ethics committee and the Center.

14.3. The principal investigator/investigator shall suspend the clinical trial or its separate stages if the risk to the subjects’ health or life increases, and officially inform the sponsor, the Center and the ethics committee.

14.4. The Center may suspend or fully stop (by the agreement with CEB) if there are objective grounds for considering that the requirements in the application for obtaining the Center’s conclusion are no longer met or there is information raising doubts about the subjects’ safety or scientific validity of the clinical trial, or data pointing out the adulteration. The Center shall notify the sponsor, the principal investigators/investigators/HCS and the ethics committee concerned, and publish its decision on the Center’s web-site.

14.5. Resumption of the temporally suspended clinical trial is possible in case of the full elimination of reasons for the temporary suspension and the notification of the ethics committee and the Center so that they take the appropriate decision.

14.6. In case of the full stoppage of the clinical trial its resumption is possible provided the repeated positive conclusion of the Center and the repeated approval of the ethics committee(s) at appropriate HCS(s) are available.

(Procedure in wording of MOH Ukraine Order №523 as of 12.07.2012)

**Yu. B. Konstantinov**

**Director,**

**Department for Regulatory Policy**

**in Circulation of Medicines and Healthcare Products**