



# Ministry of Health of Ukraine

## ORDER

23.09.2009 № 690

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 Ethics Committees

{amended by MoH Orders

№ 523 of 12.07.2012

№ 304 of 06.05.2014

№ 966 of 18.12.2014

№ 639 of 01.10.2015

№ 2609 of 25.11.2021

№ 538 of 28.03.2022

№ 190 of 31.01.2023

№ 1034 of 07.06.2023

№ 1745 of 06.10.2023

№ 138 of 26.01.2024

№ 894 of 24.05.2024

№ 2197 of 30.12.2024}

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 Ethics Committees.

3. To consider as void the MoH Ukraine Order № 66 of 13.02.2006 “About Approval of Procedure for Conducting Clinical Trials of Medicinal Products and Expert Evaluation of Materials Pertinent to Clinical Trials and Model Regulations of Ethics Committees” registered at the Ministry of Justice of Ukraine on 10.03.2006 under № 252/12126, the MoH Ukraine Order № 245 of

17.05.2007 “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 № 560 of 11.08.2006 “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**  
**№ 690 of 23.09.2009**  
**(in wording of the MoH Ukraine Order**  
**№ 523 of 12.07.2012)**

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

**PROCEDURE**  
**for Conducting Clinical Trials of Medicinal Products**  
**and Expert Evaluation of Materials Pertinent to Clinical Trials**

*{In the text of the Procedure and its annexes, the words “Ukrainian”, “investigational”/”subject”, “sponsor” in all cases and numbers are replaced by the words “state”, “trial subject”, “clinical trial sponsor” in the appropriate cases and numbers, except for the word “investigational” in the phrase “investigational medicinal product” in accordance with the Order of the Ministry of Health № 894 of 24.05.2024}*

**I. General**

*1.1. This Procedure was developed in accordance with articles 7 and 8 of the Law of Ukraine "On Medicines", the Law of Ukraine "On Personal Data Protection" taking into account the requirements of Directive 2001/20/EC of the European Parliament and of the Council of April 4, 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, 2001/83/EC of November 6, 2001 on the Community code relating to medicinal products for human use (Annex I, Part IV (Advanced therapy medicinal products)), Regulation (EC) No. 536/2014 of the European Parliament and of the Council of April 16, 2014 on clinical trials on medicinal products for human use, and repealing the Directive 2001/20/EC, Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, Regulation (EC) No 1902/2006 of the European Parliament and of the Council of 20 December*

2006 amending Regulation 1901/2006 on medicinal products for paediatric use, Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products, Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products C(2019) 7140 final version of October 10, 2019, ICH GCP, ICH GLP, GTP/cGTP, international ethical principles of biomedical research involving humans, and the doctor code of ethics.

1.2. This Procedure establishes the basic requirements for conducting clinical trials in Ukraine of medicinal products, including advanced therapy medicinal products (of biological origin), which include gene therapy medicinal products, somatic cell therapy medicinal products, and tissue engineered products; combined medicinal products, including as an integral part tissues and/or cells, and one or more medical devices, which may be conducted on patients (healthy volunteers) along full or shortened program, including the bioavailability/bioequivalence studies, as well as the international multicenter clinical trials.

1.3. This Procedure applies to all types of clinical trials of medicinal products, including advanced therapy medicinal products, except for non-interventional studies.

This Procedure does not apply to clinical trials of:

whole human blood;

non-substantially manipulated transplants intended to perform the same function(s) in the recipient's body as in the donor's one (homologous use);

hematopoietic stem cells/progenitor cells from umbilical cord blood, peripheral blood or bone marrow, which are unchanged in terms of their biological characteristics, used for the production and replenishment of the lymphohematopoietic system.

The activities related to the transplantation of hematopoietic stem cells/progenitor cells are carried out in accordance with the Law of Ukraine "On the Application of Transplantation of Human Anatomical Materials" and the Procedure for Collecting and Providing Hematopoietic Stem Cells and Exchange of Information on Available Human Anatomical Materials Intended for Transplantation, approved by the Decree of the Cabinet of Ministers of Ukraine No. 257 of March 25, 2020.

1.4. The State Expert Center of the Ministry of Health of Ukraine" (hereinafter - the Center) is entrusted with the examination of clinical trial materials, as well as the clinical audit of clinical trials of medicinal products and advanced therapy medicinal products.

1.5. At the applicant's request, the Center shall provide free consultations on quality planning and conduct of clinical trials of medicinal products according to the relevant legislation and the rules of Good Clinical Practice (GCP).

*{Section I in wording of the MoH Order № 138 of 26.01.2024, taking into account the changes made by the MoH Order № 272 of 19.02.2024}*

## 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;

protein - any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. When two or more amino acid chains in an amino acid polymer are associated with each other in a manner that occurs in nature, the size of the amino acid polymer will be based on the total number of amino acids in those chains, and will not be limited to the number of amino acids in a contiguous sequence;

*{Paragraph three added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

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;

biological medicinal product - a medicinal product that contains API of biological origin (a substance or substances produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control)).

*{Paragraph six added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

biological medicinal products include advanced therapy medicinal products, immunological medicinal products, and medicinal products derived from human blood and human plasma, as well as medicinal products produced using one of the following biotechnological processes:

*{Paragraph seven added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

recombinant DNA technology;

*{Paragraph eight added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

controlled gene expression encoding biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells;

*{Paragraph nine added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

hybridoma technology for monoclonal antibody production;

*{Paragraph ten added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

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 non-clinical data on the investigational medicinal product which are relevant to its study in humans;

homologous use (same basic function/functions) - use according to the concept that the basic functions of cells or tissues in the patient are the same or very similar to their functions in the donor;

*{Paragraph fourteen added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

trial subject (patient, healthy volunteer) - a person participating in a clinical trial or taking the investigational medicinal product, or included in the control group;

*{Paragraph fifteen of item 2.1 of section II in wording of the MoH Order № 894 of 24.05.2024, taking into account changes made by the MoH Order № 1021 of 13.06.2024}*

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 non-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 – preliminary and specialized expert evaluations of documents (materials) of a clinical trial of a medicinal product in order to draw up opinions on the conduct of a clinical trial/a substantial amendment.

*{Paragraph of item 2.1 of section II in wording of the MoH Order № 1034 of 07.06.2023}*

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., clinical trial sponsor, contract research organization), who submits to the central executive body of Ukraine, which develops and ensures an implementation of the state health care policy (hereinafter – CEB), applications for conducting clinical trial of medicinal product/getting approval of the ethics committee pertinent to conducting clinical trial/substantial amendment, and to the Center - other clinical trial materials. If not a clinical trial sponsor, an applicant may submit the appropriate applications only if clinical trial sponsor's power of attorney with clearly defined powers is available.

*{Paragraph of item 2.1 of section II in wording of the MoH Order № 190 of 31.01.2023}*

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

trial subject identification code/number - a unique identifier assigned to each trial subject by the investigator to protect the trial 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 to be reported to the clinical trial sponsor on each trial subject.

informed consent – a decision, which must, be dated and personally signed by hand or electronic signature, to take part in the clinical trial, made voluntarily after having been duly informed of its nature, significance, implications and risks and appropriately documented in paper or electronic format by any person capable of giving consent or, by his or her legal representative (close relative); if the person concerned is unable to write, his/her oral consent in the presence of at least one witness who attests the trial subject's consent in the written informed consent in paper or electronic format, may be given in exceptional cases;

*{Paragraph of item 2.1 of section II in wording of the MoH Order № 538 of 28.03.2022}*

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 clinical trial sponsor or the contract research organization, 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 subjects (patients, healthy volunteers), ethical, moral, and legal aspects of conducting clinical trial;

Based on the assessment of ethical, moral, and legal aspects the ethics committee at health facility (a health care setting) approves 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 under the agreement with a clinical trial 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 clinical trial sponsor;

Combined advanced therapy medicinal products - advanced therapy medicinal products that incorporates, as an integral part of the product, one or more medical devices.

*{Paragraph thirty-two added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

A combined advanced therapy medicinal product shall fulfil the following conditions:

*{Paragraph thirty-three added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

it shall incorporate, as an integral part of the product, one or more medical devices in the meaning of Article 1(2)(a) of Directive 93/42/EEC of 14 June 1993 concerning medical devices or one or more active implantable medical devices in the meaning of Article 1(2)(c) of Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices;

*{Paragraph thirty-four added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024, taking into account changes made by the MoH Order № 272 of 19.02.2024}*

its cellular or tissue part shall contain viable cells or tissues, or

*{Paragraph thirty-five added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

its cellular or tissue part containing non-viable cells or tissues shall be liable to act upon the human body with action that can be considered as primary to that of the devices referred to;

*{Paragraph thirty-six added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

medicinal product - any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis;

*{Paragraph thirty-seven added to item 2.1 of*

*Section II according to the MoH Order № 138 of 26.01.2024}*

gene therapy medicinal product - a biological medicinal product which has the following characteristics:

*{Paragraph thirty-eight added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

API of such medicinal product contains or consists of a recombinant nucleic acid that is used or administered to human beings with a view to arranging, restoring, replacing, adding or removing the genetic sequence;

*{Paragraph thirty-nine added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

the therapeutic, prophylactic or diagnostic effect of the medicinal product is directly related to the sequence of the recombinant nucleic acid, or to the product of genetic expression of such a sequence;

*{Paragraph forty added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

gene therapy medicinal product shall not include vaccines against infectious diseases.

*{Paragraph forty-one added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

gene therapy products include non-viral (plasmids, mRNA, DNA-based) and viral vectors that are used in vivo, as well as cells that have been modified by these types of vectors ex vivo;

*{Paragraph forty-two added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

medicinal product derived from human blood or human plasma - a medicinal product based on blood constituents, which is prepared industrially. Such medicinal products include, in particular, albumin, coagulating factors and immunoglobulins of human origin;

*{Paragraph forty-three added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

advanced therapy medicinal product - a gene therapy, somatic cell therapy and tissue engineered medicinal product;

*{Paragraph forty-four added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

somatic cell therapy medicinal product - a biological medicinal product which has the following characteristics:

*{Paragraph forty-five added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the donor and the recipient;

*{Paragraph forty-six added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

is presented as having properties, used or administered to a person for the purpose of treatment, prevention or diagnosis of a disease through pharmacological, immunological or metabolic action of its cells or tissues;

*{Paragraph forty-seven added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

tissue engineered medicinal product - a medicinal product that contains or consists of engineered cells or tissues, is presented as having properties for, is used or administered to human beings with a view to regenerating, repairing or replacing a human tissue. Tissue engineered medicinal products may contain cells or tissues of human or animal origin, or both, whether viable or non-viable, as well as additional substances, including cellular products, bio-molecules, bio-materials, chemical substances, cell matrices or scaffolds;

*{Paragraph forty-eight added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

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 clinical trial sponsor or the contract research organization who controls the performance of a clinical trial in compliance with the protocol of clinical trial.

non-interventional study - 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 medical documents – original documents, data and records in paper or electronic format (including documents created, stored and transmitted via an electronic information system) (e.g., inpatient medical records, outpatient medical records, laboratory notes, memos, trial 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 documents, records kept at pharmacy, laboratory and instrumental diagnostics department) of the persons involved in a clinical trial, etc.

*{Paragraph of item 2.1 of section II in wording of the MoH Order № 538 of 28.03.2022}*

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 trial 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.

preliminary expert evaluation – a verification that data in the documents (materials) submitted in support of an application for conducting clinical trial/substantial amendment, are complete and adequate in accordance with the requirements of this Procedure.

*{Paragraph added to item 2.1 of section II by the MoH Order № 1034 of 07.06.2023}*

amendment to clinical trial protocol – a written description of changes to or formal clarification of the clinical trial protocol.

clinical trial protocol – 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.

specialized expert evaluation – an assessment of conformity and analysis of quality of documents (materials) of a clinical trial of a medicinal product to draw opinions regarding the conduct of a clinical trial or approval of a substantial amendment;

*{Paragraph added to item 2.1 of section II by the MoH Order № 1034 of 07.06.2023}*

Clinical trial sponsor – a legal entity or a natural person responsible for initiating and managing, and/or financing the clinical trial of the medicinal product.

*{Paragraph sixty-three of item 2.1 of section II in wording of the MoH Order № 894 of 24.05.2024}*

substantial manipulation - manipulation of cells or tissues so that their biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. Substantial manipulations include, but are not limited to, for example: cell expansion (culture); in vitro differentiation of cells or tissues; genetic modification; tissue enzymatic dissociation/digestion; placing cells in a medical device; mixing demineralized bone with cell and/or tissue products, and obtaining cells or tissues with modified characteristics.

*{Paragraph sixty-four added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

Manipulations such as cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, vitrification shall not be considered as substantial manipulations.

*{Paragraph sixty-five added to item 2.1 of Section II according to the MoH Order № 138 of 26.01.2024}*

substantial amendment to protocol of clinical trial - amendment to the protocol of clinical trial is regarded as substantial 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 the scientific value of the trial;

qualified person for quality (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 Fundamentals 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 trial subjects’ rights, safety and well-being. A clinical trial shall 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 designated by the CEB, if there is a CEB’s decision to authorize the conduct of clinical trials (hereinafter – the CEB’s decision), which is made based on positive opinion of the expert evaluation of materials pertinent to a clinical trial, issued by the Center (hereinafter – the Opinion).

*{Item 3.2 of section III in wording of the MoH Order № 966 of 18.12.2014; amended by the MoH Order № 190 of 31.01.2023}*

3.3. All persons involved in conducting a clinical trial shall have appropriate education, proficiency and experience to perform functions and discharge obligations pertinent to the clinical trial.

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

3.5. Any clinical trial shall only commence after the CEB makes decision, the protocol(s) of the ethics committee(s) at the HCS where the clinical trial is to be directly conducted is received regarding the approval of this clinical trial, which serves as the reason for its commencement, and an insurance contract that covers the liability of the clinical trial sponsor to third parties for possible harm to trial subjects' life and health (patients, healthy volunteers) during their participation in the clinical trial under insurance class 13 in accordance with article 4 of the Law of Ukraine "On Insurance" is concluded in the manner prescribed by law.

*{Item 3.5 of section III in wording of the MoH Orders № 966 of 18.12.2014, № 894 of 24.05.2024}*

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

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

Every clinical trial of a medicinal product shall be entered into the list of clinical trials published on the official website of the CEB prior to enrollment of the first trial subject. Entering a clinical trial into the list is for informational purposes and shall not impede its commencement and conduct.

*{Item 3.7 of section III amended by a new paragraph according to the MoH Order № 639 of 01.10.2015; as amended by MoH Order № 894 of 24.05.2024}*

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 shall be in place to ensure quality of all aspects of clinical trial.

3.10. The clinical trial information shall be recorded, processed, and stored in a way that allows its accurate reporting, interpretation and verification, irrespective of the form of creation, use of the electronic information system, method for transmission and storage."

*{Paragraph one of item 3.10 of section III in wording of the MoH Order № 538 of 28.03.2022}*

A list of essential documents pertinent to clinical trial that are to be kept at HCS/clinical trial site and clinical trial sponsor is specified in Annex 1 to this Procedure. These documents shall be kept in paper/electronic format in the archives for at least 25 years after termination of clinical trial.

*{Paragraph two of item 3.10 of section III in wording of the MoH Order № 1034 of 07.06.2023}*

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), for the advanced therapy medicinal product as well as in compliance with Good Tissue Practice (GTP/cGTP), Guideline “Good Manufacturing Practice. Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products” (CT-H MO3Y 42- 4.9:2020)

*{Paragraph one of item 3.11 of section III in wording of the MoH Order № 138 of 26.01.2024}*

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 end the Center may conduct clinical audit of clinical trial on compliance with GCP as per section XIII of this Procedure.

*{Item 3.12 of section III in wording of MoH Order № 639 of 01.10.2015}*

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

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

1.1. The trial subject's protection shall 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 shall 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 shall 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 shall 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 trial 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 responsible for 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 trial 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 trial 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 trial subject);

*{Subitem 1.3.6. of item 1.3 of chapter 1 of section IV is excluded based on MoH Order № 304 of 06.05.2014}*

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

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

*{Item 1.5 of chapter 1 of section IV amended by the MoH Order № 304 of 06.05.2014}*

1.6. The trial subject or legal representative/close relatives may independently (this shall 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 responsible for obtaining informed consent shall inform the patient (healthy volunteer), but if the latter is incapable to provide informed consent, the trial 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 shall be made on his own and without force or unduly influence.

2.3. None of the written and oral information concerning the clinical trial shall 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 clinical trial sponsor from liability for injuring.

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

2.5. The investigator shall provide the patient (healthy volunteer) or his legal representative (close relative) ample time to make a decision whether or not to participate in a clinical trial. All questions about the trial shall 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 of item 2.6 of chapter 2 of section IV in wording of the MoH Order № 304 of 06.05.2014}*

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

2.7. Before joining a clinical trial, a patient (healthy volunteer) or his legal representative/close relative, and the principal investigator/investigator responsible for obtaining informed consent shall personally sign and date two copies of the informed consent form in paper format by hand or sign the informed consent in electronic format by electronic signature. The informed consent shall be printed out in two copies, one copy to be left with the principal investigator/investigator, the other one - with the trial subject. It must be indicated that the informed consent was given freely by the trial subject/legal representative/close relative after receiving the full information about the clinical trial.

*{Item 2.7 of section IV in wording of the MoH Order № 538 of 28.03.2022}*

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

*{Item 2.8 of section IV in wording of the MoH Order № 538 of 28.03.2022}*

2.9. One copy of the informed consent signed and dated shall be kept with the principal investigator/investigator, and in the HCS's archives (in paper and/or electronic format) for at least 15 years after the termination of the clinical trial concerned.

*{Item 2.9 of section IV in wording of the MoH Order № 538 of 28.03.2022}*

2.10. If the patient is in a critical or emergency condition that does not allow obtaining informed consent to participate in a clinical trial, such consent shall be obtained from his/her legal representative/close relative

When the informed consent of the patient to participate cannot be obtained and his/her legal representative/close relative is not available, enrolment of such patients in a clinical trial is inadmissible, they shall be given medical assistance according to procedure established.

2.11. Informed consent shall include consent of the patient's (healthy volunteer's) or his/her legal representative/close relative for processing his/her 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 parties.

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

2.13. The Center, the ethics committee at HCS, and the clinical trial 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 trial subject (legal representative/close relative) may apply to the clinical trial 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 trial 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 in paper or electronic format of both parents has been obtained;

*{Subitem "a" of item 3.1 of section IV in wording of the MoH Order № 538 of 28.03.2022}*

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 shall give his oral consent to participate in the clinical trial;

The minor patient shall personally sign and date the informed consent in paper or electronic format, or sign the informed consent in electronic format by electronic signature.

*{Paragraph two of subitem "b" of item 3.1 of section IV in wording of the MoH Order № 538 of 28.03.2022}*

The principal investigator/investigator responsible for obtaining informed consent shall consider the explicit wish of a child under 14 or a minor to participate or refuse to participate 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 shall 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 shall 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 shall always prevail over those of science and society.

4. Clinical trials on incapacitated trial 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 trial 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 responsible for obtaining informed consent takes into account the wish of an incapacitated patient to participate or refuse to participate 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 shall relate directly to a clinical condition from which a trial subject suffers;

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

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

4.2. The interests of incapacitated trial 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 shall:**

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 shall have an expertise in clinical trials supported by information given in curriculum vitae.

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

The ethics committee is established and functions at HCS;

There are sufficient resources to provide the trial 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 trial subjects according to the clinical trial protocol;

Source medical documents are recorded according to requirements of the current legislation, and there are conditions for their archiving (in the archives facilities/electronic information system) for at least 15 years after the termination of the clinical trial.

*{Paragraph seven of item 5.2 of section V in wording of the MoH Order № 538 of 28.03.2022}*

### **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 trial 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 trial subjects;

Storage conditions for biosamples during clinical trials.

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

*{Item 5.5 of section V deleted according to the MoH Order № 2197 of 30.12.2024}*

## **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 the state language and English (for international clinical trials).

*{Paragraph one of item 6.2 of section VI in wording of the MoH Order № 894 of 24.05.2024}*

The following shall be included in labelling:

a) Name of legal entity/full name of natural person, location of legal entity/residence of natural person and contact phone number of clinical trial 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 clinical trial sponsor if not given elsewhere;

e) The trial subject identification number/trial 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 trial 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

trial 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 shall 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 device that contains the immediate container):

- a) Name of legal entity/full name of natural person of clinical trial 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 clinical trial 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 shall be provided bearing a label with those particulars. The immediate container shall nevertheless contain the following brief information:

- a) Name of legal entity/full name of natural person of clinical trial 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 clinical trial 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):

a) Name of legal entity/full name of natural person of clinical trial sponsor/manufacturer/full name of principal investigator/investigator;

b) Clinical trial reference code allowing identification of the trial, trial site, investigator and clinical trial 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 shall 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 shall 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 Order № 966 of 18.12.2014}*

7.1. To conduct clinical trials of medicinal products the applicant shall submit to the CEB documents (materials) of clinical trial in paper and electronic format specified in subitems 7.1.1 and 7.1.2 of this item; to the Center – those specified in subitems 7.1.3 -7.1.21 of this item inclusive. Documents (materials) of clinical trial may be submitted by the applicant in electronic format, if technically feasible:

*{Paragraph 1 of item 7.1 of section VII in wording of the MoH Orders № 966 of 18.12.2014, № 2609 of 25.11.2021}*

Documents (materials) of clinical trial include:

*{Item 7.1 of section VII amended by new paragraph according to the MoH Order № 2609 of 25.11.2021}*

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

*{Subitem 7.1.1 of item 7.1 of section VII amended by the MoH Order № 304 of 06.05.2014}*

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 of item 7.1 of section VII amended by the MoH Order № 304 of 06.05.2014; in wording of the MoH Order № 966 of 18.12.2014}*

7.1.3. Protocol of the clinical trial of the medicinal product with all amendments to it that shall 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 shall 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 of subitem 7.1.7 of item 7.1 of section VII amended by the MoH Order № 304 of 06.05.2014}*

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 an opinion on a clinical trial of the medicinal product concerned.

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

For comparators and placebo the simplified dossier or summary of 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).

During clinical studies for demonstration of bioequivalence or therapeutic equivalence, if the clinical trial sponsor within the European Union purchases the investigational medicinal product used as a comparator, the applicant may provide a certificate of GMP compliance of a manufacturer for the purchased batch of the investigational medicinal product from the EU country, instead of the batch certificate (certificate of analysis, certificate of quality), issued by the qualified person for quality (of a manufacturer).

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.

*{Subitem 7.1.8 of item 7.1 of section VII in wording of the MoH Order № 894 of 24.05.2024, taking into account changes made by the MoH Order № 1021 of 13.06.2024}*

*{Subitem 7.1.9 of item 7.1 of section VII deleted according to the MoH Order № 894 of 24.05.2024}*

7.1.9. Results of the previous expert evaluations and/or the Center's opinion on a non-clinical study and clinical trial of a medicinal product (if any).

7.1.10. List of authorized competent authorities of other countries where applications for the clinical trial have been also submitted, and detailed information on their decisions made (if any). For clinical trials involving an investigational advanced therapy medicinal product, a copy of the document from a strict regulatory authority on classification of the advanced therapy medicinal product shall be provided, and domestic manufacturers shall provide one from the Center on received scientific recommendations on advanced therapy medicinal product classification.

*{Subitem of item 7.1 of section VII in wording of the MoH Order № 138 of 26.01.2024}*

7.1.11. A power of attorney from a clinical trial sponsor with clearly specified granted powers if a clinical trial applicant differs from the clinical trial sponsor.

7.1.12. The draft informed consent and other written information to be provided to a patient (healthy volunteer) (in the state language and English (for international clinical trials). The draft shall envisage a patient's consent to use his/her personal data for processing the study results.

*{Subitem 7.1.8 of item 7.1 of section VII as amended by the MoH Order № 894 of 24.05.2024, taking into account changes made by the MoH Order № 1021 of 13.06.2024}*

7.1.13. Brief data on all ongoing clinical trials involving the investigational medicinal product concerned (if any).

7.1.14. Previously granted expert evaluation of the clinical trial (if any). For clinical trials using an advanced therapy as the investigational drug, provide a copy of the expert opinion of a strict regulatory authority.. For clinical trials involving an investigational advanced therapy medicinal product, a copy of the document concerning previous expert evaluation from a strict regulatory authority shall be provided.

*{Subitem of item 7.1 of section VII in wording of the MoH Order № 138 of 26.01.2024}*

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

*{Subitem of item 7.1 of section VII amended by the MoH Order № 304 of 06.05.2014}*

7.1.16. Information on HCS and clinical trial site according to the form given in Annex 7 to this Procedure, which is current at the time of submission of documents (materials).

*{Subitem of item 7.1 of section VII amended by the MoH Order № 304 of 06.05.2014}*

7.1.17. Information on principal investigator/investigator (Curriculum vitae, hereinafter - CV)) shall 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 shall be submitted if doctors of different specialties are to be involved.

7.1.18. 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 qualified person for quality (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).

*{New paragraph added to subitem of item 7.1 of section VII amended by according to MoH Order № 966 of 18.12.2014}*

7.1.19. A sample labeling of an investigational medicinal product in the state language and English (for international clinical trials).

*{Subitem 7.1.19 of item 7.1 of section VII in wording of the MoH Order № 894 of 24.05.2024, taking into account changes made by the MoH Order № 1021 of 13.06.2024}*

7.1.20. 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 of item 7.1 of section VII is excluded according to the MoH Order № 304 of 06.05.2014}*

*{Subitem 7.1.23 of item 7.1 of section VII is excluded according to the MoH Order № 304 of 06.05.2014}*

*{Subitem 7.1.24 of item 7.1 of section VII is excluded according to the MoH Order № 304 of 06.05.2014}*

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

Within 30 days of receipt at the Center of the CEB's letter of referral the applicant shall submit 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 of section VII in wording of the MoH Order № 966 of 18.12.2014}*

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 receipt in corpore by the Center according to item 7.1 of this section. The Center shall conduct expert evaluation within 30 calendar days.

The expert evaluation of documents (materials) of a clinical trial of a medicinal product includes stages of preliminary and specialized expert evaluations.

The preliminary expert evaluation of materials of a clinical trial of a medicinal product starts from the date of receipt by the Center of the documents (materials) of a clinical trial of a medicinal product after the cost of expert work is paid in full according to the invoice.

The period of preliminary expert evaluation by the Center is no more than 5 calendar days.

During the preliminary expert evaluation, the Center may make one time a written remark for the applicant on the completeness and adequacy of the submitted documents (materials) of a clinical trial. After receiving a response to the remark, the Center shall inform the applicant within two calendar days whether the submitted application for conducting a clinical trial of a medicinal product and a set of documents (materials) comply with the requirements of this Procedure and they can be sent for a specialized expert evaluation. If the Center has not informed the applicant within the period set out for the preliminary expert evaluation, the application and set of documents (materials) of a clinical trial shall be regarded as complete in accordance with the requirements of the Procedure.

The time required to respond to remarks is not included in the period of preliminary expert evaluation.

If, within 20 calendar days from the day following the date of receipt of such remarks, the applicant does not respond to the remarks on completeness or provide the documents (materials) to the Center or a letter justifying the time required to finish them up, the review of clinical trial documents (materials) shall be rejected, the applicant and the CEB shall be notified about this in writing.

Specialized expert evaluation of clinical trial materials shall start in the case of positive results of the preliminary expert evaluation provided that all documents specified in subitems 7.1.3 - 7.1.21 of item 7.1 of this section are available, taking into consideration the ethical, moral, and legal aspects of the clinical trial. The period of specialized expert evaluation by the Center is no more than 23 calendar days.

In the event of a public health emergency of international concern (an event which is determined to constitute a public health risk to citizens of other countries through the international spread of disease and/or to potentially require coordinated international response), the Center shall conduct an expert evaluation of documents (materials) of clinical trials of medicinal products, and vaccines or other medical immunobiological products for treatment and specific prevention of infectious and non-infectious diseases within 5 calendar days (preliminary expert evaluation by the Center - 1 calendar day; specialized expert evaluation by the Center - 4 calendar days).

*{Paragraph nine of item 7.4 of section VII in wording of the MoH Order № 138 of 26.01.2024}*

The period of expert evaluation of materials of a clinical trial involving an investigational advanced therapy medicinal product is 79 calendar days.

*{New paragraph added to item 7.4 of section VII according to the MoH Order № 138 of 26.01.2024; as amended by MoH Order № 894 of 24.05.2024}*

The period of preliminary expert evaluation by the Center is not more than 15 calendar days.

*{New paragraph added to item 7.4 of section VII according to the MoH Order № 138 of 26.01.2024; as amended by MoH Order № 894 of 24.05.2024}*

The period of specialized expert evaluation by the Center is not more than 64 calendar days.

*{New paragraph added to item 7.4 of section VII according to the MoH Order № 138 of 26.01.2024; as amended by MoH Order № 894 of 24.05.2024; taking into account changes made by the MoH Order № 272 of 19.02.2024}*

The Center may extend the period of expert evaluation by additional 50 calendar days for clinical trials involving an investigational advanced therapy medicinal product for the purpose of consulting specialists, of which the applicant shall be notified.

*{New paragraph added to item 7.4 of section VII according to the MoH Order № 138 of 26.01.2024; taking into account changes made by the MoH Order № 272 of 19.02.2024}*

*{Paragraph 7.4 of section VII in wording of the Orders of the Ministry of Health № 966 of 18.12.2014, № 190 of 31.01.2023, № 1034 of 07.06.2023}*

7.5. During the specialized expert evaluation of clinical trial materials, based on the observations and remarks of experts, the Center may one time request in writing additional materials from the applicant.

*{Paragraph one of item 7.5 of section VII as amended by the MoH Order № 1034 of 07.06.2023}*

The time required for their preparation shall not be included in the period of specialized expert evaluation. If the applicant fails to provide the Center with additional materials or a letter justifying the time required to finish them up within 60 calendar days, the review of clinical trial materials shall be rejected.

*{Paragraph two of item 7.5 of section VII as amended by the MoH Order № 1034 of 07.06.2023}*

The Center shall inform the applicant about the decision made in writing with no cost of expert works to be reimbursed to the applicant. Further on, at applicant's request, the materials shall be submitted in due course to gain the Center's opinion.

7.6. Based on results of expert evaluation, the Center shall provide the CEB with an Opinion: positive, negative. Based on the Center's Opinion the CEB shall make a decision to authorize a

clinical trial or refuse the authorization of a clinical trial on duly justified grounds. The CEB shall make a decision within 5 calendar days.

The title of clinical trial, its code, version and date of protocol, clinical trial sponsor, applicant and/or legal or physical person who acts under the power of attorney issued by the clinical trial sponsor or applicant for importing investigational medicinal products (registered or unregistered) and ancillary supplies, principal investigator, trial site, list of investigational medicinal products, comparators and ancillary supplies shall be approved by the decision to authorize a clinical trial.

*{Paragraph two of item 7.6 of section VII in wording of MoH Order № 639 of 01.10.2015}*

*{Item 7.6 of section VII in wording of the MoH Order № 966 of 18.12.2014; amended by the MoH Order № 190 of 31.01.2023}*

7.7. If the applicant doesn't agree with the CEB decision to refuse the authorization of a 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 made. The final decision with appropriate grounds 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 of section VII in wording of the MoH Order № 966 of 18.12.2014}*

### **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. A positive opinion of the ethics committee shall be documented in the relevant minutes of its meeting and is an approval to conduct a clinical trial in a specific HCS where the trial site(s) is(are) directly located.

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

8.4. To obtain the ethical appraisal for a clinical trial the applicant shall submit the following documents in paper or electronic format to the ethics committee at HCS:

*{Paragraph one of item 8.4 of section VIII in wording of the MoH Order № 538 of 28.03.2022}*

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

*{Subitem 8.4.1 of item 8.4 of section VIII amended by the MoH Order № 304 of 06.05.2014}*

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

*{Subitem 8.4.2 of item 8.4 of section VIII amended by the MoH Order № 304 of 06.05.2014}*

8.4.3. The protocol of clinical trial of medicinal product with all available amendments, which shall contain information given in section 6 of the GCP, in the language of the original document, and a summary (synopsis) of clinical trial protocol in Ukrainian.

*{Subitem 8.4.3 of item 8.4 of section VIII in wording of the MoH Order № 639 of 01.10.2015}*

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

8.4.5. A copy of the Center's opinion approved by CEB (if any).

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

8.4.7. The draft informed consent and other written information to be provided to a patient (healthy volunteer) (in the state language and English (for international clinical trials)).

*{Subitem 8.4.7 of item 8.4 of section VIII as amended by the MoH Order № 894 of 24.10.2024}*

8.4.8. Information on trial subject recruitment procedures (information and promotional materials to be used for trial 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 shall be submitted at HCS where the ethics committee is located.

*{Subitem 8.4.10 of item 8.4 of section VIII amended by the MoH Order № 304 of 06.05.2014}*

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 of item 8.4 of section VIII amended by the MoH Order № 304 of 06.05.2014}*

8.4.12. Information on principal investigator/investigator (CV) shall 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 shall be submitted if doctors of different specialties are involved in the clinical trial.

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

8.4.14. Clinical trial 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 trial subjects' health and life.

8.4.15. Copy of certificate to the insurance contract that covers the liability of the clinical trial sponsor to third parties for possible harm to trial subjects' life and health (patients, healthy volunteers) during their participation in the clinical trial.

*{New subitem added to item 8.4 of section VIII according to the MoH Order № 639 of 01.10.2015; in wording of the MoH Order № 894 of 24.05.2024}*

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 added in an electronic medium.

*{Item 8.5 of section VIII amended by the MoH Order № 304 of 06.05.2014}*

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 approval 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 exceed 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 made in writing.

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

## **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 minutes of the 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 an insurance contract that covers the liability of the clinical trial sponsor to third parties for possible harm to trial subjects' life and health (patients, healthy volunteers) during their participation in the clinical trial under insurance class 13 in accordance with article 4 of the Law of Ukraine "On Insurance" in the manner prescribed by legislation.

*{Paragraph 1 of item 9.1 of section IX in wording of the MoH Order № 966 of*

Clinical trial sponsor (contract research organization on behalf of the clinical trial 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 clinical trial sponsor (contract research organization on behalf of the clinical trial sponsor), HCS, and research institution or higher medical school shall be envisaged.

The clinical trial sponsor or contract research organization (on behalf of the clinical trial 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 clinical trial sponsor (contract research organization on behalf of the clinical trial sponsor) according to the contract concluded with the HCS which, in particular, shall include a provision regarding such obligation of the clinical trial sponsor (contract research organization on behalf of the clinical trial sponsor) or principal investigator/investigator/co-investigator according to the separate contract concluded between him and HCS.

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

*{Item 9.1 of section IX amended by a new paragraph according to the MoH Order № 639 of 01.10.2015}*

9.2. Import/export in/from the territory of Ukraine, records keeping and storage of an investigational medicinal product and ancillary supplies 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 Drugs Control Committee.

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 clinical trial 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 of item 9.3 of section IX amended by the MoH Order № 304 of 06.05.2014}*

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

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

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

### **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 of chapter 1 of section X amended by the MoH Order № 304 of 06.05.2014}*

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

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

*{Item 1.4 of chapter 1 of section X amended by the MoH Order № 304 of 06.05.2014; in wording of the MoH Order № 966 of 18.12.2014, № 639 of 01.10.2015, № 538 of 28.03.2022}*

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

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 of chapter 1 of section X amended by the MoH Order № 304 of 06.05.2014}*

1.7. The investigator shall continue clinical trial in compliance with substantial amendment(s) made to the clinical trial protocol, only if the CEB makes 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 of chapter 1 of section X in wording of the MoH Order № 966 of 18.12.2014}*

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 trial subjects, the clinical trial sponsor and/or the investigator shall take appropriate urgent safety measures to protect the trial subjects. The clinical trial 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 an opinion on substantial amendments based on their expert evaluation.

2.2. The Center shall conduct the expert evaluation (preliminary and specialized) of the submitted materials in order to make a reasoned opinion on the conduct the clinical trial according to the amendments to the clinical trial materials.

A contract for expert works pertinent to a substantial amendment shall be concluded between the Center and an applicant. The expert evaluation of changes specified in amendments to the clinical trial materials to support the substantial amendment application shall be paid for. The period of expert evaluation by the Center is no more than 25 calendar days.

The preliminary expert evaluation of substantial amendment materials shall start from the date of receipt by the Center of a full set of substantial amendment documents (materials) and after the cost of expert work is paid in full according to the invoice.

The period of preliminary expert evaluation by the Center is no more than 4 calendar days.

During the preliminary expert evaluation, the Center may make one time a written remark for the applicant on the completeness of the submitted substantial amendment materials. After receiving a response to the remark in full, the Center shall inform the applicant about the transfer of materials to the specialized expert evaluation within one calendar day. If the Center has not informed the applicant within the time frame specified for the preliminary expert evaluation, the substantial amendment application with a set of materials shall be regarded as complete in accordance with the requirements of the Procedure.

The time required to respond to remarks is not included in the period of preliminary expert evaluation.

If, within 15 calendar days from the day following the date of receipt of such remark, the applicant does not respond to the remark on completeness and/or submit a set of documents (materials) to the Center or a letter justifying the time necessary to finish them up, the review of substantial amendment documents (materials) shall be rejected, the applicant and the CEB shall be notified about this in writing.

Specialized expert evaluation shall start at the Center provided a full set of substantial amendment documents is available. The period of specialized expert evaluation by the Center is no more than 20 calendar days.

In the event of a public health emergency of international concern (an event which is determined to constitute a public health risk to citizens of other countries through the international spread of disease and/or to potentially require coordinated international response), the Center shall conduct an expert evaluation of substantial amendment documents (materials) related to clinical trials of medicinal products, and vaccines or other medical immunobiological products for treatment and specific prevention of infectious and non-infectious diseases within 5 calendar days (preliminary expert evaluation by the Center - 1 calendar day; specialized expert evaluation by the Center - 4 calendar days).

*{Paragraph nine of item 2.2 of chapter 2 of section X in wording of the MoH Order № 138 of 26.01.2024}*

The period of expert evaluation of substantial amendment related to a clinical trial involving an investigational advanced therapy product is not more than 68 calendar days.

*{New paragraph added to item 2.2 of chapter 2 of section X according to the MoH Order № 138 of 26.01.2024; taking into account changes made by the MoH Order № 272 of 19.02.2024; in wording of the MoH Order № 894 of 24.05.2024}*

The period of preliminary expert evaluation by the Center is not more than 11 calendar days.

*{New paragraph added to item 2.2 of chapter 2 of section X in wording of the MoH Order № 138 of 26.01.2024; in wording of the MoH Order № 894 of 24.05.2024}*

The period of specialized expert evaluation by the Center is not more than 57 calendar days.

*{New paragraph added to item 2.2 of chapter 2 of section X in wording of the MoH Order №*

*138 of 26.01.2024; in wording of the MoH Order № 894 of 24.05.2024}*

The Center may extend the period of expert evaluation by additional 50 calendar days for clinical trials involving an investigational advanced therapy medicinal product for the purpose of consulting specialists, the applicant shall be notified thereof.

*{New paragraph added to item 2.2 of chapter 2 of section X according to the MoH*

*Order № 138 of 26.01.2024; taking into account changes made by the MoH Order № 272 of 19.02.2024}*

*{Item 2.2 of chapter 2 of section X in wording to the MoH Order № 1034 of 07.06.2023}*

2.3. During the expert evaluation of the amendments in order to issue an opinion 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 reasoned time frame necessary for their preparation within 30 calendar days, the review of amendments shall be rejected. The Center shall inform the applicant about the decision made in writing with no cost of expert evaluation to be reimbursed to the applicant. The applicant may resubmit materials to receive the Center's opinion.

2.4. Based on results of expert evaluation, the Center shall issue to the CEB a positive or negative opinion on substantial amendment. Based on the opinion the CEB shall make a decision to approve a substantial amendment or refuse the approval of a substantial amendment specifying the grounds for the refusal. The CEB shall make a decision within 5 calendar days.

*{Item 2.4 of chapter 2 of section X in wording of the MoH Order № 966 of 18.12.2014; amended by the MoH Order № 190 of 31.01.2023}*

2.5. If the applicant doesn't agree with the Center's decision to cancel the review of substantial amendment or with an opinion on substantial amendment, he may submit a reasoned application to a head of the Center or CEB. The applicant shall submit 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 make 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. The principal investigator shall submit (in paper or electronic format) to the ethics committee at HCS a cover letter using the form given in Annex 10 to this Procedure, an application using the form given in Annex 11 to this Procedure and documents (materials) according to item 1.4 of chapter 1 of section X of this Procedure in order to gain its approval of substantial amendments.

*{Paragraph one of item 3.3 of section X in wording of the MoH Order № 538 of 28.03.2022}*

The 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 made.

*{Paragraph two of item 3.3 of chapter 3 of section X in wording of MoH Order № 639 of 01.10.2015}*

3.4. If the principal investigator/investigator doesn't agree with the ethics committee's decision he/she may submit a reasoned application. A properly reasoned application shall be submitted by the principal investigator/investigator within 10 calendar days of receipt of the relevant decision, and reviewed by the ethics committee within 10 calendar days after its receipt in order to make 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 clinical trial sponsor shall inform the Center and the ethics committee about termination of the clinical trial (date of last visit of the last trial subject) in Ukraine within 90 days of its end using the form given in Annex 12 to this Procedure.

*{Item 11.1 of section XI amended by the MoH Order № 304 of 06.05.2014}*

11.2. In case of international multicenter clinical trials, the clinical trial 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 clinical trial 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 clinical trial 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 of section XI amended by the MoH Order № 304 of 06.05.2014}*

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 clinical trial sponsor.

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

The clinical trial 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 final report on conducted clinical trial (in all countries) shall be accompanied by a brief written description (Summary of clinical trial results) in a plain and understandable language for laypersons. A brief written description of clinical trial results for laypersons shall include the following information: name of clinical trial, protocol code; name and contact details of clinical trial sponsor/applicant; general data about clinical trial (including the trial site and time, its main objectives and explanation of the reason for its conduct); population and number of subjects included in a trial in Ukraine and in the world; differentiation of groups by age and gender; inclusion/exclusion criteria; investigational medicinal products that were used; description and frequency of adverse reactions; general results of clinical trial; comments on clinical trial results; follow-up if it is foreseen; references for further information sources.

A summary of clinical trial results shall be provided in English and translated into the state language. A summary of clinical trial results shall be published on the information resource "List of clinical trials of medicinal products in Ukraine".

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 of section XI amended by the MoH Order № 304 of 06.05.2014; in wording of the MoH Order № 1034 of 07.06.2023}*

## **XII. Reporting adverse events and reactions**

### **1. Reporting by principal investigator/investigator**

1.1. During the clinical trial the principal investigator/investigator shall report to the clinical trial sponsor immediately all serious adverse events, except for those the protocol or Investigator's brochure identifies as not needing immediate reporting, but in any case, not later than 24 hours after he becomes aware of them. The primary and follow-up reports shall identify trial subjects by trial subject identification code assigned to them during the study.

*{Item 1.1 of chapter 1 of section XII in wording of the MoH Order № 1034 of 07.06.2023; as amended by the MoH Order № 894 of 24.05.2024}*

1.2. The principal investigator/investigator shall also report to the clinical trial 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 clinical trial sponsor in the protocol.

1.3. The principal investigator/investigator shall record all suspected unexpected serious adverse reactions associated with the investigational medicinal product, which resulted in death or were life-threatening to the trial subject's life and occurred in the clinical trial in the trial site concerned, and report to the ethics committee within 7 calendar days after he becomes aware of them. The additional information on this case shall be given to the ethics committee within subsequent 8

calendar days. Requirements to preparing report on suspected unexpected serious adverse reactions are specified in Annex 15 to this Procedure.

*{Paragraph one of item 1.3 of chapter 1 of section XII as amended by the MoH Order № 894 of 24.05.2024}*

Suspected unexpected serious adverse reactions reports shall be submitted to the ethics committee at HCS in paper or electronic format to the ethics committee's email address, or entered into the electronic information system.

The submission of safety reports (reporting period) to the clinical trial sponsor and the ethics committee by the principal investigator/investigator shall begin from the date of the start of the clinical trial in the trial site concerned (informed consent signed by the first trial subject) and terminate with the end of the clinical trial in the trial site concerned (the date of the last visit of the last trial subject), unless otherwise provided by the clinical trial protocol.

*{Item 1.3 of chapter 1 of section XII as amended by the MoH Order № 304 of 06.05.2014; in wording of the MoH Order № 1034 of 07.06.2023}*

1.4. The principal investigator/investigator shall report to the ethics committee all other suspected unexpected serious adverse reactions associated with the investigational medicinal product, which have occurred in the clinical trial at the trial site concerned not later than 15 calendar days after he/she becomes aware of which.

*{Item 1.4 of chapter 1 of section XII as amended by the MoH Orders № 1034 of 07.06.2023, № 894 of 24.05.2024}*

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

## 2. Reporting by clinical trial sponsor

2.1. Reporting the suspected unexpected serious adverse reactions in paper or electronic format to the Center (reporting period) shall begin from the date of approval by the CEB of the Center's opinion on clinical trial and terminate with the end of clinical trial in Ukraine, unless otherwise provided by the clinical trial protocol.

According to this Procedure suspected unexpected serious adverse reaction reports and/or other safety information on investigational medicinal product shall be submitted to the email address of the Center, the ethics committee at HCS, principal investigators in paper or electronic format, valid at the time of reporting, or via the electronic information system.

*{Item 2.1 of chapter 2 of section XII in wording of the MoH Orders № 538 of 28.03.2022; № 1034 of 07.06.2023}*

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

*{Item 2.2 of chapter 2 of section XII as amended by the MoH Order № 304 of 06.05.2014; in wording of the MoH Order № 1034 of 07.06.2023}*

2.3. The clinical trial sponsor shall report to the Center and principal investigator/investigator all other serious unexpected adverse reactions associated with the investigational medicinal product, which have occurred in the clinical trial approved in Ukraine within 15 calendar days after he becomes aware of them.

*{Item 2.3 of chapter 2 of section XII as amended by the MoH Order № 1034 of 07.06.2023; in wording of the MoH Order № 894 of 24.05.2024}*

2.4. The clinical trial sponsor shall report to all principal investigators/investigators involved in conducting the clinical trial of the given investigational medicinal product and ethics committees concerned (at a trial site where a clinical trial has started) all identified cases of suspected unexpected serious adverse reactions associated with an investigational medicinal product, in the form of a periodic listing, which include information about changes in the safety profile. The periodicity of the listing of suspected unexpected serious adverse reactions provided by the clinical trial sponsor is determined by the specifics of the clinical trial and the amount of suspected unexpected serious adverse reaction reports received by the clinical trial sponsor, but at least every six months and no later than 60 calendar days after the report is prepared.

*{Item 2.4 of chapter 2 of section XII in wording of the MoH Order № 1034 of 07.06.2023; № 894 of 24.05.2024, taking into account changes made by the MoH Order № 1021 of 13.06.2024}*

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

2.6. During long-term clinical trials the clinical trial sponsor shall provide the Center with a written development safety update report about investigational medicinal products in paper and electronic format (to the Center's email address) at least once a year, no later 60 calendar days after the preparation of the report according to the requirements stated in Annex 16 to this Procedure.

*{Paragraph one of item 2.6 of section XII in wording of the MoH Order № 538 of 28.03.2022}*

While writing the report the clinical trial sponsor shall consider the following points: relation of the adverse reaction with the investigational medicinal product's dose, duration of the treatment; the trial subject's condition reversible on discontinuation or suspension of the treatment; evidence of previous investigational medicinal product toxicity in subjects; increase in frequency of the investigational medicinal product toxicity; overdose of the investigational medicinal product and its sequelae, 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); data on positive or negative experiences during pregnancy or lactation; investigational medicinal product abuse (if any); risks which might be associated with the investigation or diagnostic procedures; risks which might be associated with inadequate quality of the investigational medicinal product; safety and efficacy data on the investigational medicinal product obtained during the non-clinical studies.

*{Paragraph two of item 2.6 of chapter 2 of section XII in wording of the MoH Order № 1034 of 07.06.2023}*

In case of the reasoned suspicion on the increased risk for the trial subjects the Center may oblige the clinical trial sponsor to submit a safety report on medicinal products under development more frequently.

*{Item 2.6 of chapter 2 of section XII amended by the MoH Order № 304 of 06.05.2014}*

2.7. In case of conducting more than one clinical trials of the same investigational medicinal product, the clinical trial sponsor shall provide to the Center a single safety report on investigational medicinal product. In a cover letter for the report the clinical trial sponsor shall provide a list of all clinical trials conducted in Ukraine or with Ukraine's participation, which are related to the given report. In this case, the period of formation and submission of the annual report shall start with the date of the clinical trial when the clinical trial sponsor's receives the first authorization to conduct of a clinical trial of the investigational medicinal product concerned in any country worldwide (development international birth date).

*{Item 2.7 of chapter 2 of section XII in wording of the MoH Order № 1034 of 07.06.2023}*

### 3. Recording and analysis of suspected unexpected serious adverse reactions reports by the Center

3.1. The Center shall record all cases of suspected unexpected serious adverse reactions related to all clinical trials conducted in Ukraine that it has become aware of, and conduct their analysis.

*{Item 3.1 of chapter 3 of section XII in wording of the MoH Order № 1034 of 07.06.2023}*

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

*{Paragraph one of item 3.2 of chapter 3 of section XII in wording of the MoH Order № 1034 of 07.06.2023}*

If during this period the clinical trial sponsor does not provide such information or a letter with reasoned time frame for their preparation, the Center may make a decision on temporary suspension or full stoppage of the clinical trial concerned, informing the clinical trial 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 clinical trial 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 opinion are no longer met or has information raising doubts about safety of the trial 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 experts 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 clinical trial sponsor and investigators.

13.5. If applicable, other experts (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) shall be present at the clinical trial site. Also present may be the clinical trial sponsor's representatives.

13.8. During the clinical audit critical, major or minor remarks may be made.

13.8.1. The critical remarks refer to the detected shortcomings/violations affecting trial 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 major 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 made and grounds for suspension or full stoppage of the clinical trial in writing.

13.8.2. The major remarks refer to the detected shortcomings which may affect the trial subjects' rights, safety and health, and/or may affect the integrity of the clinical trial data. Major shortcomings include deviations from the clinical trial protocol and/or numerous minor remarks. Major shortcomings require their timely correction within the timelines established based on the clinical audit's results with the notification on their elimination (in writing) submitted to the Center.

13.8.3. The minor remarks refer to the detected shortcomings which do not affect the trial subjects' rights, safety and health and/or cannot affect quality and integrity of the clinical trial data and which shall 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 detected during the clinical trial audit, which do not require suspension or full stoppage of the clinical trial, the principal investigator/investigator and/or the clinical trial 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 detected shortcomings aren't eliminated (except for those for the valid reasons and force majeure) within the specified timelines 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 clinical trial sponsor, the principal investigator/investigator or the Center.

14.2. The clinical trial 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 clinical trial 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 clinical trial sponsor shall provide instructions on further administration of the investigational medicinal product to the patients. The clinical trial 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 clinical trial sponsor may resume the clinical trial after the elimination of causes 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 trial subjects' health or life increases, and officially inform the clinical trial 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 opinion are no longer met or there is information raising doubts about the trial subjects' safety or scientific validity of the clinical trial, or data pointing out the adulteration. The Center shall notify the clinical trial 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 causes for the temporary suspension and the notification of the ethics committee and the Center so that they make the appropriate decision.

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

*{Procedure in wording of MoH Order № 523  
of 12.07.2012}*

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