EURASIAN ECONOMIC COMMISSION
COUNCIL

RESOLUTION

3 November 2016 **No.79** Astana

On Approval of the Guideline for Good Clinical Practice of the Eurasian Economic Union

In accordance with Article 30 of the Treaty on the Eurasian Economic Union of 29 May 2014, Article 6 of the Agreement on the Unified Principles and Rules of Medicines Circulation within the Eurasian Economic Union of 23 December 2014, clause 83 of Annex No.1 to the Rules of Procedure of the Eurasian Economic Union approved by Resolution of the Supreme Eurasian Economic Council of 23 December 2014 No.98, and Resolution of the Supreme Eurasian Economic Council of 23 December 2014 No.108 on Implementation of the Agreement on the Unified Principles and Rules of Medicines Circulation within the Eurasian Economic Union, the Eurasian Economic Commission Council **resolved:**

1. To approve the attached Guideline for Good Clinical Practice of the Eurasian Economic Union.

2. This Resolution shall become effective upon expiration of a period of 10 calendar days after the effective date of the Protocol signed on 2 December 2015 of Accession of the Republic of Armenia to the Agreement on the Unified Principles and Rules of Medicines Circulation within the Eurasian Economic Union of 23 December 2014 but at least 10 calendar days of the date of official publication of this Resolution.

Members of the Eurasian Economic Commission Council:

For the Republic of Armenia	For the Republic of Belarus	For the Republic of Kazakhstan	For the Kyrgyz Republic	For the Russian Federation
V. Gabrielyan	**V. Matyushevsky**	**A. Mamin**	**O. Pankratov**	**I. Shuvalov**
Seal: EURASIAN ECONOMIC COMMISSION FOR DOCUMENTS	Seal: EURASIAN ECONOMIC COMMISSION FOR DOCUMENTS	Seal: EURASIAN ECONOMIC COMMISSION FOR DOCUMENTS	Seal: EURASIAN ECONOMIC COMMISSION FOR DOCUMENTS	Seal: EURASIAN ECONOMIC COMMISSION FOR DOCUMENTS

APPROVED

by Resolution of the
Eurasian Economic
Commission Council
of 3 November 2016 No.79

GUIDELINE
FOR GOOD CLINICAL PRACTICE

I. General Provisions

This Guideline is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

Compliance with this Guideline provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki adopted by the 18th World Medical Association General Assembly in 1964, and that the clinical trial data are credible.

The purpose of this Guideline is to establish a unified procedure for conducting clinical trials/studies (hereinafter "trials") of medicines to promote the common market of medicines within the Eurasian Economic Union (hereinafter the "Union"), mutual recognition of clinical trial/study data by regulatory authorities of member states of the Union (hereinafter "member states") and recognition of clinical trials/studies conducted in and outside the Union.

The numbering used in Section II of this Guideline corresponds to that used in the international version of Good Clinical Practice (GCP), for all subsections, except for subsection 1, in which the terms are listed in alphabetical order.

This Guideline is prepared based on ICH GCP (Guideline for Good

Clinical Practice), which is an E6 (R1) document, version 4, of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities of the member states.

The principles established in this Guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

This Guideline shall be revised on a regular basis, considering the experience of its application in the member states and in case of any change in the international standards for conducting clinical trials (*mutatis mutandis*).

II. Main Part

1. Definitions

For the purposes of this Guideline, the following terms shall have the following meanings:

Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Well-being (of the trial subjects)

The physical and mental integrity of the subjects participating in a clinical trial.

Investigator's Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Study Design

A general plan of the study, description of the methodology used, depending on the selection and formation of groups of trial subjects, blinding.

Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Nonclinical Study

Biomedical studies not performed on human subjects.

Audit Trail

Documentation that allows reconstruction of the course of events.

Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Opinion (in relation to Independent Ethics Committee)

A written document containing a judgement and/or advice provided by an Independent Ethics Committee in respect of participation of human subject in the trial.

Legally Acceptable Representative

An individual or juridical or other body authorised under the laws of the member state whose trial sites are involved in the trial to give an informed consent, on behalf of a prospective subject who is disabled or a minor.

Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, quality assurance agreements and any other

resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Informed Consent

A process by which a subject freely and voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate, and in case of minor and disabled subjects, an approval or consent of their legally accepted representatives to their participation in the trial. Informed consent is documented by means of a written, signed and dated informed consent form.

Investigator

A natural person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at all centres participating in a multicentre trial.

Investigator/Institution

The investigator and/or institution, as applicable.

Trial Site

The location(s) where trial-related activities are actually conducted.

Investigational Medicinal Product

A medicinal product or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation (when used or assembled in a way different from the approved form, or when used for an

unapproved indication, or when used to gain further information about an approved use).

Clinical Trial/Study

A clinical investigation that meets at least one of the following conditions:

a therapeutic strategy (intervention) is administered to the trial subject in advance and is not routine clinical practice in the member state, whose trial sites participate in the trial;

a decision on administering the investigational medicinal product is made simultaneously with a decision on inclusion of the subject in the clinical study;

alongside the routine clinical practice, additional diagnostics and monitoring procedures are performed for trial subjects.

Contract Research Organisation (CRO)

A natural person or an organisation (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Coordinating Committee

A committee that a sponsor may organise to coordinate the conduct of a multicentre trial.

Confidentiality

Prevention of disclosure, to other than authorised individuals, of a sponsor's proprietary information or of a subject's identity.

Multicentre Trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

Monitor

A natural person appointed by the sponsor's or Contract Research Organisation who works jointly with the Coordinating Investigator or Coordinating Committee and controls the conduct of the clinical trial in accordance with the protocol, assesses the degree of its completion and assists the investigator in analysing, interpreting and extrapolating data.

Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Good Clinical Practice (GCP)

A set of ethical and scientific requirements for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Adverse Drug Reaction (ADR)

An unintended adverse response related to the use of a medicine (investigational product) meaning that a causal relationship between the medicine (investigational product) and the adverse reaction is at least a reasonable possibility.

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event

(AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and/or the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), established in accordance with the laws of the member state and constituted of medical professionals and non-medical members entitled to provide opinions for the purpose of implementation of this Guideline (taking into account views of non-professionals, especially patients and patient organisations) and ensuring the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with this Guideline.

Impartial Witness

A natural person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information or the Investigator's Brochure (for an unapproved investigational product).

Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented, and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Approval (in relation to Institutional Review Boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution's internal regulations, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Institution (medical)

A healthcare institution (organisation), regardless of its organisational legal form, where a clinical trial is conducted, which has a permit (licence) to perform medical activities and is authorised to conduct clinical trials.

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

Monitoring Report

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

Audit Report

A written evaluation by the sponsor's auditor of the results of the audit.

Clinical Trial/Study Report

A written description of a trial/study provided in the format allowing for an easy search, made in the form of Annex No.1 to this Guideline and section 5 of part 1 of Annex No.1 to the Guideline for Registration and Expert Examination of Medicines for Medical Use approved by the Eurasian Economic Commission, when submitting a registration application.

Original Medical Record (Source Documents)

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Protocol Amendment

A written description of changes, a notice of changes made to or formal clarification of a protocol.

Comparator (Product)

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

Applicable Regulatory Requirement(s)

Regulations constituting the legislation of the Union and laws of member states in the field of medicines circulation addressing the conduct of clinical trials of investigational products.

Interim Clinical Trial/Study Report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. For the purposes of this Guideline, the term protocol refers to all further versions of the clinical trial protocol and protocol amendments.

Direct Access

Permission issued by the trial site management to interested parties to examine, analyse, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor’s proprietary information.

Randomisation

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Routine Clinical Practice

Standard (same-type) medical diagnostic and treatment procedures, technologies and measures to be conducted, used and taken in respect of a particular group of patients and a particular standard of medical aid.

Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place.

Serious Adverse Event (SAE, Serious Adverse Drug Reaction, Serious ADR)

Any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, requires medical intervention for preventing development of the above conditions.

Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

Subinvestigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

Sponsor

An individual or an organisation responsible for the initiation, management, and/or financing of a clinical trial.

Sponsor-Investigator

A person who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual. The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Standard Operating Procedures (SOPs)

Detailed written instructions aimed to achieve uniformity of the performance of a specific function.

Subject/Trial Subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

Regulatory Authorities

Bodies having the power to regulate. For the purposes of this Guideline, Regulatory Authorities include the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

Vulnerable Subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior

members of a hierarchy in case of refusal to participate. Examples are medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention as well as patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, persons under guardianship and custody and those incapable of giving consent.

Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing, approving (issuing an opinion), and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects. This terms applies to clinical trials conducted in countries that do not have independent ethics committees.

2. THE PRINCIPLES OF GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki adopted by the 18th World Medical Association General Assembly in 1964, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems and operating procedures that assure the quality of every aspect of the trial should be implemented.

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 Responsibilities

3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2 The IRB/IEC should obtain the following documents:

trial protocol(s)/amendment(s),

written informed consent form(s) and consent form updates that the investigator proposes for use in the trial,

subject recruitment procedures (e.g. advertisements),

written information to be provided to subjects,

Investigator's Brochure (IB),

available safety information,

information about payments and compensation available to subjects,

the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and

any other documents that the IRB/IEC may need to fulfil its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

- approval/favourable opinion;
- modifications required prior to its approval/favourable opinion;
- disapproval / negative opinion; and
- termination/suspension of any prior approval/favourable opinion.

3.1.3 The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

3.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5 The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgement of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects.

3.1.6 When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7 Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e. in emergency situations).

3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other

written information to be provided to subjects. The way payment will be prorated should be specified.

3.2 Composition, Functions and Operations

3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

At least five members.

At least one member whose primary area of interest is in a non-scientific area.

At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter. A list of IRB/IEC members and their qualifications should be maintained.

3.2.2 The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5 The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6 An IRB/IEC may invite non-members with expertise in special areas for assistance.

3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2 Scheduling, notifying its members of, and conducting its meetings.

3.3.3 Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review, as appropriate.

3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC.

3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial.

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).

Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2).

All adverse drug reactions (ADRs) that are both serious and unexpected.

New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

Its trial-related decisions/opinions.

The reasons for its decisions/opinions.

Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies). The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Obligations

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol,

in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with this Guideline and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities (premises, equipment) for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician, who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided

to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the

regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.5.2 The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

to the IRB/IEC for review and approval/favourable opinion,

to the sponsor for agreement, and

if required, to the regulatory authority(ies).

4.6 Investigational Product(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided in the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomisation Procedures and Unblinding

The investigator should follow the trial's randomisation procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Subjects

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to this Guideline and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised/corrected whenever important new information becomes available that may be relevant to the subject's consent. Any revised/corrected written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent

aspects of the trial including the written information and the approval/ favourable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative,

and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

That the trial involves research.

The purpose of the trial.

The trial treatment(s) and the probability for random assignment to each treatment.

The trial procedures to be followed, including all invasive procedures.

The subject's responsibilities.

Those aspects of the trial that are experimental.

The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

The compensation and/or treatment available to the subject in the event of trial-related injury.

The anticipated payment, if any, to the subject for participating in the trial.

The anticipated expenses, if any, of the subject for participating in the trial.

That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the laws of the member states and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorising such access.

That records identifying the subject will be kept confidential and, to the extent permitted by the laws of the member states, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

The expected duration of the subject's participation in the trial.

The approximate number of subjects to be involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.

The foreseeable risks to the subjects are low.

The negative impact on the subject's well-being is minimised and low.

The trial is not prohibited by law.

The approval/favourable opinion of the IRB/IEC on the inclusion of such subjects covering this aspect is expressly sought.

Such trials, unless an exception is justified, should be conducted in patients having a disease, for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available,

enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9 Records and Reports

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, that are derived from source documents, should be consistent with the source documents, or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialled, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents in accordance with subsection 8 of this Guideline and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1 The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects

by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) and requirements set forth in Annex 11 to this Guideline related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

5. SPONSOR

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, this Guideline, and the applicable regulatory requirement(s).

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.48) to all trial related sites, source data/documents, and reports for the purposes of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2 Contract Research Organisation (CRO)

5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

5.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

5.3 Medical Expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4 Trial Design

5.4.1 The sponsor should utilise qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analysing and preparing interim and final clinical trial reports.

5.4.2 The sponsor should take into account the requirements of subsection 6 of this section and Annex 11 to this Guideline.

5.5 Trial Management, Data Handling, and Record Keeping

5.5.1 The sponsor should utilise appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).

Maintain SOPs for using these systems.

Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail).

Maintain a security system that prevents unauthorised access to the data.

Maintain a list of the individuals who are authorised to make data changes (see 4.1.5 and 4.9.3).

Maintain adequate backup of the data.

Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

5.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5 The sponsor should use an unambiguous subject identification code (in accordance with clause 1.11 of this Guideline) that allows identification of all the data reported for each subject.

5.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial (see subsection 8 of this section).

5.5.7 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8 If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

5.5.10 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11 The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the

investigator(s)/institution(s) in writing when the trial related records are no longer needed.

5.6 Investigator Selection

5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organisation of a coordinating committee and/or selection of coordinating investigator(s) are to be utilised in multicentre trials, their organisation and/or selection are the sponsor's responsibility.

5.6.2 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3 The sponsor should obtain the investigator's/institution's agreement:

to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC (see 4.5.1);

to comply with procedures for data recording/reporting;

to conduct monitoring, auditing and inspection (see 4.1.4), and

to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12).

The sponsor and the investigator/institution should sign a document to confirm this agreement.

5.7 Allocation of Responsibilities

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

5.8 Compensation to Subjects and Investigators

5.8.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3 When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9 Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.10 Notification/Submission to Regulatory Authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

The sponsor should notify the regulatory authority of the commencement of clinical trials in the manner established in the laws of the member state.

5.11 Confirmation of Review by IRB/IEC

5.11.1 The sponsor should obtain from the investigator/institution:

The name and address of the investigator's/institution's IRB/IEC.

A statement obtained from the IRB/IEC that it is organised and operates according to this Guideline and the laws of the relevant member state.

Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2 If the IRB/IEC conditions its approval/favourable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favourable opinion was given by the IRB/IEC.

5.11.3 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of approval/favourable opinion.

5.12 Information on Investigational Product(s)

5.12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2 The sponsor should update the Investigator's Brochure as significant new information becomes available (see subsection 7 of this section).

5.13 Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)

5.13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterised as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14 Supplying and Handling Investigational Product(s)

5.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favourable opinion from IRB/IEC and regulatory authority(ies)).

5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorised by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4 The sponsor should:

Ensure timely delivery of investigational product(s) to the investigator(s).

Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see subsection 8 of this section).

Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).

Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

5.14.5 The sponsor should:

Take steps to ensure that the investigational product(s) are stable over the period of use.

Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15 Record Access

5.15.1 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2 The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16 Safety Information

5.16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

5.17 Adverse Drug Reaction Reporting

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2 Such expedited reports should comply with the applicable regulatory requirement(s) and Annex 11 to this Guideline.

5.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s) and Annex 11 to this Guideline.

5.18 Monitoring

5.18.1 Purpose

The purposes of trial monitoring are to verify that:

The rights and well-being of human subjects are protected.

The reported trial data are accurate, complete, and verifiable from source documents.

The conduct of the trial is in compliance with the currently approved protocol/amendment(s), this Guideline, and applicable regulatory requirement(s).

5.18.2 Selection and Qualifications of Monitors

Monitors should be appointed by the sponsor.

Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, this Guideline, and the applicable regulatory requirement(s).

5.18.3 Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general, there is a need for on-site monitoring, before, during, and after the trial; however in

exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with this Guideline. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

5.18.4 Monitor's Responsibilities

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

(a) Acting as the main line of communication between the sponsor and the investigator.

(b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

(c) Verifying, for the investigational product(s):

That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

(d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

(e) Verifying that written informed consent was obtained before each subject's participation in the trial.

(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

(h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorised individuals.

(i) Verifying that the investigator is enrolling only eligible subjects.

(j) Reporting the subject recruitment rate.

(k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(m) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:

The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.

Any dose and/or therapy modifications are well documented for each of the trial subjects.

Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorised to initial CRF changes for the investigator. This authorisation should be documented.

(o) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by this Guideline, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(p) Determining whether the investigator is maintaining the essential documents (see subsection 8 of this section).

(q) Communicating deviations from the protocol, SOPs, this Guideline, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5 Monitoring Procedures

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6 Monitor's Report

The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance with the requirements of the protocol, this Guideline and regulatory authorities.

The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

5.19 Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, this Guideline, and the applicable regulatory requirements.

5.19.2 Selection and Qualification of Auditors

The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3 Auditing Procedures

The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

The observations and findings of the auditor(s) should be documented.

To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious non-compliance with this Guideline exists, or in the course of legal proceedings.

When required by applicable law of the member state, the sponsor should provide an audit certificate.

5.20 Noncompliance

5.20.1 Noncompliance with the protocol, SOPs, this Guideline, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the

trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21 Premature Termination or Suspension of a Trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

5.22 Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) (in accordance with applicable requirements in the form of Annex 1 to this Guideline). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of Annex 1 to the Guideline for Registration and Expert Examination of Medicines for Medical Use approved by the Eurasian Economic Commission.

5.23 Multicentre Trials

For multicentre trials, the sponsor should ensure that:

5.23.1 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favourable opinion by the IRB/IEC.

5.23.2 The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

5.23.3 The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4 All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

5.23.5 Communication between investigators is facilitated.

6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1 General Information

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorised to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2 Background Information

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with the protocol, this Guideline and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

6.4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

6.4.3 A description of the measures taken to minimise/avoid bias, including:

Randomisation.

Blinding.

6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8 Maintenance of trial treatment randomisation codes and procedures for breaking codes.

6.4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

6.5 Selection and Withdrawal of Subjects

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/ investigational product treatment.

(b) The type and timing of the data to be collected for withdrawn subjects.

(c) Whether and how subjects are to be replaced.

(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6 Treatment of Subjects

6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7 Assessment of Efficacy

6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

6.8 Assessment of Safety

6.8.1 Specification of safety parameters.

6.8.2 The methods and timing for assessing, recording, and analysing safety parameters.

6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4 The type and duration of the follow-up of subjects after adverse events.

6.9 Statistics

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be

specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

6.9.7 The selection of subjects to be included in the analyses (e.g. all randomised subjects, all dosed subjects, all eligible subjects, evaluable subjects).

6.10 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

6.11 Quality Control and Quality Assurance

6.12 Ethics

Description of ethical considerations relating to the trial.

6.13 Data Handling and Record Keeping

6.14 Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

6.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

6.16 Supplements

7. INVESTIGATOR'S BROCHURE

7.1 Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This Guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's

written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs.

In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2 General Considerations

The IB should include:

7.2.1 Title Page

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided.

7.2.2 Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

7.3 Contents of the Investigator's Brochure

The IB should contain the following sections, each with literature references where appropriate:

7.3.1 Table of Contents

7.3.2 Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3 Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4 Physical, Chemical, and Pharmaceutical Properties and Formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5 Nonclinical Studies

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

Species tested

Number and sex of animals in each group

Unit dose (e.g., milligram/kilogram (mg/kg))

Dose interval

Route of administration

Duration of dosing

Information on systemic distribution

Duration of post-exposure follow-up

Results, including the following aspects:

Nature and frequency of pharmacological or toxic effects

Severity or intensity of pharmacological or toxic effects

Time to onset of effects

Reversibility of effects

Duration of effects

Dose response.

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation. The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

Single dose

Repeated dose

Carcinogenicity

Special studies (e.g. irritancy and sensitisation)

Reproductive toxicity

Genotoxicity (mutagenicity)

7.3.6 Effects in Humans

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).

Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.

Population subgroups (e.g., gender, age, and impaired organ function).

Interactions (e.g., product-product interactions and effects of food).

Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

(b) Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7 Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

7. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

7.1 Introduction

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in

a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated:

1) before the clinical phase of the trial commences (see 8.2),

2) during the clinical conduct of the trial (see 8.3), and

3) after completion or termination of the trial (see 8.4).

In clauses of subsection 8 of this section below, a description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this Guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.2.1	INVESTIGATOR'S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	CLINICAL TRIAL PLANNING DOCUMENTS: SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	INFORMATION GIVEN TO TRIAL SUBJECT - INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent	X	X
	- ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X

	- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
8.2.5	INSURANCE STATEMENT (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.: - investigator/institution and sponsor - investigator/institution and CRO - sponsor and CRO - investigator/institution and authority(ies) (where required)	To document rights, obligations and relations between the parties	X X X	X X (where required) X X
8.2.7	DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: - protocol and any amendments - CRF (if applicable) - informed consent form(s)	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X	X

	- any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - subject compensation (if any) - any other documents given approval/ favourable opinion			
8.2.8	INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION	To document that the IRB/IEC is constituted in agreement with this Guideline	X	X (where required)
8.2.9	REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL (where required)	To document appropriate authorisation/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
8.2.10	CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S)	To document normal values and/or ranges of the tests	X	X

	INCLUDED IN THE PROTOCOL			
8.2.12	MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
8.2.13	SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
8.2.14	INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
8.2.15	SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
8.2.16	CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED	To document identity, purity, and strength of investigational product(s) to be used in the trial		X

8.2.17	DECODING PROCEDURES FOR BLINDED TRIALS	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
8.2.18	MASTER RANDOMISATION LIST	To document method for randomisation of trial population		X (third party if applicable)
8.2.19	PRE-TRIAL MONITORING REPORT	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	TRIAL INITIATION MONITORING REPORT	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X
8.2.21	SPONSOR'S NOTICE OF THE COMMENCEMENT OF THE CLINICAL TRIAL GIVEN TO THE REGULATORY AUTHORITY	To document the fact of commencement of the clinical trial	X	

8.3 During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.1	INVESTIGATOR'S BROCHURE UPDATES	To document that investigator/institution is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2	ANY REVISION TO: - protocol/amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	X
8.3.3	DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).	X	X

	- protocol amendment(s) - revision(s) of: - informed consent form - any other written information to be provided to the subject - advertisement for subject recruitment (if used) - any other documents given approval/favourable opinion - continuing review of trial (where required)			
8.3.4	REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR: - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)	(see 8.2.10)	X	X
8.3.6	UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X

8.3.7	UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8	DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT	(see 8.2.15.)	X	X
8.3.9	CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS	(see 8.2.16)		X
8.3.10	MONITORS' VISIT REPORTS	To document site visits by, and findings of, the monitor		X
8.3.11	RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
8.3.12	SIGNED FORMS OF PATIENT'S	To document that consent is obtained in	X	

	INFORMED CONSENT (INFORMATION SHEET)	accordance with this Guideline and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)		
8.3.13	SOURCE DOCUMENTS	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
8.3.14	SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15	DOCUMENTATION OF CRF CORRECTIONS	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16	NOTIFICATION BY INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS	Notification by investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X
8.3.17	NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR/INSTITUTION, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES)	Notification by sponsor and/or investigator/institution, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and	X (where required)	X

	AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION	4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2		
8.3.18	NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)
8.3.20	SUBJECT SCREENING LOG	To document identification of subjects who entered pre-trial screening	X	X (where required)
8.3.21	SUBJECT IDENTIFICATION CODE LIST	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
8.3.22	SUBJECT ENROLMENT LOG	To document chronological enrolment of subjects by trial number	X	
8.3.23	INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE	To document that investigational product(s) have been used according to the protocol	X	X

8.3.24	SIGNATURE SHEET	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X
8.3.25	RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)	To document location and identification of retained samples if assays need to be repeated	X	X

8.4 After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.4.1	INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site/institution, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	DOCUMENTATION OF INVESTIGATIONAL PRODUCT	To document destruction of unused investigational products by sponsor or at	X (if destroyed	X

	DESTRUCTION	site/institution	at site)	
8.4.3	COMPLETED SUBJECT IDENTIFICATION CODE LIST	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	AUDIT CERTIFICATE (if available)	To document that audit was performed		X
8.4.5	FINAL TRIAL CLOSE-OUT MONITOR'S REPORT	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4.6	TREATMENT ALLOCATION AND DECODING DOCUMENTATION	Returned to sponsor to document any decoding that may have occurred		X
8.4.7	FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)	To document completion of the trial	X	
8.4.8	CLINICAL STUDY REPORT	To document results and interpretation of trial	X (if applicable)	X

Seal:

EURASIAN ECONOMIC COMMISSION
FOR DOCUMENTS

APPENDIX №1

to Good Clinical Practice Regulations
of the Eurasian Economic Union

REQUIREMENTS
to a clinical study report structure and content

I. General provisions

This document is developed with regard to the requirements of the ICH Harmonised Tripartite Guideline «Structure and Content of Clinical Study Reports (E3)» (version 4, 1995).

The requirements to the clinical study report (hereinafter- the report) structure and content set forth herein are general and applicable for description of the results of any treatment medication, preventive drug and diagnostic medicinal product clinical trial performed with patients (healthy volunteers). A clinical and statistical description of the trial results, representation and analysis of data received in the course of the trial is made in the form of a single report containing tables and pictures in the main text of the report or in the end of the report text. Supplements to such a report shall include:

a protocol;

case report forms samples;

information associated with investigators;

information associated with an investigational medicinal product (study drug) including comparator products (control drugs);

technical statistical documentation;

appropriate publications;

patients data lists;

such technical statistical data as conclusions, interim calculations, analysis and resolutions made on the computed data basis;

etc.

Though this document mainly refers to efficacy and safety study, the basic principles of the report representation and its structure may be used to prepare reports on different types of trials (for example, clinical pharmacology trails). Depending on such trials specifics and significance a less detailed report may be made.

This document is purposed to assist sponsors in representation of a report which will be full, void of ambiguity, well formed and simple for later study and assessment. The report shall give a clear explanation of the basis for study design critical singularities selection, information about a trial plan, method and procedure, so that there is no ambiguity in the trial process. The report and its appendixes shall also contain a sufficient amount of individual patient data, including demographical and source data, so that, if required, regulatory authorities (expert organization) of the Eurasian Economic Union member–state (hereinafter – member-state) will be able to reproduce the main types of analysis. It is also important to indicate clearly in the text and in the appendixes the particular groups of patients having passed relevant analysis, for which charts and diagrams were made.

Depending on the member-state regulatory authority policy in the field of the non-controlled and other studies aiming at efficiency (except for the controlled studies aiming at safety), to some extent inadequate or terminated trials or studies, which goals are not connected with the evidences claimed, it is allowed to present brief reports based on gross data or without some sections included. But in such cases it is necessary to present a full description of all aspects of safety. If a brief report is presented, it shall

contain sufficient information about the trial design and results so that the regulatory authority will be able to decide upon a full report submission necessity. If reports presentation necessity arises, one shall contact the regulatory authority.

With a detailed description of the trial procedure it is allowed to repeat the trial description from the protocol draft. In some cases if it refers to the method standard procedure, it is allowed to present the trial method more briefly in the form of a separate section. In each section describing the trail plan and procedure it is necessary to indicate the trial findings which are not sufficiently described in the protocol, to analyze how the trial differed from the protocol, and to discuss statistical methods and analysis used for substantiation of these deviations from the trial procedure planned by the protocol.

A separate clinical trial full report shall include a detailed description of individual adverse events or laboratory deviations, but this data shall be re-studied during general safety analysis upon all current reports of the drug registration dossier.

The report shall contain demographical and other potentially significant characteristics of the population under study, and if it is quite a large scale trial, data on the demographical parameters (for example, age, gender, race, body weight) and other indexes of the subgroup (for example, renal or hepatic functions) shall be presented, so that possible difference in efficacy or safety could be found. But a patient subgroup reaction shall be studied within the aggregated database used in the general statistical analysis.

A data list inquired within a report (usually as a report supplement) means the data required for confirmation of the basic (critical) types of the statistical analysis. The data lists which are a part of the report shall be of a readily usable form for a reviewer performing the report expert evaluation.

Thus, it is necessary to include as much variables as possible in order to limit information volume, but that shall not cause the submitted data clearness (understandability) decline. One shall prevent data excess combining with over-usage of symbols and well-understandable abbreviations (common professional abbreviations) or causing images displaying on a scale too small for perception, etc. In this case it is better to make several data lists.

Data shall be presented in the report with different detail levels:

numeric data and general tables representing demographical parameters most significant for this trial, efficacy and safety parameters may be put into the text for important issues illustration;

all other aggregated parameters, tables and lists of the demographical data, efficacy and safety indexes shall be given in section 14 of the report (according to sections system of headings given in part II hereof);

individual patient data by separate subgroups shall be presented in the form of data lists in supplement 16.2 to the report (according to sections system of headings given in part II hereof);

all individual patient data shall be given in supplement 16.4 to the report (according to sections system of headings given in part II hereof).

In any table, data list or diagram estimated (theoretical) figures and derived indexes, if applicable, shall be single-valued and clearly identified. At the same time there shall be a detailed explanation of how these values were rated or this data was received and what main suppositions were made.

Below guidelines are maximally detailed and purposed for reminding an applicant about the maximal volume of information which shall be given by an applicant in the report so that after information submission any additional data inquiries will be minimized. Nevertheless, in each individual case the requirements to the data presentation and (or) analysis may depend on a particular situation, may change in the course of time, differ depending

on the investigational medicinal product class, differ in different regions, and cannot be described in the form of general requirements in this document. That is why during reports preparation it is necessary to use special (particular) clinical practice guidelines of the regulatory authorities in the field of drugs circulation and, when possible, to discuss submission of data and analysis with the regulatory authority. In some member-states regulatory authorities one may receive detailed consultations and statistical methods guidelines.

Each report shall contain all below sections described (except for the cases when these sections are not required), at the same time to keep logic of a particular trial it is allowed to change sequence or grouping of the report sections. Indication of particular information in supplements to the report is the requirement of some of the regulatory authorities, and these supplements shall be submitted when required. In all above cases it is necessary to amend the report sections numbering appropriately.

Some requirements of this document referring to large-scale trials may appear difficult to fulfill or impractical. During planning and presentation of large-scale trials results it is necessary to consult the regulatory authority and discuss the report format.

This document provisions shall be taken into consideration together with the requirements of other documents regulating clinical trials procedure and their results presentation.

II. Requirements to the report structure and content

1. Title page

A title page of the report shall contain the following information:

a report name and the investigational medicinal product name, indications for use under which the trial was performed;

if not indicated in the name – a brief description of the design (parallel, cross-over, blinding, randomized), type of comparison (placebo control, active control, dose-effect control), the trial duration, the investigational medicinal product dosing and trial subjects cohort;

sponsor name;

protocol identification (a code or number);

trial phase;

a trial commencement date (a date of the first patient joining the trial or other date of initiation), a trial or its stage completion date (the last patient treatment completion date), the date of a trial completion ahead of time (if any);

surnames and positions at primary place of employment of the chief investigator (s) or coordinating investigator (s) or the sponsor's authorized representative;

information about the authorized person signed the trial report on behalf of the sponsor (a surname of the company (sponsor) representative signed the report and responsible for this report). Besides, on the title page or in the accompanying letter it is necessary to indicate surnames, telephone and fax numbers of the contacting persons of the company-sponsor responsible for receiving questions concerning the report;

indication that the trial including the trial essential documents archiving is performed in compliance with the good clinical practice regulations approved by the Eurasian Economic Commission (hereinafter – the regulations);

the report date (besides, it is necessary to indicate the name and dates of previous reports prepared within this trial procedure).

2. Synopsis (a brief description of the clinical trial)

It is necessary to present synopsis (usually about 3 pages) generalizing information about the trial (according to Appendix №2 to the Regulations). To show results, the synopsis shall include numerical data but not only the text and p-values.

3. Report content

The report content shall contain pages numbers or other indication to each section position in the text, including aggregated tables, pictures and diagrams; the list and location of supplements, tables and presented case report forms (hereinafter - CRF).

4. List of abbreviations and terms definition

The report shall contain a list of abbreviations and definitions of the special or unusual terms, as well as units of measurement applicable in the report. When mentioned first in the text the abbreviated terms shall be provided in full and their abbreviation shall be placed in brackets.

5. Ethics issues

5.1. Institutional Review Board (Independent Ethics Committee).

There shall be a confirmation that the trial protocol and any amendments hereof were reviewed by the Institutional Review Board (Independent Ethics Committee) (hereinafter – IRB (IEC)). A list of all IRB (IEC) which were addressed to shall be provided in supplement 16.1.3 to the report (according to sections system of headings mentioned in this part of the document), as well as a surname, name and patronymic (if available) of IRB (IEC) Chairman if that is required by the regulatory authority.

5.2. Clinical trial application in accordance with the ethical principles.

It is necessary to provide confirmation that the trial was performed in accordance with the ethical principles of Declaration of Helsinki adopted by the XVIIth session of the World Health Assembly in 1964.

5.3. Informed consent.

There shall be described when the informed consent of the patients selected for trial was received (for example, during selection for the trial, preliminary screening). In supplement 16.1.3 (according to sections system of headings mentioned in this part of the document) to the report a sample of the written information for patients and a sample of the patient's consent shall be attached to the report.

6. Investigators and the trial administrative structure

The trial administrative structure (for example, chief investigator, coordinating investigator, managing committee, administration, data monitoring and evaluation committees, engaged subdivisions, statistic specialists, central laboratory, contract research organization (hereinafter – CRO), deliveries management within clinical trials) shall be briefly described in this section of the report.

In supplement 16.1.4 to the report (according to sections system of headings mentioned in this part of the document) there shall be provided a list of investigators and their organizations, their role (duties) in the trial, information about investigators' qualification (CV or equivalent document). Besides, in supplement 16.1.4 to the report (according to sections system of headings mentioned in this part of the document) it is necessary to provide a similar list of other persons whose participation makes significant influence on the trail procedure. For large-scale trials with participation of a large number of investigators the above requirements may be reduced to general information about qualification of the persons carried out the trial, with

indication of each investigator and other participants name, scholastic degree, place of employment and role.

The list shall include the following information:

investigators;

any other person engaged in monitoring over primary or other efficacy parameters (for example, study nurse, physician's assistant, clinical psychologist, clinical pharmacologist or staff physician). It is not necessary to include in this list a person engaged in episodic duties fulfillment within the trial (for example, a physician called for due to the drug administration possible adverse reaction or who substituted somebody of the above persons);

the report author (s), including responsible biostatistics.

If the regulatory authorities require samples of the chief investigator's or coordinating investigator's signatures, their signatures shall be included in supplement 16.1.5 to the report (according to sections system of headings mentioned in this part of the document, in accordance with Appendix №3 to the Regulations form). If signatures samples are not required, supplement 16.1.5 to the report (according to sections system of headings given in part II hereof) shall provide the trial sponsor's responsible specialist signature sample.

7. Introductory

Introductory shall contain a brief description (as a rule, not more than 1 page) of the trial within the context of the investigational medicinal product development, discussion of the critical singularities of the trial (for example, substantiation and purposes, target group, treatment, duration, primary endpoints).

It is necessary to specify all documents on basis of which the protocol was elaborated and other significant contracts or agreements between the sponsor (company) and the regulatory authorities.

8. Trial goal and tasks

This section shall specify information providing the trial general goals and tasks.

9. Clinical investigation plan

9.1. General design and clinical investigation description plan.

General clinical investigation plan and trial design (configuration) (for example, parallel, cross-over) shall be described briefly but clearly using charts and diagrams (if required). If in other trials a similar protocol is used, it is useful to give a reference to such protocol and to describe any significant difference from it. Current edition of the protocol and any amendments shall be included as supplement 16.1.1 to the report (according to sections system of headings mentioned in this part of the document), and CRF sample (only unique pages; i.e. without identical pages of the form referring to different visits) in the form of supplement 16.1.2 to the report (according to sections system of headings mentioned in this part of the document). If any information in the section of the report is taken from other sources (besides protocol) they shall be mentioned.

The submitted information shall include:

studied methods of treatment (particular medicinal products, doses and procedures);

investigational population of patients and amount of patients who shall be included in the trial;

degree and method of blinding (masking) (for example, open, double blind, single blind, analytical blinding and non-blinding of patients and (or) investigators);

type of control (for example, placebo, treatment-free, active control, dose-effect control, historical (nonconcurrent) control) and the trial configuration (parallel, cross-over);

method of subjects distribution among investigational groups (randomization, stratification);

sequence and duration of all period of the trial, including the period preceding randomization, and the follow-up period, the treatment free follow up and the period of single blind and double blind treatment. It shall be indicated when the patients were randomized. It is recommended to indicate design in the form of a graphical diagram including history of the evaluations made (in accordance with the graphical diagrams forms of Appendix №4 to the Regulations);

any safety, data monitoring committees or special managing or review teams;

any interim statistical analysis and reviews.

9.2. Substantiation of the trial design, including control groups selection.

It is necessary to substantiate a type of the selected control and trial design. Some aspects of the trial design subject to review are given below.

Generally there are the following competitive control groups (comparator groups):

placebo control;

treatment-free control;

active control;

dose-ranging;

historical control.

In addition to the control type description, another key features of the design are usage of cross-over configuration (diagram) and selection of patients with a history of definite states: for example, particular medicinal product or a group of drugs responsiveness or resistance. If randomization was not applied, it is necessary to explain what methods were used for elimination of the systematic selection bias.

It is necessary from the perspective of the investigated disease or applied way of treatment to explain potential or foregoing difficulties driven by the selected trial design or control group. Thus, for the cross-over design possibility of spontaneous metabasis in the course of the trial and carry-over effect appearance shall be provided.

If efficacy is determined by confirming equivalence at which a new form of treatment efficacy is not less than a definite threshold in the compassion with the accepted form of treatment (not less efficacy), it is necessary to review possible difficulties due to the selected trial design. In particular, it is necessary to substantiate that the selected design is able to establish differences between effective and non-effective therapy. For that it is recommended to analyze similar, previously performed trials in the context of the key singularities of the design (patients selection, endpoints, duration, dose of the medicinal product being an active control, concomitant treatment, etc.) confirming persistent capability to identify inferiority of the active control over placebo. It is necessary to describe methods of detection of differences between effective and ineffective therapy. For example, a sharp distinction (on the basis of previously performed trials) between a group of the patients treatment-experienced and a group of naive patients may be considered efficacy availability. Variation of the target index value from the initial level, or other criteria, for example, amount of recoveries or

survivability may service as a efficacy measure. Achievement of such a result will confirm the trial capability to establish differences between effective and non-effective medicinal products. It is also necessary to substantiate that in the course of trial the non-inferiority (safety) margin (delta) was not exceeded.

Special substantiation in the report shall be made in relation to the historical control, application of which in the trial has some limitation (difficulty in providing comparability of the compared groups, impossibility of investigators "blinding", approach to treatment or course of disease change, differences caused by placebo effect).

Some other singularities of the trial design also require substantiation, including availability or non-availability of washout period and duration of the treatment period, which is especially important for chronic illnesses. If it is not so obvious, it is required to substantiate a dose and dosing interval choice. For example, once a day administration of a medicinal product with a short elimination phase half-life for which effect is closely connected with its concentration in plasma is usually ineffective. If within the trial such mode of dosing is applied, then it shall be substantiated by, for example, the fact that pharmacodynamic effect duration exceeds duration of the medicinal product appearance in blood. It is necessary to describe applied procedures aiming at finding an effect of "escape" from the medicinal product action in the end of the dosing interval, for example, specifying pre-dose medicinal product action. In the dose-effect trial with parallel design it is also necessary to substantiate the selected range of doses.

9.3. Investigational population selection.

9.3.1. Inclusion criteria. The report shall contain description of the patients population and selection criteria used for patient trial inclusion, and analysis of suitability of the selected population for the trial goals. Definite

applicable diagnostic criteria shall be presented, as well as particular requirements to disease (for example, definite degree of a diseases severity and duration, analysis results of particular laboratory parameters or rating scale, physical examination, medical history special characteristics (previous therapy failure or success) or other potential prognostic factors and any age-specific, gendered or ethical factors.

Selection criteria and any additional criteria of randomization (patient selection in the group with investigation medicinal product treatment) shall be described. If there are grounds to suppose that during the trial there were additional criteria of inclusion in the trial which were not defined in the trial protocol, their possible consequences shall be discussed. For example, if some investigators could exclude or transfer patients with definite diseases or definite initial characteristics to other trials

9.3.2. Exclusion criteria. There shall be indicated criteria for patient exclusion from the trial at the selection stage, as well as substantiation of these criteria (for example, safety or administration reasons, or unsuitability for a trial). The exclusion criteria influence on possibility to distribute results of the trial over the whole population generally shall be analyzed in section 13 of the trial report (according to sections system of headings mentioned in this part of the document) or in the safety and efficacy review of module 2 of the medicinal product registration dossier.

9.3.3. Criteria of exclusion from the clinical or analytical field of the trial. There shall be described the planned reasons of patient exclusion from the therapy or baseline observation (if available), as well as character and duration of any planned further follow-up of these patients.

9.4. Therapy.

9.4.1. Assigned therapy. There shall be described exact methods of treatment or diagnostic facilities applied in each group of patients and period of the trial, including methods of the medicinal product administration, doses and dosage schedules.

9.4.2. Investigational medicinal product description. The following information shall be provided in the report:

a brief description of the investigational medicinal product (study drug) (dosage form, dosing, batch number). If not series 1 of the investigational product (study drug) is used, the patients receiving the drug from each batch shall be identified in supplement 16.1.6 to the report (according to sections system of headings mentioned in this part of the document);

source of placebo and comparator product. The comparator product usual commercial formulation modification shall be indicated in the report, and there shall be provided measures undertaken to ensure that bioavailability was not changed due to the modification;

supply logistics for long-term trials where investigational medicinal drugs with a limited shelf life or incomplete data on stability are used. Information about investigational medicinal products intake after their expiration date, and identification of the patients taking those products, as well as storage requirements if there are special requirements to storage

9.4.3. Methods of trial subjects allocation to groups. The methods applied for allocating trial subjects to treatment groups, for example, centrally-controlled disposition, disposition within particular medical institutions, adaptive allocation (disposition on the basis of previously received assessment or response to therapy) shall be described in the report text, including stratification procedures or randomization units sizing. Any

characteristics of a patient disposition shall be analyzed in a separate part of this section of the report.

A detailed description of randomization, including method of execution, shall be given with reference to the sources in supplement 16.1.7 to the report (according to sections system of headings mentioned in this part of the document) (if required). A table containing randomization codes, an individual identification code of the patient in the trial and the assigned therapy shall also be provided in the supplement. In the multi-centre trial the report information shall be provided separately by centres. A random number-generation method shall be explained.

For non-concurrent trials it is important to explain how a particular control was chosen, what alternative non-concurrent trial was under review (if any) and how results received were compared with the applicable control.

9.4.4. Dose selection for study. Doses or dose ranges applied in the trial shall be provided by all types of therapy and a dose selection rationale shall be described (for example, data on previous experience of people and animals).

9.4.5. The medicinal product dose, intake time and the medicinal product timing selection for each patient. It is necessary to describe the investigational medicinal product and comparator product (active control) dose selection procedure for each patient. These procedures may cover random selection of the fixed dose or dosing mode selection, as well as a special selection of the dose or detailed developed selection mechanism based on the individual reaction of a patient, for example, if a dose is being increased up to the maximum tolerated dose or till a definite result. If there is a dose decline approach, it is also necessary to describe it.

Dosing timeframe (time of a day and intervals) and dosing and food intake ratio shall be described, and, if not indicated in the protocol, that shall be specially pointed out in the report.

Any particular patient information for the dose time and administration route shall be described.

9.4.6. Data masking («blinding» method) (if available). There shall be provided a description of particular procedures used for data masking (for example, packages marking method, usage of labels which disclose masking codes, sealed lists of codes (envelopes), and double dummy technique). Besides, there shall be described circumstances under which masking violation of one or all patients happened (for example, in the case of serious adverse events), procedures applied there, as well as a list of persons having access to the patient identification codes. If a trial let some investigators be informed about a cycle of treatment held (for example, to adjust the medicinal product administration schedule), it is necessary to explain other investigators confidentiality protection procedure.

Measures taken for making the investigational medicinal product and placebo undistinguishable shall be described and evidence that they were indistinguishable in exterior, form, smell and taste shall be provided. Measures for prevention of the trial data based on the laboratory measurements (if available) masking violation shall be described. If there is the data monitoring committee having access to the unmasked data, the procedures providing trial general masking maintaining shall be described. Besides, a procedure of masking maintaining during interim analysis performance shall be explained.

It is necessary to explain why to reduce subjectiveness of blinding of some or all observation, application, for example, of a random-zero

sphygmomanometer was not required – it eliminates possible investigational subjectiveness during arterial tension value interpretation, and tapes received during the Holter monitoring are sometimes interpreted automatically, which probably makes it possible to avoid investigational subjectiveness. If it was a desirable but impossible blinding, it is necessary to give reasons of non-adoption and consider consequences. In some cases blinding is performed but it is known beforehand about its imperfectness due to obvious drug reaction of, at least, some patients (dry mouth, bradycardia, fever, injection site reactions, laboratory parameters change). Such kinds of problems or potential difficulties shall be identified beforehand and it is necessary to describe if attempts to measure or to solve them were taken (for example, some measurements could be made by the persons who had not right to disclose blinding).

9.4.7. Pre-study and concomitant therapy. It shall be described what medicinal products or procedures were allowed before and during a trial, if their application was recorded and how, and other specific regulations and procedures associated with the permitted or forbidden concomitant therapy. It shall be described how permitted concomitant therapy can influence on the result due to different medicinal products interaction, or direct action on endpoints (main variables) of the trial, and how independent effects of the concomitant and investigational therapy can be determined.

9.4.8. Measures taken to provide therapy regimen compliance. Measures taken for provision and recording in the documents of the therapy regimen compliance shall be described, for example, medicinal products accountability, patient's diary, characteristics of the medicinal product content in blood, urine and other body fluids, or the product action monitoring.

9.5. Efficacy and safety data.

9.5.1. Efficacy and safety parameters measured and a block diagram. Particular parameters of efficacy and safety shall be measured, and laboratory trials shall be performed. At the same time a schedule of these parameters study shall be indicated (trial performance days, the time of day, connection with food intake, and critical timeframe of the parameters measurement in relation to the investigational medicinal product intake, for example, directly before the next dose, in 2 hours after the dose), as well as methods of their measurement and persons responsible for measurement. If personnel performing clinically significant measurement changed, the changes shall be indicated.

Frequency and time of the efficacy and safety parameters measurement shall be shown graphically as block diagrams (in accordance with Appendix №4 to the Regulations). Visits numbers and time, or time only (if only numbers of visits are indicated, data is difficult to perceive and interpret) shall be provided. Besides, it is necessary to indicate all specific instructions for patients (for example, their application of the information for investigational medicinal products intake, or a diary).

Definitions used for trial outcome characteristics (for example, criteria of an acute myocardial infarction event determination, myocardial infarction localization, a stroke characteristic as a thrombotic apoplexy or a cerebral hemorrhage, differences between a transient ischemic attack and a stroke, assignment of cause of death) shall be explained in details. Any methods applied for standardizing or comparison of the laboratory trials results or other clinical measurements (for example, ECG, chest X-ray examination) shall be also described. This is especially important for multi-centre trials.

If clinical outcome is reviewed by other persons in addition to investigators (for example, a sponsor or an independent commission reviewed X-ray film or ECG, or found a patient's stroke, acute miocardial infarction or sudden death), these persons shall be clearly indicated in the report. It is necessary to give a full description of a procedure, including methods of blinding maintaining, centrally-controlled measurements and their results interpretation.

Methods of adverse events data delivery shall be described (voluntary reports, application forms completing or interviews), as well as applied special rating scale and specially planned follow-up procedures aiming at elimination of the adverse events, or a planned procedure of rechallenge.

All types of assessment used by the investigator, sponsor or independent group for the adverse event (for example, severity score, or probability that the adverse events are caused by the investigational medicinal product) shall be described. These assessment criteria (if available) shall be taken into consideration and the persons responsible for assessment shall be clearly indicated. If efficacy or safety were rated by categorical, point, etc. scale the criteria applied for scoring (for example, points rating by a scale) shall be provided. For multi-centre trials it is necessary to indicate how methods were standardized.

9.5.2. Measurement compliance. If any of efficacy or safety assessment was not standard, i.e. was not commonly used, accepted reliable, accurate and significant (capable to distinguish effective and ineffective medicinal products), then its reliability, accuracy and significance shall be documentarily confirmed. One shall describe reviewed, though rejected alternatives in this section of the report.

If a surrogate endpoint (laboratory findings, physical measurement or characteristic which is not a direct index of the clinical outcome) was used as

the trial endpoint that shall be substantiated, for example, with a reference to the clinical data, publications, guidelines or resolutions of the regulatory authorities.

9.5.3. Primary efficacy parameters. It is necessary to list in details the primary parameters and endpoints used for efficacy measurement. In spite of the fact that the efficacy key parameters can seem obvious, with many variables or multiple determination it is necessary to indicate efficacy primary parameters in the protocol (choice substantiated), or to determine a set of significant parameters or other method of information grouping which can be interpreted as the efficacy parameter. If primary efficacy parameters are not provided in the protocol, it is necessary to give explanations in the report how these key parameters were chosen (for example, on the basis of publications, guidelines or resolutions of the regulatory authorities), and when they were identified (before or after trial completion and blinding withdrawal). It is necessary to point out if the efficacy threshold described in the protocol.

9.5.4. Medicinal product concentration measurement. Any measured concentration of the product, as well as sampling time and periods in relation to the treatment time shall be described. Any association of treatment and sampling with food intake, body position and possible effect of co-meditation (alcohol, caffeine, nicotine) shall be also provided. A type of the biological sample, samples treatment and a method of measurement with a reference to the published and (or) internal validation documentation upon trial procedure for methodological singularities characteristic shall be described. If for pharmacokinetics assessment other factors are also considered important (for example, solvable circulating receptors, kidney and liver functions), then timeframe and plans for these factors measurement shall also be indicated.

9.6. Data quality assurance. A brief description of the quality assurance systems and quality control systems implemented for data quality assurance shall be provided. If such systems were not used, that shall be indicated. Inter-laboratory methods of standardization and quality assurance procedures documentation (if available) shall be presented in accordance with supplement 16.1.10 to the report (according to sections system of headings mentioned in this part of the document).

Any measures taken in the investigational centre or centralized in order to provide application of the standard terminology and collection of accurate, subsequent, full and reliable data, for example, trainings, monitoring of investigators by the trial sponsor personnel, instructing manuals, data check-up, cross-checking, usage of the central laboratory for particular analysis performance, in-house interpretation of ECG or data auditing, shall be described. One shall point out if conferences for investigators were held, or other steps were undertaken for investigators training and work standardization.

If a sponsor used procedures of independent internal or external auditing, that shall be indicated in this section of the report and described in details in supplement 16.1.8 to the report (according to sections system of headings mentioned in this part of the document). In this supplement the audit certificated (if available) shall be provided.

9.7. Statistical methods provided by the protocol and sampling range setting.

9.7.1. Statistical plan and analysis plan. In the trial protocol the statistical analysis plan and all its changes made prior to data on outcome obtaining shall be described. In this section of the report it is necessary to give a detailed description of the trials planned in accordance with the trial

protocol, but not really performed analysis, comparison and statistical tests. It is necessary to indicate if key parameters were measured more than 1 time, to list particular measurements (for example, an average value of several measurements during the whole trial, values in definite time points, values for the subjects completed the trial, or values in the end of the therapy), planned as a basis for comparison between the investigational medicinal product and control. It is necessary to mark the planned approach by similar way if there is more than 1 analytical approach, for example, change from baseline, curve slope analysis, mortality tables analysis. Besides, it is necessary to mention if adjustment for covariates was provided within the primary analysis.

It is necessary to describe if grounds were planned for exclusion of the patients with the collected data from the analysis. It is necessary to indicate if subgroups which results are analyzed separately were provided. If during the results analysis the categorical scale was used (global rating scale, severity rating, results of a definite value), it shall be clearly defined.

It is necessary to describe the planned monitoring of the trials results. If the trial provided participation of the data monitoring committee controlled or not controlled by the sponsor, it is necessary to describe its membership and operating procedures, as well as procedures providing the trial blinding maintaining. It is required to describe frequency and essence of the planned interim analysis, to indicate all circumstances established in the trial protocol beforehand, due to which the trial shall be terminated, and to indicate all statistical corrections made on the basis of the interim analysis.

9.7.2. Sampling range setting. It is necessary to present the planned scope of sampling and method of its calculation, for example, statistical estimations or practical limitation. Together with the sampling range calculation methods it is necessary to provide substantiation of calculations

or references to such substantiation. It is necessary to give estimates used in the calculations, and to explain how these estimates were received. In the trials aiming at confirmation of differences between therapy methods, it is necessary to stipulate a range of difference found. In the trials with a positive control aiming at confirmation of not less efficacy in the comparison with the standard therapy, definition of sampling range shall include difference between the compared methods which is considered unacceptably large and may be excluded within the planned trial.

9.8. Changes in the course of the trial procedure or in the planned analysis.

Any change in the trial procedure or the planned analysis (for example, exclusion of some of the compared treatment groups, change of inclusion criteria or the medicinal product dose, correction of sampling range, etc.) made after the trial commencement shall be described. Time and reasons of such changes, procedures applied for taking decision on introduction of changes, person or group of persons responsible for changes, current data character and content and a list of persons who have access to them as on the date of the change introduction shall be also described regardless the fact if this change was recorded as an official protocol amendment or was not (This section shall not include changes in staffing and staff solutions). Any possible consequences of changes in the trial results interpretation shall be briefly described in this section and more detailed in other corresponding sections of the report. In each section of the report there shall be a clear difference made between conditions (procedures) planned in the protocol and amendments or additions. It is considered that generally changes in the planned data analysis made before masking data disclosure insignificantly influence on the trial results interpretation. It is especially important to have changes introduction

time clearly indicated in relation to the masking data disclosure and endpoints obtaining time.

10. Information about the trial subjects

10.1. Subjects disposition in groups.

It is necessary to carry out detailed and clear records of all patients who took part in the trial using the graphical or table representation of data in the report text. There shall be indicated the amount of patients randomized, joined the trial and completed each of its stage (every week (month) of the trial), as well as reasons of all post-randomized treatment termination, grouped by treatment and main reason (observation withdrawal, adverse events, therapy regimen incompliance, etc.). Besides, in some cases it is required to indicate the amount of patients reviewed (selected) for inclusion in the trial, and to give the analysis of the reasons of the patient exclusion during the screening, if that can help to clarify the selection grounds of the patient population using the medicinal product, actually formed in the trial. As a rule, it is more convenient to represent the data in the form of a block diagram (in accordance with Appendix №5 to the Regulations). At the same time there shall be clearly indicated if the patients were under observation during the whole period of the trial even if they stopped taking the medicinal product.

Supplement 16.2.1 to the report (according to sections system of headings mentioned in this part of the document) shall contain a list of all patients stopped joining the trial after they were included in it, by investigation centres and treatment groups, with indication of the patient identification code, a particular reason of the trial or treatment withdrawal (a medicinal product and a dose), gross dose taken (if applicable), as well as therapy duration till termination. There shall be indicated if the patient

treatment data was de-masked at the date of therapy termination. Besides, it is necessary to include other information like critical demographical data (for example, age, gender and race), concomitant therapy and the main changes in the patient's state at the date of therapy termination. A sample of the mentioned list is provided by Appendix №6 to the Regulations.

10.2. Protocol deviations.

All important (significant) deviations associated with inclusion or exclusion criteria, trial procedure, patient management or patient's state evaluation shall be described.

In the text of the protocol deviation report the following shall be properly summarized by investigational centres and grouped by different categories:

the patient joined the trial even if they do not satisfy the inclusion criteria;

the patients who got compliant with the trial exclusion criteria during the trial procedure but did not terminate it;

the patients who were treated wrong or took a wrong dose of the medicinal product;

the patients who got unauthorized concomitant therapy.

Supplement 16.2.2 to the report (according to sections system of headings mentioned in this part of the document) shall specify particular patients with these protocol deviations by centres for multi-centre trials.

11. Efficacy assessment

11.1. Data subject to analysis.

It is necessary to indicate clearly what patients were included in every efficacy analysis, for example, the patient taken some of the investigational medicinal products, the patients with any data on efficacy or with definite

minimum number of observations, the patients terminated the trial, the patients under observation within a definite period of time, the patients with a definite compliance rate, etc. It is necessary to indicate clearly if that is not described in the protocol, when (in relation to blinding withdrawal) and how analyzed data sets inclusion and exclusion criteria were formed. If a primary analysis offered by an applicant is based on the limited amount of patients, it is necessary to try to determine efficacy by additional analysis using data of all randomized or otherwise included patients with any volume of data.

Supplement 16.2.3 to the report (according to sections system of headings mentioned in this part of the document) shall present a table list of all patients, visits and observations excluded from the efficacy analysis (in accordance with Appendix №7 to the Regulations). It is also required to analyze in dynamic the reasons of exclusion of the patients, visits and observations in all treatment groups (in accordance with Appendix №8 to the Regulations).

11.2. Demographical and other initial characteristics.

It is necessary to provide the group data on important demographical and initial characteristics of the patients, as well as other factors arising in the course of the trial, which could influence on the trial outcome. In section 14.1 it is necessary to present comparability of treatment groups by all significant characteristics using tables and diagrams. First it is necessary to describe data for the patients included in groups “all patients with data”. Then there can be data on other groups included in the basic analysis, such as the analysis “as per protocol”, and others, for example, the groups selected by therapy compliance, concomitant disease (therapy) or demographical (initial) characteristics. When using these groups, it is necessary to provide data on excluded groups complementing them. In the multi-centre trials the groups

comparability shall be assessed, as far as possible, inside one centre, as well as between centres.

It is necessary to present a diagram displaying interrelation between the whole sample group and every analyzed group.

The most important variables depend on disease nature and the protocol requirements. As a rule, these variables include:

demographical variables: age, gender, race;

disease factors:

special criteria of inclusion (if not unified), disease duration, stage and severity, and other types of the clinical classifications and groups which are often used or have a predictive value;

initial values of the main clinical measurements made in the course of the trial and set as important parameters of the prognosis or treatment response;

concomitant disease in the beginning of the trial, such as renal failure, diabetes mellitus, cardiac failure;

significant diseases in past medical history;

significant previous therapy of the disease for treatment of which the trial is in progress;

concomitant therapy even with dosing change in the course of the trial, including hormonal contraception or hormonal replacement therapy, terminated or changed treatment due to the trial commencement;

other factors which may influence on the treatment response (for example, body weight, rennin status, antibody level, metabolic status);

other potentially significant variables (for example, smoking, alcohol consumption, special diets), and for women – menstrual status and last menstruation date (if applicable for this trial).

In addition to the tables and graphs with data on the mentioned initial variables supplement 16.2.4 to the report (according to sections system of headings mentioned in this part of the document) shall provide the table data on significant individual demographical and initial characteristics, including the laboratory parameters and all concomitant medications per each randomized patient (by treatment, and for multi-centre trial – by centres). In spite of the fact that some regulatory authorities ask for all initial data in the form of tables, in the supplement to the trial report it is necessary to indicate only that information which is most significant (as a rule, that is variable mentioned above).

11.3. Treatment compliance measurement.

Supplement 16.2.5 to the report (according to sections system of headings mentioned in this part of the document) shall summarize, analyze by treatment groups and time intervals and present in a table form all measurements of a particular patient investigational treatment regimen compliance and the medicinal product concentration in the body fluids.

11.4. Results of efficacy measurement and summary tables of patient individual information.

11.4.1. Efficacy analysis. It is necessary to compare all treatment groups by all significant efficacy parameters (studied primary and secondary endpoints, all pharmacodynamic endpoints), as well as by evaluation of a benefit-risk balance for each patient, if applicable. In the trials aiming at efficacy setting, it is necessary to present results of all analysis planned in the protocol and the analysis including all patients with the data under study. In the analysis it is necessary to show a value (point estimate) of differences between treatment groups, associated confidence interval and hypothesis test results, if applicable.

The analysis based on continuous (for example, mean arterial pressure and depression scale score) and categorical variables (for example, resolution of infection), may be similarly acceptable. As a rule, both of them shall be presented, if they were planned and there are accessible data for them. If the categories were developed for the first time (i.e. not included in the statistical plan), then it is necessary to explain their background. If even a main focus is on one variable (for example, that may be the arterial pressure value in the supine arterial blood pressure trial on week "x"), it is required to evaluate at least briefly other important parameters, too (for example, standing arterial blood pressure and in other time points). Besides, if it is possible, a dynamic of response to treatment through time shall be described. For multi-centre trials in order to give a clear picture of analysis with each centre, especially a big one, in relation to significant variables it is required to present data and results of analysis by each centre (if required).

If significant measurements or efficacy or safety outcome assessment were made by more than one party (for example, an investigator and expert commission could make a conclusion if a patient has or has not an acute myocardial infarction), it is necessary to show overall differences in assessment indicating each patient with incompliant opinions. Assessment method shall be clearly described in each analysis.

When there are many trials it is difficult to draw the line between efficacy and safety parameters (for example, fatal outcome in the lethal disease study). Most of the below principles shall be applied for significant parameters of safety assessment.

11.4.2. Statistical (analytical) results. For the trial clinical and statistical part experts it is necessary to describe the statistical analysis in the report. Supplement 16.1.9 to the report (according to sections system of headings mentioned in this part of the document) shall present the detailed

documentation for statistical methods (in accordance with Appendix №9 to the Regulations). It is required to describe significant elements of the analysis including applied methods, adjustment for demographical and initial characteristics or concomitant therapy, withdrawals and missing data treatment, adjustment for multiple comparisons, special analysis for multi-centre trials and adjustment for interim analysis. It is necessary to provide information about all changes in the analysis made after blinding withdrawal.

In addition to the general description this section of the report shall review the following issues (if applicable):

11.4.2.1. Adjustment for covariates. The report shall contain explanations of selection and adjustment for the demographical and initial characteristics, concomitant therapy and any other covariates or prognostic factors. Amendments procedure, results of the analysis and auxiliary information (for example, covariance analysis, Cox regression values) shall be included in the detailed documentation for the statistical methods. If covariates or methods used in this analysis differ from those planned in the protocol, then it is necessary to explain current differences and provide results of the planned analysis (if required). Not making a part of a separate report on the trial, comparison of the adjustment for covariates and prognostic factors between particular trials may become important in the clinical efficacy data summary.

11.4.2.2. Dropout trial subjects' or missing data treatment. There are several factors which may influence on the dropout rate. They are: trial duration, disease nature, investigational medicinal product efficacy and toxicity and other factors not referring to therapy. Ignoring the dropout patients and making conclusions only on the basis of the patients terminated the trial dropped may cause wrong conclusions. But a large scope of

dropouts, even included in the analysis, may deceive, in particular, if in one of the comparator groups there were many dropout patients with early stage, or the dropout is caused by treatment or its outcome. In spite of the fact that early dropout influence and in some cases even the essence of the mistake can be difficult to establish, their possible influence shall be analyzed in the fullest possible manner. It is recommended to study observed cases at different points of time, or, if dropouts were rather frequent, to make analysis in the point of time when most of the patients were under observation and when a full effect of the medicinal products revealed. It is recommended to use simulation for such incomplete data set assessment.

It is necessary to evaluate results of the clinical trial not only for the subgroup of the patients terminated the trial, but also for the whole randomized population of the patients, or, at least, for that part in relation to which any measurements were made. During dropout analysis it is necessary to take into consideration and to compare several factors of the study groups: dropout reasons, time before dropout and dropout patients' share in the study groups at different intervals of time.

It is necessary to describe the missing data treatment procedure, for example, usage of the expected or derived data. It is required to provide a detailed explanation how these estimates or derived data were received and on what assumptions they are based on.

11.4.2.3. Interim analysis and data monitoring. A process of review and analysis of the data received within the clinical trial (on a formal or informal basis) can deliver performance bias and (or) enhance type I error. That is why it is necessary to give a full description of all interim analysis, on a formal or informal basis, planned and situational, performed by any investigational party, sponsor's representatives or data monitoring commission, even if

treatment groups were not identified. One shall take into consideration the necessity to make statistical amendments due to such analysis. It is necessary to describe all instructions and procedures applied for such analysis performance. Any data monitoring commission meetings protocols or reports on the data reviewed at such meetings, especially if meetings were followed by amendments to the protocol or early study termination, can make it possible to explain that and shall be provided in supplement 16.1.9 to the report (according to sections system of headings mentioned in this part of the document). It is necessary to describe the data monitoring performed without codes disclosure, even if it is considered that such kind of monitoring does not enhance type I error.

11.4.2.4. Multi-centre trials. A multi-centre trial is a study performed under a single protocol including several investigational centres (for example, clinics, ambulatory-care clinics, hospitals) where collected data are analyzed as a single unit (differing from the next solution on data or particular trials results combining). It is necessary to provide results by each centre. As far as possible, for example, if there is a satisfactory amount of patients in the centres in order to increase such analysis value, it is required to establish availability of qualitative or quantitative dependence between study groups from different centres. It is necessary to describe and explain all outlying or opposite results of the centres taking into consideration differences in the trial procedure, patients' characteristics or clinical trials database. Comparison of the groups shall include analysis which makes it possible to find differences between centres concerning groups response to treatment. As far as possible it is required to present demographical, initial and overall data (initial data change result), as well as efficacy data by each centre, even if the combined analysis is a primary one.

11.4.2.5. Multiple comparisons (multiplicity). Upon growth of the amount of the performed tests of significance (amount of comparisons), a number of false-positive results is increasing. If there is more than 1 primary endpoint (outcome variable), over 1 analysis of the particular endpoint or multiple study groups or subgroups of the patients studied, it is required to show that multiplicity in the statistical analysis, to present a statistical adjustment for prevention of type I error enhancement, or to give explanations why this adjustment was not provided.

11.4.2.6. Usage of a subgroup of the patients who showed efficacy. It is necessary to give a special analysis of the withdrawn patients with current data due to a low compliance, visits missed, nonconformance of the trial requirements or other reasons. As it is given above, by using all current data it is required to analyze all trials aiming at efficacy, even if such analysis is not provided by an applicant as a primary one. It is recommended to prove efficacy of the main results of the trial as in the case of the alternative analyzed population of the patients. Any significant deviations arising out of the patient population for the analysis shall be explained in details.

11.4.2.7. Equivalence trial with an active control. If a trial with an active control aims at proving equivalence (i.e. there is no pre-established value of differences) between the medicinal product under study and the active control (comparator product), the analysis shall show a confidence interval for this comparison between two medicinal products by the most significant endpoints and relation of this interval to pre-agreed inferior efficacy (safety) rate which is considered unacceptable (requirements to the main conditions of the active control application description in the equivalence trials are given in section 9.2 hereof).

11.4.2.8. Subgroups study. If range of the trial sampling allows, it is necessary to analyze subgroups formed by important demographical and initial characteristics for availability of unexpectedly high or low response, and to present corresponding results of the analysis in the report, for example, comparison of age, gender, race, disease severity, prognostic factors, history of the same class medicinal products previous treatment, etc. influence. If there was a hypothesis on differences between some subgroups, then the hypothesis and testing shall be a part of the statistical analysis.

11.4.3. Individual effect data summary tables. In addition to the tables and data graphs per groups, the tables shall provide information about individual response and other information significant for the trial. The regulatory authorities have the right to inquire data on all patients in the form of the archive tables by each patient. The requirements to the report content may vary from trial to trial and from one class of the medicinal products to the other one, that is why an applicant shall determine, as far as possible, after being consulted by the regulatory authority, what information shall be included in the trial report supplement. In the trial report it is necessary to provide what data is included as a supplement, and what data is presented in more detailed archive tables by particular patient, if that is required by the regulatory authority, and what data is accessible upon inquiry.

In the controlled trials where the most significant measurements and efficacy evaluation (for example, blood and urine culture, lungs functional tests, repeat periodically, lists of data for each patient attached to the report shall include: patient identification, all measured and observed valued of the most significant parameters, including initial ones, indication of measurements time (for example, therapy day and time of a day, if important), a medicinal product (a dose) (if required, in mg/kg), all

compliance parameters and concomitant therapy at the moment of measurement (evaluation) or a close period of time. If together with re-evaluation the trial made comparison of the patients responded and not responded to treatment (bacteriological cure or failure), that shall be described. In addition to the most significant measurements description the tables shall provide information if this patient was included in the efficacy analysis (and in which one if they were several), information about patient compliance to treatment (if available), a reference to corresponding CRF, if included in the report. Besides, it is reasonable to indicate important initial information, like gender, age, body weight, disease under study (if the trial included patients with different diseases), its stage and severity. With efficacy evaluation the initial data of the most significant measurements are usually indicated as zero data.

Described table data shall be given in supplement 16.2.6 of the report (according to sections system of headings mentioned in this part of the document), instead of including bulky tables for CRF required by some regulatory authorities as they represent basic data on efficacy on the basis of which summarized tables are generated. But such types of bulky tables may be inconvenient for analysis during expertise, and it is preferable to have tables of practical interest in the report. For example, if the report informs about multiple measurements, tables of particular patients with the most significant measurements will be useful for the control of the trial individual results where response of each patient is summarized in one line of the table or in a small number of the table lines.

11.4.4. Product dose, concentration and effect dependence. If a patient's dose may vary, it is required to describe doses actually taken by the patient and to provide in the table data all values of the doses prescribed within the trial. In spite of the fact that in the trials not aiming at a dose-effect

study, possibility to find a dose and effect dependence is limited, it is required to analyze accessible data for such dependence. During a dose-effect study it is recommended to calculate the dose in mg/kg of the body weight or mg/m^2 of the body surface area.

Information about the medicinal product concentration (if available) shall be provided in the table data of supplement 16.2.5 to the report (according to sections system of headings mentioned in this part of the document), including indication of the pharmacokinetic parameters and, as far as possible, in interrelation with the clinical response.

More detailed principles of the trial design and analysis aiming at dose-effect or concentration-effect dependence identification are given in the methodical guidelines for clinical trials procedure in order to choose the medicinal product dose.

11.4.5. Drug interaction and concomitant diseases influence. It is necessary to indicate availability of any supposed response-concomitant therapy or previous or current diseases dependence.

11.4.6. Representation of data on each patient. In spite of the fact that data on each patient are usually provided in tables, in some cases it is recommended to make profiles of parameters for particular patients in other formats, for example, in the form of graphs. That helps to analyze a value of particular parameters through time, a dose of the medicinal product for the same period of time and definite events time (for example, adverse events or concomitant therapy change). If in the main analysis the averaged group data were used, such kind of "individual data withdrawal" is of a low value. But if individual responses are a main part of the analysis, such data can be useful.

11.4.7. Opinion of efficacy.

It is necessary to provide, in the fullest possible manner, the important conclusions on the medicinal product efficacy, including description of the primary and secondary endpoints, using planned and alternative statistical approaches and research study results.

12. Safety assessment

Safety data analysis shall be made in three stages. In the first stage in order to determine safety level which may be evaluated within the trial, it is necessary to study an exposure level (a dose, duration, amount of patients). In the second stage it is necessary to indicate adverse events, changes of the laboratory and other parameters grouped by some definite feature, between the compared groups and analyzed, if required, with regard to the factor which may influence on the adverse reactions (events) frequency (such as time dependence, demographical characteristics dependence, the medicinal product dose or concentration, etc). It is required to indicate serious adverse events and other significant adverse events (usually accompanied with a thorough examination of the patients) early terminated due to the adverse events regardless if they were caused by the medicinal product intake or not, or died.

At the same time a term «serious adverse events» is considered in the meaning established by the regulations, and a term «other significant adverse events» means marked hematological and other laboratory violations and any adverse events leading to interference, including medication cancellation, a dose decline or add-on therapy order.

In the next sections it is required to analyze and provide the following information:

summarized data with tables and graphs given in the main part of the report;

lists of data by particular patients;

comments on the events of special value for this study.

In all tables and analysis information about events caused by the investigational medicinal product or control shall be provided.

12.1. Exposure level.

It is necessary to characterize the investigational medicinal product exposure level, as well as an active control and placebo, and to indicate a number of patients under exposure, the exposure duration and a dose of exposure.

12.1.1. Duration. Any dose exposure duration may be expressed by a median or mean value, besides, it is recommended to indicate a number of patients exposed for a definite period of time, for example, 1 day and less, from 2 days to 1 week, from 1 week to 1 month, from 1 to 6 months, etc. A number of the patients under the investigational medicinal product exposure shall be grouped by age, gender, race and other significant parameters like disease (if the trial includes patients with difference diseases), its severity and co-morbidity.

12.1.2. Dose. It is necessary to provide a mean or a median of the dose used in the trial and a number of the patients whom it was prescribed, the dose which exposure the patients were subject to most long, or a mean daily dose. It is recommended to present the combined dose-duration information, for example, a number of patients most frequently subject to exposure of the applied dose during the set period of time, a minimum dose, maximum recommended dose, etc. In some cases a cumulated dose is important. The dose amount depending on circumstances may be expressed in the form of a real daily dose, in mg/kg or mg/m^2. All patients subject to exposure with

different doses shall be grouped by age, gender, race and other significant parameters.

12.1.3. Medicinal product concentration. If there is information about the medicinal product concentration (for example, concentration during a definite event, maximum plasma concentration, area under a curve «concentration-time») the latter may appear useful for identification of connection between the adverse event or laboratory parameters change and administration of the investigational medicinal product to particular patients. This information is given in supplement 16.2.5 to the report (according to sections system of headings mentioned in this part of the document).

It is supposed that all patients included in the trial and got at least 1 dose administration will be included in the safety analysis. If this condition is not satisfied, it is necessary to provide appropriate explanations.

12.2. Adverse events.

12.2.1. A brief summary on adverse events. It is necessary to give a brief summary of all adverse events recorded in the course of the trial (represented in other sections of the detailed tables and analysis). These tables and analysis shall include the events caused by investigational product and by control.

12.2.2. Presentation of data on the adverse events. In the summary tables given in section 14.3.1 of the table (according to sections system of headings mentioned in this part of the document) it is required to show all adverse events arising after the investigational medicinal products administration commencement (including the events probably caused by diseases or co-morbidity, unless there is an agreement achieved beforehand with the regulatory authority on referring of the above events to the associated diseases). The tables shall include information about vital

parameters change and any changes of the laboratory parameters which are considered as serious adverse events or other significant adverse events.

In most of the cases these tables shall provide features and symptoms arising in the course of the therapy (features and symptoms where were not recorded before the trial commencement, or intensified in the course of the trial if available before).

The table shall specify all adverse events, amount of the patients in each treatment group where adverse events occurred, and their frequency. If therapy is of cyclic nature, for example, anti-cancer therapy, such results shall be provided for each cycle independently. The adverse events shall be grouped by organs systems. Then, if severity rating system was applied (for example, mild, moderate, high), each event may be characterized from this point of view. The tables may allocate the adverse events per cause-effect relations degree, for example, possibly tied and untied, or to apply another scale, for example, associated or possible, probably, definitely associated. Even if to use cause-effect relations evaluation, it is necessary to include all adverse events in the table regardless the administrated medicinal product interaction level, including the events which are considered intercurrent diseases manifestation. Further analysis of the trial or summary safety database can help to reveal adverse events which are caused or not caused by the investigational product. That is why to analyze and evaluate data provided in these tables it is necessary to identify each patient who got the adverse event under review. Such table example is given below.

Table sample
Adverse events: amount of observation and frequency, patient identification

Treatment group X N = 50

	Lungs		Moderate level		Severe		Total		Grand total
	C*	HC	C	HC	C	HC	C	HC	C+HC
System of organs A	6 (12%)	2 (4%)	3 (6%)	1 (2%)	3 (6%)	1 (2%)	12 (24%)	4 (8%)	
Event 1	N 11**	N 21	N 31	N 41	N 51	N 61			
	N 12	N 22	N 32		N 52				
	N 13		N 33		N 53				
	N 14								
	N 15								
	N 16								
Event 2	…	…	…	…	…	…	…	…	…

Notes: * C – associated, HC – not associated. Rating «associated» may be enlarged, to, for example, «definitely», «possibly», «probably».
** Patient identification number

In addition to such detailed tables given in section 14.3.1 to the report (according to sections system of headings mentioned in this part of the document), in the main part of the report it is necessary to present additional summary table in which the investigational and control groups will be compared without patient identification numbers being indicated, being limited to frequent adverse events (for example, those which occurred not less than with 1% of the patients of the group).

To establish a true frequency of the adverse events, during their description it is necessary not only to show the original definition given by the investigator, but to try to group the associated events (the events which may be one and the same phenomena). One of these methods is application of the standard vocabulary of adverse reactions (events).

12.2.3. Adverse events analysis. In the interest of comparing the group under study and control group it is necessary to use basic information on frequency of the adverse events which were analyzed in section 12.2.2 of the report and the information on which was presented in section 14.3.1 of the report (according to sections system of headings mentioned in this part of the

document). For such an analysis it is required to combine all the events regardless of severity and cause-and-effect dependence for the purpose of easier parallel comparison of the compared groups. Although such analysis is usually performed with coherent safety analysis, if allowed by trial scale and design, it is recommended to study more frequent adverse events that are suspected as being caused by the treatment for their occurrence depending on a dose (including mg/kg and mg/m^2), dosage regimen, treatment duration, overall dose, demographical characteristics like age, gender, race and other original features (e.g. kidney function), outcomes of efficacy and concentration of the medicinal product. It is also recommended to study the time of adverse effects occurrence and their duration. Based on the results of the trials or pharmacological properties of the investigational medicinal product other line of analysis may be allowed to be carried out.

Conducting a thorough statistical evaluation of every adverse event is not necessary. During the initial presentation and study of the data it can be found that a considerable part of the events is not determined by demographical and other original parameters. If the trial is carried out with a small subject population and the amount of the events is comparatively low, it is sometimes sufficient to be limited to the comparison of the treatment and control groups.

In certain cases in the comparison with presentation of a general frequency of the adverse events, it is more informative to use mortality tables or other analysis of the same nature. For cyclical treatment, for example, with the antineoplastic therapy, it is recommended to conduct an analysis of the results within the scope of every given cycle.

12.2.4. List of adverse events by every patient. In supplement 16.2.7 to the report (according to sections system of headings mentioned in this part of

the document) it is required to list all adverse events by every patient including the same event occurring multiple times, with indication of the approved standard term and the original term applied by an investigator. The list is composed by each investigator and treatment trial group and shall include the following information:

Patient identification;

Age, race, gender, body weight (height if applicable);

CRF place in the report (if present);

Adverse event (approved standard term, original term);

Adverse event duration;

Severity (mild, moderate, high);

Seriousness (serious or not serious);

Measures taken (no intervention, dose decline, treatment termination, add-on therapy prescription and so on); outcomes (i.e. in CIOMS format);

Cause-and-effect connection evaluation (i.e. associated or not associated not). Its application algorithm shall be described using a table format or other way;

Date of occurrence or date of visit on which the adverse event was detected;

Time of adverse event occurrence in relation to the last taken dose of the medicinal product (if applicable);

Therapy on the moment of occurrence or recently applied therapy;

Amount of a dose of the investigational medicinal product in absolute terms, in mg/kg or mg/m^2 at the moment of the event occurrence;

Concentration of the medicinal product (if known);

Duration of investigational medicinal product treatment;

Concomitant therapy during the trial

In the beginning of the list or on every page (a more preferable option) all abbreviations and acronyms shall be expanded.

12.3. Lethal outcomes, other serious adverse events and other significant adverse events.

Lethal outcomes, other serious adverse events and other significant adverse events shall be put special emphasis on.

12.3.1. List of lethal outcomes, other serious adverse events and other significant adverse events. In regards to the events stated below it is required to submit lists containing the information described in section 12.2.4 of the report (according to sections system of headings mentioned in this part of the document).

12.3.1.1. Lethal outcomes. Section 14.3.2 of the report shall list every patient's lethal outcomes registered during the trial, including a period of monitoring upon therapy completion, as well as lethal outcomes occurred due to a process started during the trial.

12.3.1.2. Other serious adverse events. In section 14.3.2 of the report (according to sections system of headings mentioned in this part of the document) it is required to present all serious adverse events (except for the lethal outcomes but including the serious adverse events associated by time or preceding death). The list shall contain clinical deviations, pathologically changed vital readings and pathological survey data evaluated as serious adverse events.

12.3.1.3. Other significant adverse events. In section 14.3.2 of the report (according to sections system of headings mentioned in this part of the document) it is required to present intense hematological and other clinical deviations (apart from the events falling into the definition of adverse events) and other events that led to interception, including cancelation of

investigational medicinal product therapy, dose decline or significant supplemental add-on therapy reduction, which does not fall into the definition of the serious adverse events.

12.3.2. Description of lethal outcomes, other serious adverse events and other significant adverse events. It is required to present a brief description of every lethal outcome, every other serious adverse event and other significant events that are evaluated as especially significant due to their clinical significance. Depending on quantity such descriptions shall be provided either in the main section of the report or in section 14.3.3 of the report (according to sections system of headings mentioned in this part of the document). Events that are definitely not associated with the investigational medicinal product are allowed not to be described or described very briefly. Usually the description shall contain the following information:

Characteristics and intensity of the event;

Course of the disease causing the event and time of the investigational medicinal product administration;

Significant laboratory values;

If the medicinal product was discontinued and when;

Countermeasures;

Autopsy findings;

Investigator's and sponsor's opinions (if required) with regard to cause-and-effect connection.

Additionally the following information shall be presented:

Patient identifier;

Patient's age and gender;

General clinical condition of the patient (if required);

Disease on the basis of which a patient was included in the trial (if it is the same for all the patients it shall not be included) including its duration (current episode);

Significant concurrent diseases and (or) previous diseases, time of their occurrence and duration;

Significant concurrent and (or) previous medication and a dosage regime;

Prescribed investigational medicinal product, dosage (if it differed from patient to patient) and duration of administration

12.3.3. Analysis and discussion of lethal outcomes, other serious adverse events and other significant adverse events. In relation to the investigational medicinal product safety it is required to evaluate the significance of lethal outcomes, other serious adverse events and other significant adverse events caused cancelation of the investigational medicinal product, its dose decline or application of a supplementary therapy. It is especially required to analyze if any of these events is a previously unforeseen significant event of the investigational medicinal product. In relation to serious adverse events this circumstance is especially critical. In order to find dependence of the events on time of the investigational medicinal product administration and to evaluate the risk through time it is recommended to use mortality tables or similar analysis.

12.4. Evaluation of the laboratory values.

12.4.1. List of individual laboratory data by every patient (provided in section 16.2.8 of the report) and the laboratory data deviation from the norm (provided in section 14.3.4 of the report). Upon request of the regulatory authorities the results of all safety related laboratory trials shall be available in the form of line listings in the following format: every line of data is

related to a patient's visit during which laboratory trials were conducted, in which patients were grouped by investigator (if there were several investigators in the trial) and therapy; every column includes significant demographic data, information on dose of the medicinal product and results of laboratory trials. As one table cannot contain all trials, they shall be logically grouped (hematologic studies, liver bioorganics, electrolytes, uroscopy, etc.). It is required to highlight all values deviating from the norm by underlining, parenthesizing or other way. If that is required by the regulatory authority, the list shall be provided not in the report but as a separate part of the medicinal product registration dossier, or this list shall be ready in case of inquiry.

Table sample
List of laboratory measurements

Patient	Time	Age	Gender	Race	Body weight	Dose	Laboratory tests		
							ALT	AST	ALP
№ 1	T_0	70	m	C	70 kg	400 mg	V_1*	V_5	V_9
	T_1						V_2	V_6	V_{10}
	T_2						V_3	V_7	V_{11}
	T_3						V_4	V_8	V_{12}
№ 2	T_{10}	65	f	N	50 kg	300 mg	V_{13}	V_{16}	V_{19}
	T_{21}						V_{14}	V_{17}	V_{20}
	T_{32}						V_{15}	V_{18}	V_{21}

Note: * V_n – value of a laboratory parameter.

Section 14.3.4 of the report (according to sections system of headings mentioned in this part of the document) shall provide the regulatory authorities with a list of all laboratory deviations by each patient, using aforementioned template. It is required to present additional info on the laboratory deviations of a special significance (laboratory deviations with potential clinical significance), e.g. normal values before and after the deviations, values of interconnected laboratory parameters. In some cases it is preferred to exclude some laboratory deviations from the consecutive analysis. For example, isolated non-recurring small deviations of some

laboratory parameters (e.g. uric acid concentration or electrolytes) or accidentally low values of some laboratory trials (e.g. activity of transaminase, alkaline phosphatase, concentration of nitrogen in uric blood and so on) can be evaluated as clinically insignificant and thus be discarded. But all such decisions shall be clearly justified, and every laboratory deviation shall be indicated in the presented (available for presentation upon the regulatory authority request) full list of values.

12.4.2. Evaluation of every laboratory parameter. The required evaluation of the laboratory values shall be determined by the results obtained, but, generally, the report shall provide results of the below-described analysis. In relation to every laboratory trial there shall be the trial and control groups comparison (if applicable and trial scale allows). Additionally the analysis shall specify a normal values range for each laboratory parameter.

12.4.2.1. Dynamics of laboratory factors through time. The following data shall be indicated in the report by each parameter in every period of time during the whole trial (e.g. during every visit): group mean indicator or median, span of values, a number of patients with values deviating from the norm (e.g. 2-times exceeding upper normal level, 5 times above the normal limit and this choice shall be justified). Graphs are allowed.

12.4.2.2. Individual changes. Each individual trial group changes analysis shall be presented. For that purpose various approaches may be applied, including:

Shift tables – tables reflecting a number of patients that are below, within or above the normal parameter values in defined intervals of time;

Tables containing information about quantity or ratio of patients with the laboratory parameter changed to a predetermined value in definite

intervals of time. For example, for nitrogen in blood urea a decision on necessity to describe it may have been made if its fluctuation exceeds 10mg/dL. For this parameter it was necessary to provide a number of patients with change exceeding or not exceeding the given limit during one or more visits, usually patients are grouped separately depending on the initial amount of nitrogen in blood urea (normal or high). Possible advantage of this method of presentation in the comparison with shift tables is ability to find changes of a certain value even if the end value is normal;

Graph comparing the initial value and laboratory parameters values observed during the treatment by each patient, in the form of a point defined by 2 coordinates: on X axis – initial laboratory parameters values, on Y axis – values of these parameters through time (after a therapy cycle). If there are no changes, then the point representing a patient shall be on a 45 degree line. General graphic shift towards high values will occur in the form of dot cluster above the 45 degree line. As such method of representation usually shows only 1 time point for 1 group, in order to interpret data, a series of such graphs through time for the trial and control groups. On the other hand, the mentioned method of presentation makes it possible to show the initial and most deviated values. It easily reveals outlying data (for that type of data it is recommended to indicate patients' identifiers).

12.4.2.3. Clinically significant individual deviations. It is necessary to analyze clinical changes defined as significant by an applicant. In sections 12.3.2 and 14.3.3 of the report (according to the system of headings of the report sections noted in the present part of the document) a description of every patient whose laboratory deviations were evaluated as a serious adverse event and in some cases as other serious adverse event shall be presented. When using toxicity level scale (e.g. WHO, NCI of USA) the changes qualified as severe shall be described regardless of severity. It is required to

provide by each parameter analysis of clinically significant changes and to give a short summary of therapy cancelation due to the clinical measurements. It is required to evaluate the significance of the changes and their cause-and-effect relationship with the studied therapy, for example, by analyzing such attributes as dose dependency, concentration of the medicinal product, disappearance during therapy, positive reaction to the cancelation, positive reaction to resuming and a concomitant therapy character.

12.5. Vital readings, objective trials data and other observations affecting safety. Similarly to laboratory specifications, vital readings, other objective trials data and other observations affecting safety shall be analyzed. If there are proofs of pharmacological effect, any sort of dependence on dose and concentration of the medicinal product or correlation with patient's characteristics (e.g. sickness, demographical data, concomitant therapy) shall be established, as well as description of observations clinical significance. In the analysis report a special attention shall be paid to the changes which were not categorized as efficacy variables, and thus evaluated as adverse events.

12.6. Opinion on safety.

General safety of the investigational medicinal product shall be analyzed by analyzing thoroughly the events resulted from a dose change, necessity of concomitant therapy, serious adverse events, and events occurred as a response to the therapy cancelation, and fatal outcomes. All patients or groups of patients at risk shall be revealed by analyzing thoroughly those of them who are potentially vulnerable and can be presented by a small amount of subjects (e.g. children, pregnant women, frail elderly people, patients with significant metabolic disease and drug clearance and so on). Consequences of the medicinal product possible administration safety evaluation shall be described.

13. Discussion and general conclusion

The results of efficacy and safety evaluation, benefit-risk balance shall be outlined and discussed with references to tables, pictures and corresponding parts of the report (if required). This part shall not be a simple citation of data overview or shall not introduce new data.

Discussion and summary shall clearly characterize all new and unforeseen data available after the trial, comment on its significance and discuss all potential problems, for example, contradictions between interrelated tests. A clinical value and significance of the results shall also be discussed on the basis of other data available. All specific advantages or special warnings required both for particular patients and risk groups shall be provided, as well as any consequences for further trials. Alternatively, the results of such discussions may be included in the summary of safety and efficacy as a part of the registration dossier (integrated summary).

14. Tables, pictures, graphs referred to but not included in the report text

Pictures shall be used for a graphical representation of the significant results or for explaining results difficult for comprehension, in the form of tables.

Significant demographical data, as well as efficacy and safety data, shall be provided in the consolidated pictures and tables in the report text. If for some reason that is impossible to do, for example, because of dimensions or quantity, they shall be presented in this section of the report with cross-references to the text, as well as supplementary and additional pictures, tables or lists.

In this section of the clinical trial report the following information can be presented:

14.1. Demographical data (summary pictures, tables).

14.2. Efficacy data (summary pictures, tables)

14.3. Safety data (summary pictures, tables):

adverse events data;

list of death cases and other serious and significant adverse events;

description of death cases and other serious and some other significant adverse events;

list of the clinical trial readings deviating from the norm (per each patient).

15. Reference list

A list of research articles from the literature relating to the trial results evaluation shall be presented. Copies of significant publications shall be provided in additions to supplement 16.1.11 and 16.1.12 to the report (according to sections system of headings mentioned in this part of the document). Reference to the literature shall be presented in accordance with the international standards (Vancouver declaration of 1979 «Uniform Requirements for Manuscripts Submitted to Biomedical Journals»), international standard GOST 7.1-2003 («Bibliographic record. Bibliographic description. General requirements and rules of composition») or the system applied in «Chemical Abstracts» abstract journal.

16. Supplements

This part shall provide a list of all the supplements presented in the clinical trial report. If approved by the regulatory authority, there is no need to present certain supplements in the report, but those shall be ready for submission upon demand. An applicant shall clearly state the supplements to be presented with the report. To make supplements accessible upon demand,

it is necessary to have them finally approved by the time of the report submission to the regulatory authority.

Report supplements are listed in the following order and are numbered with the following system of headings:

16.1. Information about a clinical trial:

16.1.1. Protocol and amendments to the protocol;

16.1.2. Example of a case report form;

16.1.3. list of IRBs, examples of a written information for patients and forms for the informed consent;

16.1.4. a list and characteristics of investigators and other responsible persons of the trial, including a short CV (1 page) or an equivalent description of education and work experience associated with the clinical trial procedure;

16.1.5. signatures of head investigators, coordinating investigators or sponsor's representative in charge – depending on regulatory authority requirements;

16.1.6. in case of using more than one series of the investigational medicinal product – lists of codes of patients who took products of different series;

16.1.7. randomization schedule and codes (patients' identification and prescribed therapy);

16.1.8. Audit certificate (if conducted);

16.1.9. Statistical methods documentation;

16.1.10. Documentation on inner laboratory standardization methods and quality assurance procedures (if conducted);

16.1.11. Publications based on this trial;

16.1.12. Significant publications referred to in this report.

16.2. List of data by trial subjects:

16.2.1. a list of the subjects early discontinued;

16.2.2. protocol deviations;

16.2.3. the patients excluded from the efficacy analysis;

16.2.4. Demographical data;

16.2.5. treatment regimen compliance and (or) medicinal product concentration data (if available);

16.2.6. individual data on efficacy;

16.2.7. a list of the adverse events (by each subject);

16.2.8. a list of individual parameters of the patient clinical studies, if required by the regulatory authority.

16.3. Case report form (CRF).

16.3.1. CRF on death cases, other serious adverse events and cases of patient withdrawal from clinical study due to adverse events development;

16.3.2. Other CRFs submitted for review.

16.4. List of data by each trial subject.

APPENDIX №2

to Good Clinical Practice Regulations
of the Eurasian Economic Union

SYNOPSIS TEMPLATE
(A BRIEF DESCRIPTION OF CLINICAL STUDY)

<table>
<tr><td>Name of Sponsor/Company:</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:</td></tr>
<tr><td>Name of Active Ingredient:</td></tr>
<tr><td colspan="3">Title of study:</td></tr>
<tr><td colspan="3">Investigators:</td></tr>
<tr><td colspan="3">Study Center(s):</td></tr>
<tr><td colspan="3">Publication (reference):</td></tr>
<tr><td colspan="2">Studied period (years):
(date of first enrolment)
(date of last visit)</td><td>Phase of development:</td></tr>
<tr><td colspan="3">Objectives:</td></tr>
<tr><td colspan="3">Methodology:</td></tr>
<tr><td colspan="3">Number of patients (planned and analyzed):</td></tr>
<tr><td colspan="3">Diagnosis and main criteria for inclusion:</td></tr>
<tr><td colspan="3">Test product, dose and mode of administration, batch number:</td></tr>
<tr><td colspan="3">Duration of treatment:</td></tr>
<tr><td colspan="3">Reference therapy, dose and mode of administration, batch number:</td></tr>
</table>

<table>
<tr><td>Name of Sponsor/Company:</td><td rowspan="4">Individual Study

Table Referring to

Part of the

Dossier

Volume:

Page:</td><td rowspan="4">(For National Authority Use Only)</td></tr>
<tr><td>Name of finished product:</td></tr>
<tr><td>Name of active ingredient:</td></tr>
<tr><td colspan="2">Criteria for evaluation:
Efficacy:

Safety:</td></tr>
<tr><td colspan="3">Statistical methods:</td></tr>
<tr><td colspan="3">SUMMARY — CONCLUSIONS

EFFICACY RESULTS:

SAFETY RESULTS:

CONCLUSION:

Date of the report:</td></tr>
</table>

APPENDIX №3

to Good Clinical Practice Regulations
of the Eurasian Economic Union

Template of page of signature principal investigator
or coordinating investigator

PRINCIPAL INVESTIGATOR OR COORDINATING INVESTIGATOR(S) SIGNATURE(S) OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

_____

STUDY TITLE: .....

STUDY AUTHOR(S): .....

I have read this report and confirm that to the best of my knowledge of this study it accurately describes the conduct and results of the study.

INVESTIGATOR:_____SIGNATURE(S) _____
OR SPONSOR'S RESPONSIBLE
MEDICAL OFFICER

AFFILIATION: _____ _____

_____

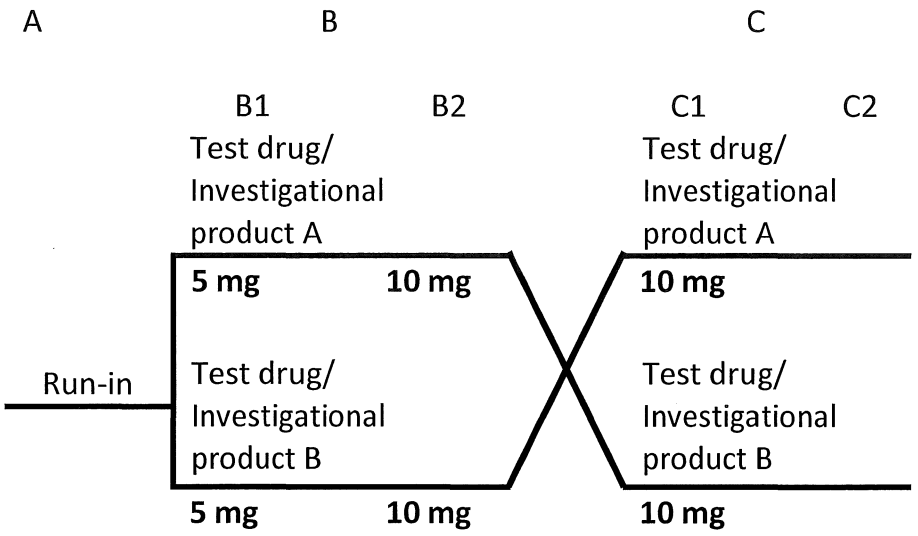
DATE: _____

APPENDIX №4

to Good Clinical Practice Regulations
of the Eurasian Economic Union

Plan and study design templates

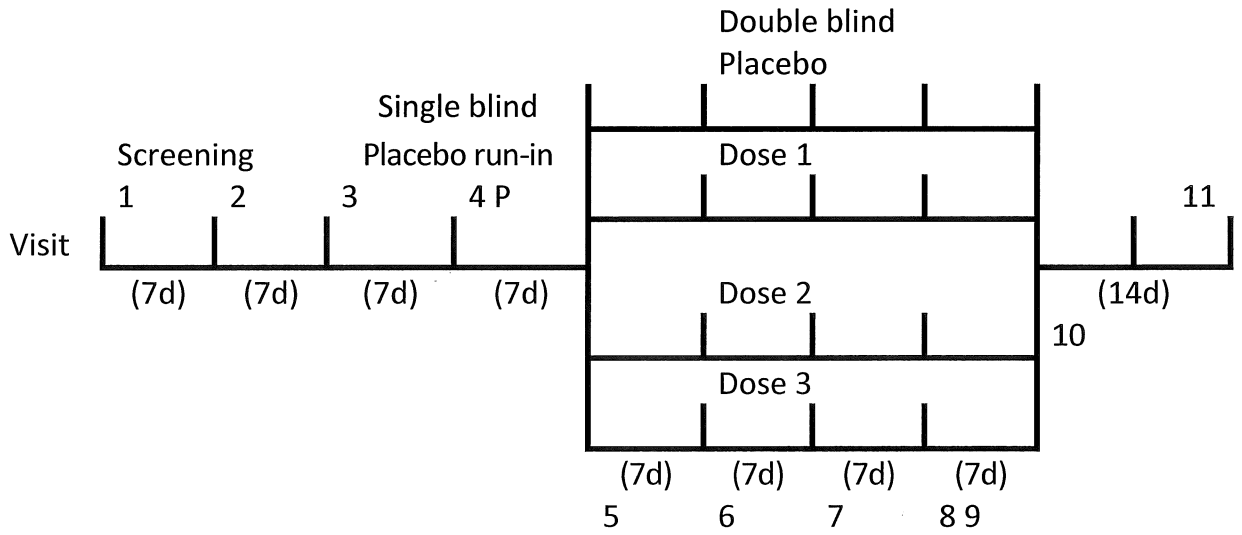
1. STUDY PLAN AND SCHEDULE OF ASSESSMENTS



Weeks	-2 (-3)		0	3	6	9	12
Visit	1		2	3	4	5	6
Exercise test 24 h		X[1]	X[2]	X	X	X	X
Medical history	X						
Physical examination	X						X
ECG	X						X
Lab. investigations	X						X
Adverse events			X	X	X	X	X

[1] — *14-20 days after visit 1*
[2] — *1-7 days after the first exercise test*

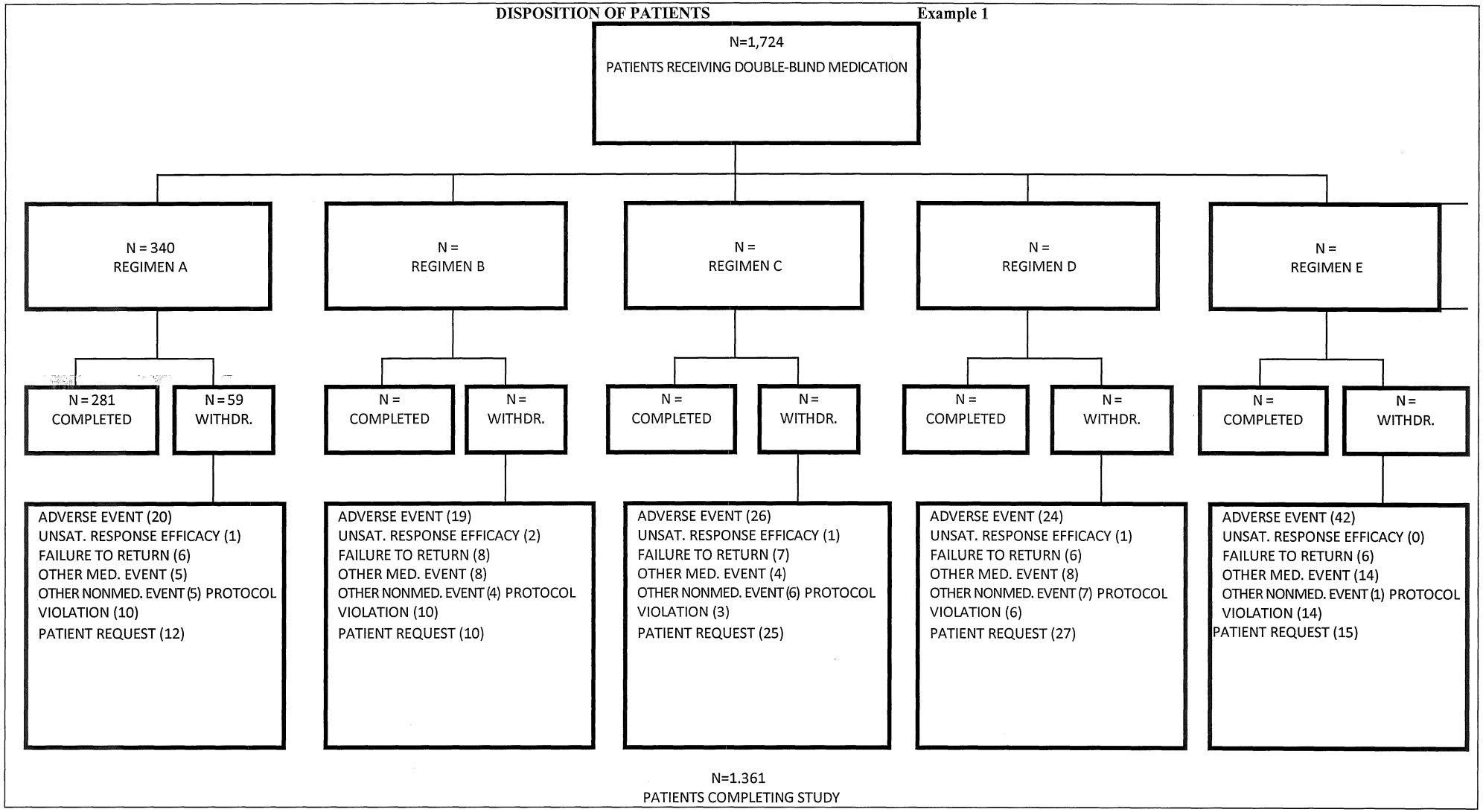
2. STUDY DESIGN AND SCHEDULE OF ASSESSMENTS



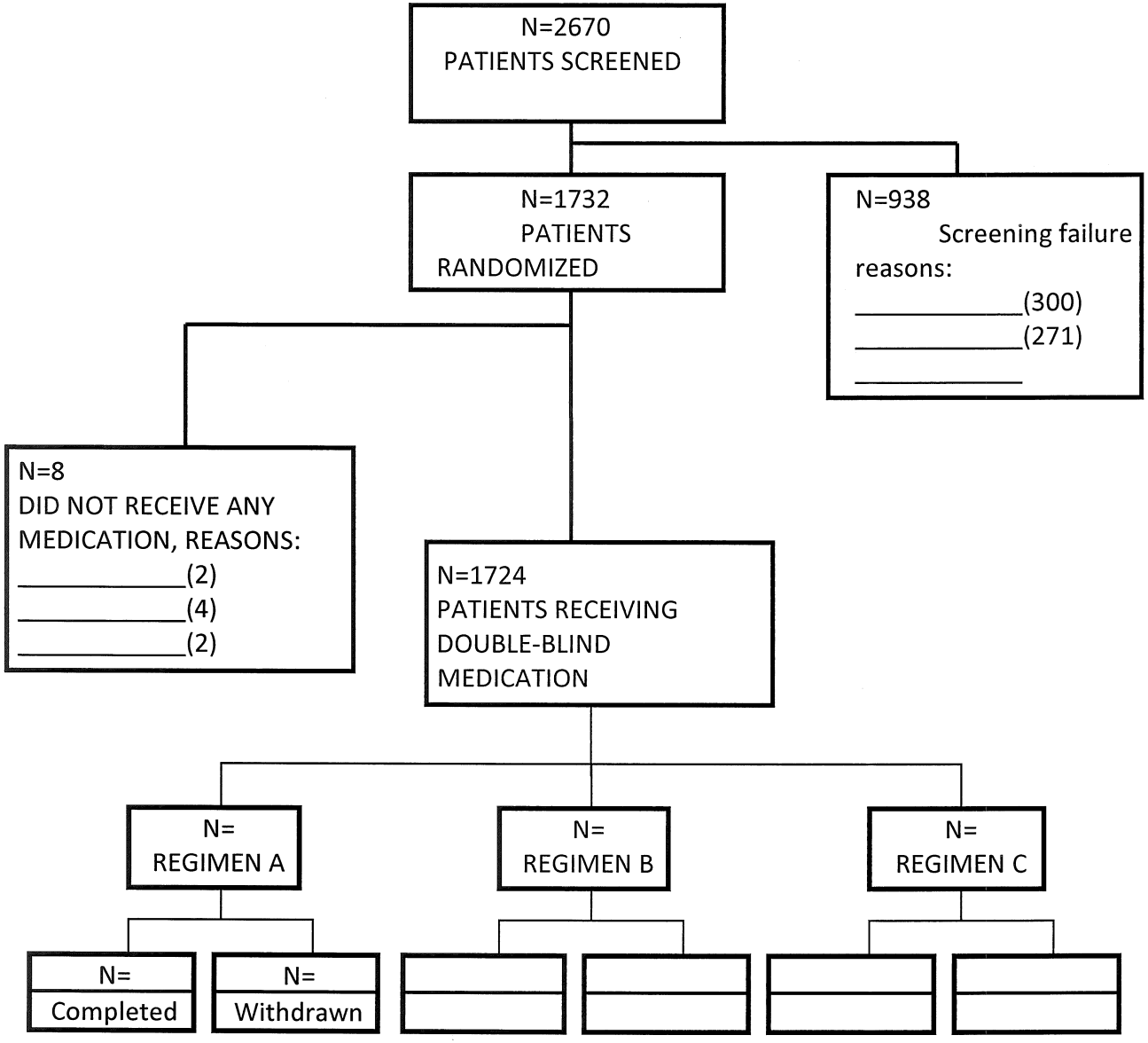
Assessment	Screening	Run-in	Baseline	Treatment				Follow-up		
Week	-2	-1	0	1	2	3	4	5	6	7
Informed cons.	X									
History	X									
Physical exam.	X									X
Effectiveness:										
Primary variable	X	X	X	X	X	X	X	X	X	X
Secondary variable	X	X	X	X		X			X	X
Safety:										
Adverse events	X	X	X	X	X	X	X	X	X	X
Lab. tests	X	X	X			X		X	X	
Body weight	X		X						X	X

APPENDIX №5
to Good Clinical Practice Regulations
of the Eurasian Economic Union

DISPOSITION OF PATIENTS TEMPLATE



DISPOSITION OF PATIENTS TEMPLATE **example 2**



ADVERSE EVENT (20)
UNSATISFACTORY RESPONSE (32)
etc. .....
etc. .....

APPENDIX №6
to Good Clinical Practice Regulations
of the Eurasian Economic Union

LISTING OF PATIENTS WHO DISCONTINUED THERAPY TEMPLATE

STUDY No.
(Data Set Identification)
LISTING OF PATIENTS WHO DISCONTINUED THERAPY

Center:

Treatment	Patient No.	Sex	Age	Last visit	Duration	Dose	Concomitant medication	Reason for discontinuation
Test drug/ Investigational product								Adverse reaction* • • • Therapy failure
Treatment	Patient No.	Sex	Age	Last visit	Duration	Dose	Concomitant medication	Reason for discontinuation
Active control/Comparator								
Treatment	Patient No.	Sex	Age	Last visit	Duration	Dose	Concomitant medication	Reason for discontinuation
Placebo *(Repeat for other centers)*								

* *The specific reaction leading to discontinuation*

APPENDIX №7

to Good Clinical Practice Regulations
of the Eurasian Economic Union

LISTING OF PATIENTS AND OBSERVATIONS EXCLUDED FROM EFFICACY ANALYSIS TEMPLATE

STUDY No.
(Data Set Identification)

LISTING OF PATIENTS AND OBSERVATIONS EXCLUDED FROM EFFICACY ANALYSIS

Center:

Treatment	Patient No.	Sex	Age	Observation excluded	Reasons
Test drug/ Investigational product					
Treatment	Patient No.	Sex	Age	Observation excluded	Reasons
Active drug/Comparator					
Treatment	Patient No.	Sex	Age	Observation excluded	Reasons
Placebo					

(Repeat for other centers)

Reference tables

Summary:

APPENDIX №8

to Good Clinical Practice Regulations
of the Eurasian Economic Union

NUMBER OF PATIENTS AND OBSERVATIONS EXCLUDED FROM EFFICACY ANALYSIS TEMPLATE

STUDY No.
(Data Set Identification)

NUMBER OF PATIENTS EXCLUDED FROM EFFICACY ANALYSIS

Test drug/Investigational product N =

	Week			
Reason	**1**	**2**	**4**	**8**
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
Total _____	_____	_____	_____	_____

Similar tables should be prepared for the other treatment groups.

APPENDIX №9
to Good Clinical Practice Regulations
of the Eurasian Economic Union

REQUIREMENTS

to section 11.4.2 "statistical/analytical aspects"

of clinical trial report and

of the appendix 16.1.9 to clinical trial report

I. Statistical Analysis

The appendix should provide a detailed description of statistical analysis for each primary endpoint. Minimum requirements for the detailed report include:

a) The statistical model forming the basis for the analysis. It is subject to careful and comprehensive description, accompanied by literature references, where appropriate.

b) Statement of the clinical study's hypothesis in explicit statistical terms, e.g., in terms of null and alternative hypotheses.

c) Statistical methods used to evaluate the effect, to generate confidence intervals etc. Where applicable, literature references should be listed.

d) Assumptions underpinning statistical methods. It is essential to demonstrate (as far as statistical calculations provide basis for it) that the results support key assumptions, especially when the need arises to justify the conclusions. If the applicant has performed extensive statistical analyses, it is necessary to compare them to those planned prior to the study. If they are not equivalent to one another, it is necessary to describe how in drawing the conclusions the particular method of analysis was chosen to eliminate subjective error. This is of particular importance for subgroup analysis because if not planned, such analyses usually do not provide any valid basis for definite conclusions. However:

If event data have been transformed, justification of data transformation should be provided together with interpretation of treatment outcomes evaluation based on the transformed data.

Discussion of adequacy of statistical procedures employed as well as the validity of statistical conclusions will be a benchmark for a regulatory statistician in determining relevance of data reanalysis.

e) Significance test, sampling distribution for significance test when null hypothesis is found to be true, significance test values, confidence level (i.e., p-value) and interim cumulative results in a form suitable to quickly and easily verify the analysis results. It is necessary to state whether p-values are one- or two-tailed. It is essential to justify the use of one-tailed tests.

f) Student's test analysis (t-test) should include t-statistics values, associated degrees of freedom, p-value, sizes of two samples (groups), mean and variance of two samples, pooled estimate of variance. Documentation of multi-center studies analyzed using analysis-of-variance should, at minimum, contain the following information: table for analysis-of-variance with highlighted centers, drug products, the interaction effect of these factors, residual and total variance. For studies with cross-over design, the documentation should include data on sequence assignment, patients in each sequence, baseline values for each period, wash-out and period of wash-out, drop-outs in each period, drug products, periods, variance due to interaction of these factors (drug products and periods), residual and total variance. For each variation source (excluding total variance) the table should list degrees of freedom, sum of squares, quadratic mean, appropriate F-test, p-value and mean sum of squares.

g) At each time point of observations, interim cumulative results should take into account demographic data as well as data on treatment responses (averaged or otherwise combined) by each combination "center-treatment" (or other aspect of design, e.g., sequence).

II. Format and contents of information required for submission to regulatory authority in response to regulatory request from expert statistician

2. Each controlled clinical trial report should contain listings (tabular) of patients, included in statistical analysis by the sponsor and tables supporting conclusions and major findings. These listings are necessary for the regulatory statistician, therefore regulatory authorities have a right to request such data in an electronic format from the sponsor.

APPENDIX №8

to Good Clinical Practice Regulations
of the Eurasian Economic Union

NUMBER OF PATIENTS AND OBSERVATIONS EXCLUDED FROM EFFICACY ANALYSIS TEMPLATE

STUDY No.
(Data Set Identification)

NUMBER OF PATIENTS EXCLUDED FROM EFFICACY ANALYSIS

Test drug/Investigational product N =

	Week			
Reason	**1**	**2**	**4**	**8**
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
_____	_____	_____	_____	_____
Total _____	_____	_____	_____	_____

Similar tables should be prepared for the other treatment groups.

APPENDIX №7

to Good Clinical Practice Regulations
of the Eurasian Economic Union

LISTING OF PATIENTS AND OBSERVATIONS EXCLUDED FROM EFFICACY ANALYSIS TEMPLATE

STUDY No.
(Data Set Identification)

LISTING OF PATIENTS AND OBSERVATIONS EXCLUDED FROM EFFICACY ANALYSIS

Center:

Treatment	Patient No.	Sex	Age	Observation excluded	Reasons
Test drug/ Investigational product					

Treatment	Patient No.	Sex	Age	Observation excluded	Reasons
Active drug/Comparator					

Treatment	Patient No.	Sex	Age	Observation excluded	Reasons
Placebo					

(Repeat for other centers)

Reference tables

Summary:

APPENDIX №6
to Good Clinical Practice Regulations
of the Eurasian Economic Union

LISTING OF PATIENTS WHO DISCONTINUED THERAPY TEMPLATE

STUDY No.
(Data Set Identification)
LISTING OF PATIENTS WHO DISCONTINUED THERAPY

Center:

Treatment	Patient No.	Sex	Age	Last visit	Duration	Dose	Concomitant medication	Reason for discontinuation
Test drug/ Investigational product								Adverse reaction* • • • Therapy failure
Treatment	Patient No.	Sex	Age	Last visit	Duration	Dose	Concomitant medication	Reason for discontinuation
Active control/Comparator								
Treatment	Patient No.	Sex	Age	Last visit	Duration	Dose	Concomitant medication	Reason for discontinuation
Placebo *(Repeat for other centers)*								

** The specific reaction leading to discontinuation*

APPENDIX №10
to Good Clinical Practice Regulations
of the Eurasian Economic Union

THE LIST
of Amendments to the Clinical Trial Sections That Are Regarded as Substantial

1. When amending the sections of the clinical trial protocol, the sponsor should assess the significance of the amendment with respect to the risks and anticipated benefits for the study patient as well as with respect to scientific value in order to consider whether an amendment is a substantial one.

2. Amendments to the clinical trial sections shall be regarded as "substantial" where they are likely to have an impact on:

a) the safety or physical or mental integrity of the subjects

b) scientific value of the study.

3. The following changes may be regarded as substantial amendments to the clinical trial sections[1].

4. Amendments related to the trial protocol:

Purpose of trial;

Design of trial;

Informed consent;

Recruitment procedure;

Measures of efficacy;

Schedule of samples;

[1] Other amendments to the clinical trial sections shall be considered non-substantial.

Addition or deletion of tests or measures;

Number of subjects (patients);

Age range of subjects (patients);

Inclusion criteria;

Exclusion criteria;

Safety monitoring;

Duration of exposure to the investigational medicinal product(s);

Change of posology of the investigational medicinal product(s);

Change of comparator;

Statistical analysis.

5. Amendments related to the clinical trial arrangements:

Change of the principal investigator or addition of new ones;

Change of the coordinating investigator;

Change of the trial site (medical institution) or addition of new sites (medical institutions);

Change of sponsor or legal representative;

Change of the CRO responsible for significant tasks;

Change of the definition of the end of the trial.

6. Changes to investigational medicinal product data concerning:

Immediate packaging material;

Manufacturer(s) of active substance;

Manufacturing process of the active substance;

Specifications of active substance;

Manufacture of the investigational medicinal product;

Specification of the investigational medicinal product;

Specification of excipients where these may affect product performance;

Shelf-life including after first opening and (or) reconstitution;

Major change to the formulation;

Storage conditions;

Test procedures of active substance;

Test procedures of the investigational medicinal product;

Test procedures of non-pharmacopoeial excipients.

7. Changes to non-clinical data where the risk-benefit assessment is altered. Amendments to non-clinical pharmacology and toxicology data where this is relevant to the ongoing clinical trials with the altered risk-benefit assessment. For example concerning:

Results of new pharmacology tests;

New interpretation of existing pharmacology tests;

Result of new toxicity tests;

New interpretation of existing toxicity tests;

Results of new interaction studies.

8. Changes to clinical trial data where the risk-benefit assessment is altered. Amendments to clinical trial and human experience data where this is relevant to the ongoing clinical trials with the altered risk-benefit assessment. For example concerning:

Safety related to a clinical trial or human experience with the investigational medicinal product;

Results of new clinical pharmacology tests;

New interpretation of existing clinical pharmacology tests;

Results of new clinical trials;

New interpretation of existing clinical trial data;

New data from human experience with the investigational medicinal product;

New interpretation of existing data from human experience with the investigational medicinal product.

9. The procedure for consideration of amendments to the clinical trial

sections by the regulatory authorities shall be determined by the requirements in accordance with the national law of the Member States of the Eurasian Economic Union.

APPENDIX №11
to Good Clinical Practice Regulations
of the Eurasian Economic Union

GUIDELINES
on safety reporting in the course of clinical trials

1. Responsibilities of the Sponsor on submission of safety information in the course of a clinical trial

1.1. Arrangement of a system of written standard procedures

The sponsor should arrange for systems and written standard operating procedures to ensure compliance with the necessary quality standards at every stage of case documentation, data collection, validation, evaluation, archiving, reporting and following-up for adverse reactions identified during clinical trials.

1.2 Reporting timelines for serious unexpected adverse reactions.

1.2.1 The sponsor shall submit information about all serious unexpected adverse reactions (SUAR) for investigational product arising from clinical trials, approved on the territory of Member State of EurAsian Economic Union (further referred as EAEU) to the competent authority of Member State where the clinical trial is conducted, and to the Institution Review Board (Independent Ethics Committee) (further referred as IRB (IEC)) of relevant clinical sites in accordance to the IRB (IEC) procedures:

no later than 7 calendar days after knowledge by the sponsor of SUAR that are fatal or life-threatening;

no later than 15 calendar days after knowledge by the sponsor of SUAR for all other serious unexpected adverse reactions.

1.2.2. In case of incomplete information at the time of expedited reporting of a fatal or life threatening case the sponsor should actively sought for full information which is subsequently communicated as a follow-up expedited report on serious unexpected adverse reaction within an additional 8 calendar days after submission of initial report.

1.2.3. If significant new information on an already reported serious unexpected adverse reaction is received by the sponsor, this information should be reported as a follow-up report within 15 calendar days from the date of its receipt.

1.2.4. Requirements for reporting of serious unexpected adverse reactions are applicable to investigational products, including comparators and placebo.

1.3. Requirements to information on a serious unexpected adverse reaction.

1.3.1. Required minimum information on a serious unexpected adverse reaction.

The minimum information for submission of initial report on a serious unexpected adverse reaction within designated timelines includes:

suspected study drug, identifiable coded subject of a trial, who had adverse reaction;

description of an adverse reaction or its outcome, which is identified as serious and unexpected and which is supposed to have a causal relationship to administration of a study drug;

a causality assessment;

source of information on a serious unexpected adverse reaction;

safety report unique identifier assigned by the Sponsor;

study number.

1.3.2. Full information on a serious unexpected adverse reaction.

Further collection and reporting of full follow-up information on case of a serious unexpected adverse reaction which must comply with The International Conference on Harmonization "Guideline On Clinical Safety Data Management: Data Elements For Transmission Of Individual Case Safety Reports" E2B should be organized.

1.4. Reference safety information

1.4.1 Reference study drug safety information

The current IB that is valid on the date of observing a serious adverse reaction (SAR) to the study drug is used to determine the expectedness of the SAR identified during the clinical trial.

1.4.2. The reference safety information on approved medicinal product.

The current version of prescribing information is used to determine the expectedness identified during a clinical trial SAR to a medicinal product approved for marketing in a country where SAR was identified.

1.5. Reporting of other safety information

The sponsor shall submit other safety information that may alter the current benefit-risk assessment of a study drug or be the reason for changing prescribing information as well as the reason for reconsidering the further conduct of the clinical trial, to the competent authority of Member State where the clinical trial is conducted and to the IRB (IEC) of relevant clinical sites in accordance to the IRB (IEC) procedures within 15 calendar days after knowledge by the sponsor of such information:

a) clinically significant increase of expected frequency and modification of expected serious adverse reactions;

b) serious unexpected adverse reactions observed in a subject after completion of participation in the clinical trial;

c) new events related to the conduct of a trial or the development of an IMP likely to affect the safety of subjects, such as:

a serious adverse events which could be associated with the trial procedures and which could modify the conduct of the trial,

lack of efficacy of a study drug used for the treatment of a life-threatening condition,

a major safety finding from a newly completed animal study (such as carcinogenicity or effects of similar seriousness and importance),

a temporary halt of a trial for safety reasons if the trial is conducted with the same study drug in another country (countries) by the same sponsor,

other safety information that changes the benefit risk ratio for the study subjects;

d) recommendations of the independent data safety monitoring board for the safety of a study drug.

1.6. Format of safety reporting

1.6.1 Format of reporting about serious unexpected adverse reactions to authorities of the Member States and IRB (IEC).

Information about serious unexpected adverse reactions is reported to the competent authority of Member States and IRB (IEC) by sponsor in the form of an adverse reaction report. The Report format should correspond to the ICH E2B guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports.

1.6.2. Format of reporting about serious unexpected adverse reactions to investigators

The information about serious unexpected adverse reactions is reported to investigators as a summary with a brief description of adverse reactions for the period defined by the study drug safety profile and the number of determined serious unexpected adverse reactions. This listing should be accompanied by a concise summary of the evolving safety profile of the study drug for the reporting period.

1.6.3. Format of reporting about other safety information

Other safety information according to paragraph 5 of the current appendix is reported to the competent authority of Member States and IRB (IEC) by sponsor in written form specifying the title of the clinical trial, the number of the study protocol and a brief description of new safety data.

1.7. Scope of safety reporting requirements

1.7.1 Reporting requirements for identified serious unexpected adverse reactions and other study drug safety information in accordance with paragraphs 1.2 - 1.5 of the current appendix are true for clinical trials approved on the territory of the Member State, for all study sites where the Sponsor or its partner, on the basis of a formal agreement, performs the clinical trial of the study drug including study sites that are located outside of the territory of the Member States.

1.7.2. Reporting requirements for identified serious unexpected adverse reactions in accordance with paragraph 1.2 of the current appendix are related to clinical trials conducted by the Sponsor or its partner, on the basis of a formal agreement, approved on the territory of the Member State where the study drug contains the same active substance (regardless of pharmaceutical form, strength, administration or indication investigated).

1.8 Serious adverse reactions not related to a study drug.

Sponsor shall report information about serious adverse reactions identified during clinical trial and considered as related to approved medicinal products that are not study drugs and administered as a concomitant treatment, to the competent authorities of Member States or to the marketing authorization holders according to the legislation of these Member States, in case there is no interaction with the study drug.

1.9 Unblinding treatment allocation.

1.9.1 Requirements of unblinding treatment allocation in case of a serious unexpected adverse reaction.

When the adverse event considered as a serious unexpected adverse reaction is reported, the sponsor should unblind the treatment allocation only for specific study subject with that adverse reaction. The sponsor should comply with the requirements of paragraph 1.2 of the current appendix for prompt reporting information about the identified serious unexpected adverse reaction to the competent authority of Member State considering the results of unblinding treatment allocation. The blind should be maintained by the sponsor for persons responsible for the ongoing conduct of the study (such as monitors, investigators) and those responsible for data analysis. Unblinded information on adverse reactions should only be accessible to those who need to be involved in the safety reporting to the competent authorities of the Member States, representatives of national competent authorities of Member States; members of IRB (IEC), members of Data Safety Monitoring Board or other persons performing continuous safety evaluations during the trial. The investigator should only unblind the treatment allocation in the course of a clinical trial if this is relevant to the safety of the study subject.

1.9.2. The results of unblinding treatment allocation are appropriately entered into the database of the sponsor and the appropriate authorities of the Member States. The safety data of the Investigator's brochure is updated based on the unblinded data analysis.

1.9.3. Special populations

For trials in high morbidity or high mortality disease, where efficacy endpoints could also be serious unexpected adverse reactions or when mortality or another 'serious' outcome is the study drug efficacy endpoint in a clinical trial, the validity of the clinical trial results may be compromised if the blind is systematically broken. Under these and similar circumstances, the sponsor should reach agreement with the competent authority of the Member State in the authorization process as to which serious events would be treated as disease-related and not subject to systematic unblinding and expedited reporting to the competent authority of the Member State. In these cases it is obligatory to appoint and ensure function of an independent data safety monitoring board in order to review safety data on the ongoing trial on a regular basis and when necessary to recommend to the sponsor whether to continue the trial, modify the protocol or terminate the trial.

Annual safety reporting

Once a year throughout the clinical trial, the sponsor shall provide the competent authority of the Member States in whose territory the clinical trial is being conducted with Periodic Safety Report (Periodic Safety Reports) of the study drug that should meet the requirements listed in Appendix 12 to the Rules on Good Clinical Practice of the EurAsian Economic Union.

Information about Periodic Safety Report of the study drug is submitted to IRB (IEC) in the form of a summary with structured listing of serious adverse reactions in accordance with Appendix 12 to the Rules on Good Clinical Practice of the EurAsian Economic Union.

2. Responsibilities of investigator in reporting information about adverse reactions identified during the clinical trial.

2.1 Safety information reporting to the sponsor

2.1.1. The investigator shall report all serious adverse events immediately, within 24 hours after the information becomes available, to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting.

The immediate report about a serious adverse event shall be followed by detailed written reports about the serious adverse event that allow the sponsor to assess the benefit-risk balance of the clinical trial.

2.1.2. Investigator should report to the Sponsor the information about adverse reactions and laboratory abnormalities defined in the study protocol as crucial for the safety assessment within the time periods specified in the protocol of the clinical study.

2.2. Reporting safety information to the authorities of the Member States

Additional requirements for reporting of identified serious adverse reactions to the study drug that are not reviewed in the current appendix, are determined by the legislation of the Member State.

APPENDIX №12
to Good Clinical Practice Regulations
of the Eurasian Economic Union

REQUIREMENTS

to Development Safety Update Report

1. Definitions

For the purposes of the present Requirements the words and expressions used have the following definitions:

"Important identified risk" and "important potential risk" are defined as an identified risk or potential risk that could have an impact on the risk-benefit balance of the drug product or have implications for public health.

"Data lock point" is the date designated as the deadline for data to be included in a DSUR for the medicinal product of interest.

"Completed clinical trial" is a clinical trial for which a final clinical study report is available.

"Identified risk" is an undesirable implication resulting from a medication-assisted treatment for which there is adequate evidence of an association with the suspected medicinal product.

"Interventional clinical trial" refers to any clinical research study that prospectively assigns people to one or more medical interventions (e.g., preventive intervention, drug prescription, the delivery of surgical interventions, behavioral therapy etc.) to assess the impact of these interventions on health outcome measures.

"Investigational drug" is one being under development by a pharmaceutical company. Within the present Appendix this term is more narrow in relation to that used in the text of Guidelines for Good Clinical Practice of the Eurasian Economic Union and does not apply to active comparators and placebo.

"Development international birth date" (DIBD) is the date of the first authorization to conduct interventional clinical trial in any country of the world.

"Adverse event of special interest" is one of scientific and medical concern specific to the investigational drug or sponsor's investigational program which can require from the investigator ongoing monitoring activities and immediate provision of information. These adverse event data may require further studies in order to properly characterize and assess these data. Depending on the adverse event of special interest it could require expedient provision of sponsor's information by a third party (e.g., to the regulatory authorities of the Member States of the Eurasian Economic Union).

"Non-interventional clinical study" is a study (trial) which complies with the following criteria:

– drug product is administered according to the labeling instructions;

– the assignment of the patient to a particular medication is not decided in advance by a trial protocol but falls within current practice and the prescription of the drug product is clearly separated from the decision to include the patient in the study;

– no additional diagnostic or control procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.

"Anticipated efficacy (benefit)" is efficacy (benefit) that has not yet been established for the investigational drug but which is anticipated based on efficacy (benefit) knowledge of the class of drugs or data from previous clinical trials or non-clinical studies.

"Clinical development programme" refers to the total of all clinical trials with the same investigational drug, regardless of indications or formulation.

"Ongoing clinical trial" is a trial where subject enrollment has begun, whether a hold is in place or analysis is complete, but for which a final clinical study report is not available yet.

"Potential risk" is an undesirable implication of medication-assisted treatment for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been properly confirmed.

"Registry" is defined as pooled data from patients presenting with the same characteristic(s). This characteristic may be a disease (disease registry) or a specific exposure (drug registry). Registry is aimed to collect certain patient data set using standardized questionnaires in a prospective fashion (Drug registries are focused on data collection over time on populations exposed to drugs of interest and/or specific populations. Patients can be included in a cohort study aimed at adverse event data collection using standardized questionnaire(s). Registries can be useful for signal amplification, particularly of rare outcomes.

"Signal" is defined as information arising from one or multiple sources that suggests a new potentially causal association, or a new aspect of a known association, between an exposure to drug product or set of related adverse events, that is judged to be sufficient to justify further action to verify the signal.

"Sponsor-investigator" is an individual who both initiates and conducts, alone or with other investigators, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

2. Background

Periodic analysis of safety data during clinical development of the investigational product is critical for ongoing risk assessment of study subjects. It is essential to ensure regular reporting to regulatory authorities of the Member States of the Eurasian Economic Union (hereinafter referred to as regulatory authorities, Member States, Union) and other concerned parties (e.g., Institutional Review Board (Independent Ethics Committee) (further in the text – IRB (IEC)) of the analysis results and the new data on safety profile of the investigational product as well as notification of action taken relating to all the emerging safety issues. Development Safety Update Report (DSUR) is a standard for periodic clinical trial safety reporting on developed (study) products (including authorized products for which development is ongoing) of the Member States.

The main purpose of DSUR is to provide comprehensive and profound annual review and assessment of safety information for the investigational product collected within the reporting period regardless of its registration status by way of:

– assessment of potential differences between safety information collected by the sponsor during the reporting period and previous knowledge on the safety profile of the investigational product;

– description of emerging aspects relevant to safety profile, that can potentially impact safety of the study subjects;

– generalization of data on current assessment and management of identified and potential risks;

– update of clinical development (development programme) status and study results.

DSUR should be concise and provide the regulatory authorities of Member States with information sufficient to ensure proper monitoring and assessment of safety profile data of the investigational product. All the safety profile aspects that have emerged during the reporting period are subject to DSUR. It should not be used for initial notification of any significant new safety issues or to identify new aspects of safety profile.

Results and other data relating to clinical studies of drug products and biological active substances regardless of their registration status is the main information to be included in DSUR. In case of post-marketing clinical development of a drug product, DSUR shall also include post-marketing studies data. The aim of DSUR is the assessment of investigational product; data on active comparators and placebo should be included only if it's relevant to the safety of subjects in the study.

DSUR should contain data from all the ongoing clinical trials and other sponsored studies whether ongoing or completed during the reporting period, including but not limited to:

– clinical trials conducted using investigational product (human pharmacology, therapeutic exploratory and therapeutic confirmatory trials (Phase I – III));

– clinical trials conducted using marketed drug in approved indications (therapeutic use trials (Phase IV));

– therapeutic use of the investigational drug (e.g. within expanded access or individual access programmes and others);

– clinical studies conducted to support drug manufacturing changes.

DSUR also includes other data significant in terms of investigational product safety, in particular:

– observational and epidemiological trials;

– non-clinical trials (toxicological and in vitro studies);

– other DSURs relevant to the investigational product;

– manufacturing and microbiological changes;

– recently published in medical literature;

– clinical trials that revealed lack of efficacy potentially having a direct impact on subjects' safety (e.g. worsening of underlying disease in case of serious or life-threatening medical condition);

– other safety data sources on the drugs of the equivalent therapeutic class;

– clinical trials conducted by co-development partners as specified by contracts.

3. General principles

3.1. Single DSUR for an active substance

In order to ensure comprehensive analysis and safety data presentation, the sponsor shall submit a single DSUR, including data for all galenic formulations, dosages, indications, study populations (wherever deemed possible). When it is not possible (e.g., sponsor has no access to the data, an appropriate explanation should be provided in the introductory part of the report.

When there is more than one sponsor, e.g., in case of co-development or based on other contracts, the parties could arrange to prepare a single DSUR.

3.2. Periodicity of DSUR submissions and data lock point

The annual period for DSUR starts from development international birth date (hereinafter referred to as DIBD). The month and date of DIBD is the reference date of the annual period for DSUR submission.

When the first clinical trial is conducted in a country having no legal procedure for clinical trials approval, the sponsor should set the appropriate date related to the start of the first clinical trial. For all the countries in which clinical trials of the investigational product are being conducted, a single DIBD is used for each DSUR.

Data lock point for DSUR corresponds to the last day of the period covered by the report that equals to 1 year. For the ease of administrative procedures, if desired by the sponsor, the data lock point may be established as the last day of the month preceding to DIBD.

If clinical development programme of a drug in a Member State after its national authorization procedure is ongoing, in accordance to the legal requirements of the Member States both DSURs and periodical safety update reports (further in the text – PSURs) for investigational product should be submitted as appropriate. If desired by the sponsor, DSUR could be prepared based on the international birth date (further in the text – IBD) used for the PSUR, so that the submission of both DSUR and PSUR can be synchronized. In synchronizing the dates for the DSUR and PSUR submission, the period covered by the next DSUR should be no longer than one year.

DSUR should be provided to all regulatory authorities of Member States where clinical studies (trials) take place and no later than 60 calendar days from the data lock point.

3.3. The period for DSUR submission

The period for DSUR submission is established by legal requirements of the Member States. When according to the legislation of Member State or other country or certain region DSUR submission terminates, the sponsor should state that the final DSUR is the last annual report for the investigational product in this State (other country, certain region). The sponsor should also state if ongoing clinical trials are currently underway in other countries.

3.4. Responsibilities for preparing and submitting a DSUR

3.4.1. Sponsor's responsibilities

The sponsor of a clinical trial is responsible for the preparation, content and submission of a DSUR. Sponsor has the right to delegate preparation of the DSUR to the third party (e.g., a contract research organization).

If the sponsor has no access to information to be included in certain sections of DSUR (e.g., sponsor-investigator may have no data on all the aspects of the manufacturing process, non-clinical data, information on drug product authorization), it should be stated accordingly in DSUR.

3.4.2. Multiple parties' responsibilities

In a situation where a clinical trial or a drug development programme is conducted by multiple sponsors, parties should arrange to prepare a single DSUR (whenever possible). This requirement applies where the sponsor is involved in co-development or licensing agreements with one or more partners or where a clinical trial or drug development programme conducted involves participation of state and private organizations, business partners or other parties. Should that be the case, the sponsor should have in place written agreements specifying the

procedures for data exchange as well as the detailed responsibilities for preparation and submission of the DSUR.

Where submission of a single DSUR is not deemed possible, multiple sponsors can agree to submit separate DSURs for the same investigational drug. This can include situations where different indications, routes of administration, or formulations are being investigated by several parties. The rationale for separate DSURs should be provided in each report.

3.4.3. DSURs for combination products

Given the potential complexities of clinical development involving combination therapies, the present Requirements cannot embrace all the possible aspects. The sponsor should select the most appropriate option to prepare DSUR based on judgement of some factors including patient population, indications, formulation etc., as well as the circumstances in which the clinical trials are being conducted and local regulatory requirements of the Member States of the Union. The rationale for this approach should be provided in the report.

In general, a single DSUR should be prepared for clinical trials involving a fixed combination product (i.e. when a formulation administered contains no less than 2 active substances in a unit dose). When clinical trials with individual components of the fixed combination are being conducted by the sponsor, a single DSUR should be provided for each component. The relevant data from each DSUR should be summarized in respective sections of other DSURs (refer to sub-section 4.11.5 of the present Requirements).

For trials involving multi-drug therapies, i.e. when combinations of medicinal products are not fixed, sponsor has the option to prepare one of the following reports:

a) DSUR of combination therapy;

b) DSURs for one or more individual components (in that case clinical trials of multi-drug therapy could be included in DSUR for one or more components).

Patterns for DSUR preparation strategy on combination therapy include:

Combination therapy in clinical trials	DSUR
investigational product (A) + authorized drug product(s) (X, Y, Z)	single DSUR for combination therapy (A + X + Y + Z) or DSUR for the investigational product (A), including data on combination therapy
two investigational products (A) + (B)	single DSUR for combination therapy (A + B) or two single DSURs for (A) and (B),each of them including data for combination therapy
two (or more) authorized drug products as a drug combination of interest (X, Y, Z)	single DSUR for combination therapy (X + Y + Z)

3.5. Reference Safety Information

The Investigator's Brochure in effect at the start of the reporting period should serve as to determine the compliance of safety information collected during the reporting period with the existing data on safety profile of the investigational product. The relevant DSUR section (refer to sub-section 4.10.1 of the present Requirements) should indicate the version number and date of the Investigator's Brochure used as Reference Safety Information. When the Investigator's Brochure is not required by local regulations of the Member States, patient information leaflet may be used as Reference Safety Information.

In general, only one document can be used as Reference Safety Information. In certain circumstances, more than 1 document could be used as the source of Reference Safety Information (e.g., when the investigational product was used both alone and as part of combination therapy).

If the Investigator's Brochure has been revised during the reporting period and not previously submitted to the regulatory authority, the sponsor should provide a copy of the revised version of the Investigator's Brochure as an appendix to the DSUR.

4. Requirements to the Format and Content of the Development Safety Update Report (DSUR)

4.1. Title page

The title page should include DSUR sequence number, name of the investigational product(s), reporting period, date of the report, sponsor name and address, confidentiality statement and warning that DSUR may include unblinded data.

4.2. Executive summary of DSUR

Together with the title page, Executive Summary may constitute a separate document appropriate for submission to IRB (IEC) within Member States (wherever required). Executive Summary should include a concise summary of the most important data included in the report:

– number of the report and the reporting period, summary of investigational product characteristics (mode of action, pharmacotherapeutic class, indications, route of administration, dosage regimen, galenic formulations);

– estimated number of subjects exposed to investigational product;

– marketing authorization status including number of countries (if the product is authorized);

– summary of overall safety profile assessment (refer to section 4.22 of present Requirements);

– summary of important risks (refer to section 4.22 of present Requirements);

– actions taken for safety reasons including significant changes to Investigator's Brochure;

– conclusion(s).

4.3. Table of contents

The section should include DSUR contents.

4.4. Introduction

Introduction should state the following information:

– DIBD or IBD (if applicable);

– reporting period and DSUR sequential number;

– description of the investigational product (mode of action, pharmacotherapeutic class, route of administration, dosage regimen, galenic formulations);

– summary of indications for use and the study populations;

– a brief description of clinical trials and of their tendency included in the report (e.g., all the clinical trials with the investigational drug);

– clinical trials for certain indications; combination therapy studies;

– a brief description and explanation of any information that has been excluded (e.g., failure to provide any safety information by co-development partners);

– rationale for submission of multiple DSURs for the investigational drug (if applicable).

4.5. Worldwide marketing authorization status

This section should provide summary of marketing authorization status (if applicable), including IBD, authorized indication(s) for use, approved doses, respective countries.

4.6. Actions taken in the reporting period due to safety information

This section should include a summary of actions taken for safety reasons by the sponsor, regulators, Independent Data Monitoring Committee, IRB (IEC) that could have an impact on the conduct of a specific trial(s) or the whole clinical development programme. This section should provide basis for the actions taken as well as potential changes of previously taken measures (e.g., clinical trial resumption after its suspension). The following actions can be taken for safety reasons:

– regulatory authorities' or IRB (IEC) refusal to authorize a clinical trial for ethical or safety reasons;

– partial (complete) clinical trial suspension or early termination of a clinical trial due to new safety information or to lack of efficacy;

– recall of the investigational product or active comparator;

– failure to obtain marketing approval for tested indications, including voluntary withdrawal of marketing authorization application;

– risk management activities (protocol modifications due to safety or efficacy aspects of the investigational drug, e.g., dosage changes, changes of inclusion/exclusion criteria, intensification of monitoring, restriction of exposure to medicinal products, restrictions in study population or indications;

– changes to the informed consent document;

– formulation changes;

– addition of a special safety reporting requirement by the regulatory authorities;

– issuance of a communication to investigators or healthcare professionals;

– plans for new trials to study safety profile aspects.

– This section shall include the following actions relating to authorized drug products (if applicable):

– regulator's' refusal to acknowledge authorization;

– suspension of marketing authorization or withdrawal of a marketed product;

– regulatory risk management activities (significant restrictions on distribution);

– significant changes in labelling instructions for use that could have an impact on clinical development programme;

– preparation of additional information and other risk minimization activities.

– post-marketing regulatory commitment(s) including post-marketing and other safety studies, e.g., pre-clinical studies.

This section also lists regulatory requests that impose certain restrictions regarding current or planned development programme for an investigational product (e.g., requirement of long-term non-clinical studies prior to initiation of long-term clinical trials, request to submit specific safety data prior to initiation of a pediatric study).

This information is arranged as a cumulative listing including updates (if applicable).

4.7. Changes to Reference Safety Information of an Investigational Product

This section should list safety-related changes to the Investigator's Brochure or other reference safety information in the reporting period due to new aspects of investigational product's safety profile. These changes may comprise information relating, e.g., to exclusion criteria, contraindications, warnings, precautions, list of serious adverse drug reactions, adverse reactions of special interest, interactions, and any important findings from non-clinical studies. Detailed information relevant to these changes should be provided in the appropriate sections of the DSUR.

4.8. Listing of clinical trials ongoing and completed during the reporting period

This section should include a brief summary on clinical trials ongoing and completed during the reporting period with a detailed listing of information (in tabular form) on the following sections presented in the appendixes:

– study identification number and phase of the trial;
– status of the study (ongoing study – study has begun);
– clinical study has begun but is currently on hold;
– study is completed, but final clinical study report is not yet available;
– Member States with at least one investigational center;
– abbreviated study title;
– study design (non-controlled, controlled, open-label, single-blind, double-blind, parallel group, cross-over etc., including treatment arms);
– doses and dosage regimens of the investigational product and comparator(s);
– characteristics of subject population (age; sex; indications; specific subject (patients) groups (e.g., trial subjects with impaired renal function or trial subjects resistant to treatment);
– date of the clinical trial initiation (according to the sponsor's definition) (e.g., the first visit of the first enrolled subject (patient));
– planned enrollment for the study;
– estimated cumulative number of exposed patients (subjects) for each treatment arm (if applicable). This section should also provide actual numbers of enrolled subjects in open-label or completed clinical trials and/or estimate based on the randomization scheme for blinded trials.

4.9. Estimated subject exposure

This DSUR section should include overall number of subjects exposed (cumulatively) in clinical trials (refer to sub-section 4.9.1 of the present Requirements) and during therapeutic use (refer to sub-section 4.9.2 of the present Requirements). The requirements to information given in this section include the following:

a) Data should be given in tabular form.

b) Provided there are significant differences between clinical trials regarding tested dose, route of administration, study population tabular data should be accordingly described or given as separate tabulations.

c) If serious adverse events in summary tabulations are given by study indication, data on exposure estimate (cumulative exposure) should be also grouped by study indications.

d) If cumulative exposure time significantly differs between clinical trials or investigational product and comparator(s) it is recommended to provide estimated exposure data using conventional units "subject-period of time" (human-day, human-month or human-year).

e) Data on healthy volunteers exposure (especially in single-dose studies) could be provided separately due to their lower relevance for safety profile assessment.

f) In order to assess cumulative exposure to authorized drug products for which a clinical development program is running, for longstanding therapeutic use and/or when there are multiple indications a less accurate approach can be used (sponsor should comment on such cases).

4.9.1. Cumulative subject exposure in clinical development programme

This sub-section shall include the following information (in tabular form):

– cumulative number of subjects from ongoing and completed clinical trials;

– the number of subjects exposed to the investigational drug, placebo, and/or active comparator(s) since the DIBD (in blinded ongoing trials the number of subject can be estimated based on the randomization scheme);

– demographic characteristics for a single trial if the trial is of particular importance (e.g., a pivotal Phase III trial).

This sub-section should also provide a description and rationale for the method(s) selected to estimate cumulative subject exposure as well as the limitations of that (these) method(s).

4.9.2. Patient exposure from marketing experience

If the investigational drug is authorized in any country(ies), the sponsor should include an estimate of the cumulative patient exposure from marketing experience, based on the information provided in the most recent PSUR or other data sources, with an explanation of the method(s) used to assess the exposure.

4.10. Data in line listings and summary (cumulative) tabulations

This DSUR section should present line listings of serious adverse events, registered by the sponsor during the reporting period as well as cumulative tabular data on serious adverse events registered by the sponsor since the DIBD, i.e. tabulations should include all the serious adverse events (further on the text – SAEs) and not just SARs for investigational drug and comparators. Blinded and unblinded clinical trial data may originate from completed trials and individual cases that have been unblinded for reasons related to safety of study subjects. Sponsors shall not unblind data for the purpose of preparing the DSUR.

At the sponsor's discretion, graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

In general SAE tabulations should include only terminology used to define whether an adverse reaction is serious or not; tabulations shall not include non-serious adverse events.

Certain adverse events can be excluded from the line listings and summary tabulations, but such exclusions should be explained in the report. Such adverse events include, for example, those defined in the protocol as not requiring special collection and entry into the safety database, and those that are integral to efficacy endpoints (e.g., deaths caused by the progression of underlying disease in clinical trials in patients with malignancies).

4.10.1. Reference information

This sub-section of the DSUR should specify the version(s) of the coding terminology dictionary used and the name of the document with its version number used as Reference Safety Information for determining expectedness for the tabulations where required by national legislation of Member States.

4.10.2. Line listing of serious adverse reactions occurred during the reporting period

This sub-section should summarize how case reports were selected for inclusion in the line listings; the line listings of serious adverse reactions reported in clinical trials during the reporting interval included as appendixes to the DSUR. This section should not serve to provide analyses or conclusions based on the SARs. The line listings should be organized by trial, then by System Organ Class.

Line listing(s) should include each subject (if applicable) only once regardless of how many SAR terms are reported for the case. If the subject developed more than one reaction, they should all be mentioned but the case should be listed under the most serious adverse reaction (complaint, symptom or diagnosis), as judged by the sponsor. If the same subject experienced different SARs on different occasions during a clinical trial (e.g., with more than a week apart), these SARs should be listed separately, and the study subjects could be included in line listings more than once.

The following information should be included in the line listings:

– study identification number;

– subject clinical trial identification number;

– sponsor's SAR reference number;

– country in which SAR occurred;

– age and sex of trial subject;

– treatment arm data or indication that the data are blinded if not otherwise;

– dose and dosing interval of investigational drug and (when relevant), dosage form and route of administration;

– date of onset and/or interval between start of therapy and the date when subject developed the SAR, the start date and the final date of the study therapy and/or estimate of treatment duration;

– name (description) of serious adverse reaction(s) (when MedDRA is used, the Preferred Term should be presented);

– SAR outcome (e.g., resolved, fatal, improved, sequelae, unknown). The outcome should be indicated; in case of more than one outcome for the patient, the worst of the different outcomes for multiple reactions should be indicated;

– comments (e.g., causality assessment if the sponsor disagrees with the investigator; concomitant medications suspected to be directly related to the adverse reaction or an interaction; indication treated with suspect drug(s); dechallenge/rechallenge results (if applicable).

4.10.3. Cumulative summary tabulations of identified serious adverse events

This section should refer to an appendix that provides a cumulative summary tabulation of identified SAEs reported to the sponsor of the clinical trials, from the DIBD to the data lock point of the current DSUR. Any omission of data should be explained. Cumulative tabulations of identified SAEs should be categorized by SOC, by the investigational drug, as well as the comparator. Data can be grouped by separate study protocols, indications, routes of administration or categorized otherwise (if appropriate). Cumulative data of identified SAEs should include data of blind and open-label clinical trials.

4.11. Significant findings from clinical trials during the reporting period

4.11.1. Completed clinical trials

In this DSUR sub-section the sponsor should provide a brief summary of significant emerging findings form clinical trials completed during the reporting period. It could include information that supports or refutes previously identified significant safety profile aspects, as well as evidence of new safety signals.

4.11.2. Ongoing clinical trials

This DSUR sub-section should briefly summarize clinically important findings from clinical trials ongoing in the reporting period (e.g. learned through interim data analyses or resulting from of unblinding of subjects with adverse events). The information could include data that supports or refutes previously identified safety profile aspects, as well as evidence of new safety signals.

4.11.3. Long-term follow-up

This sub-section should provide information (if applicable) from long-term follow-up of subjects from clinical trials. After the development programme is completed, long-term follow-up could be the only ongoing activity generating data for the DSUR. In that case this could be the only section where new information is presented.

4.11.4. Other therapeutic use of investigational drug

This sub-section should include clinically important safety data from special study protocols conducted by the sponsor, capturing and documenting data on adverse reactions (e.g., as expanded access, individual access and others).

4.11.5. New safety data related to combination therapies

If the investigational drug is being developed as a component of a fixed combination product or a multi-drug regimen, this DSUR sub-section should summarize important safety findings for the individual component from the combination therapy. If this DSUR is prepared for a combination therapy or a fixed combination product, this section should include important safety information arising from trials on the individual components.

4.12. Safety findings from non-interventional studies

This section should summarize safety information from non-interventional studies that became available to the sponsor during the reporting period (e.g., observational studies, epidemiological studies, registries and active surveillance programmes).

4.13. Safety information available from other clinical trials

This section should summarize safety information from any other clinical trial/study sources that became available to the sponsor during the reporting period (e.g., results from pooled analyses or meta-analyses of randomized clinical trials, safety information provided by co-development partners or from investigator-initiated trials).

4.14. Safety findings from marketing experience

If the investigational drug has been approved for marketing in any country, this section should include a concise summary of key safety findings that have arisen from marketing experience and became available to the sponsor during the reporting period. Special attention should be given to the findings resulted in changes to the product labelling, Investigator's Brochure, informed consent document or amendments to the product's risk management plan.

Safety information in this section should include both results of approved use and off-label use as well as results of medication errors, overdose and addiction, use in special populations (e.g., pregnant women).

4.15. Non-clinical data

This section should summarize major safety findings from non-clinical in vivo and in vitro studies ongoing or completed during the reporting period (e.g., carcinogenicity, reproduction, or immunotoxicity studies). Assessment of non-clinical findings in terms of implications for human use should be discussed in section Overall Safety Assessment (see section 4.21 of the present Requirements).

4.16. Literature data

This section should summarize new and significant safety findings relevant to the investigational drug that were became available to the sponsor during reporting period (published in the scientific literature, became available as unpublished monographs, presented at scientific conferences or published as abstracts). This section should include information from clinical and non-clinical studies and (if applicable) information on drugs of equivalent class. Sponsor should also provide copies of the abstracts relevant to this section (if possible).

4.17. Other DSURs

A sponsor should submit a single DSUR. If a sponsor prepares multiple DSURs for a single investigational drug (e.g., covering different indications, development programmes, or formulations), this section should summarize significant safety findings from the other DSURs if they are not presented elsewhere within this report. This section should summarize safety data included in DSUR from other sponsors conducting clinical trials with the same investigational drug during the reporting period (if applicable).

4.18. Lack of efficacy

Data indicating lack of efficacy, or its lower efficacy relative to established therapy(ies) used to treat serious or life-threatening illnesses (e.g., excess cardiovascular adverse events in a trial of a new anti-platelet drug for acute coronary syndromes) and that could reflect a significant risk to clinical trial subjects should be summarized in this section.

4.19. Other safety findings from clinical trials

This section could provide further safety details, e.g.:

4.19.1. Cumulative summary tabulation of serious adverse reactions

This sub-section provides information on cumulative number of serious adverse reactions categorized by:

- System Organ Class;
- terms for adverse reactions;

– treatment arm (if applicable);

– unlisted adverse reactions should be indicated.

4.19.2. A list of clinical trial subjects who died during the reporting period

This sub-section should list subjects who died during clinical trials including the following data: identification number of the fatal case, assigned medication (data may be blinded), death cause for each individual study subject. All the aspects of safety profile resulting from the overview of fatal cases should be properly documented in the section Overall Safety Profile Assessment for the DSUR investigational drug (refer to section 4.21 of the present Requirements).

4.19.3. List of subjects who dropped out of clinical trials in association with an adverse event during the reporting period

This sub-section should include all subjects who dropped out of clinical trials in association with adverse events during the reporting period, whether or not thought to be drug-related. Any safety profile aspects identified from a review of these withdrawals should be addressed in section Overall Safety Profile Assessment of the DSUR (refer to section 4.21 of the present Requirements).

4.19.4. Significant Phase I protocol modifications

This section should describe significant Phase I protocol modifications during reporting period (if not submitted previously as protocol modifications).

4.19.5. Significant manufacturing changes

This sub-section should include a summary of significant manufacturing or microbiological changes (if any) during the reporting period and discuss in section Overall Safety Profile Assessment of the DSUR potential safety profile aspects arising from these changes (refer to section 4.21 of the present Requirements).

4.19.6. Description of the general investigation plan for the coming year (if applicable)

This section should outline an investigational plan to replace that submitted for the previous year.

4.20. Late-breaking information

This section should summarize information on potentially important safety findings that arise after the data lock point but while the DSUR is in preparation. Potentially important findings include but are not limited to clinically significant new case reports, important follow-up data, clinically relevant findings and any action taken by the sponsor, regulatory authority or the Independent Data Monitoring Committee for safety reasons. The Overall Safety Assessment (see section 4.21 of the present Requirements) should also take these new data into account.

4.21. Overall safety assessment

This section should provide the overall safety assessment for the investigational drug as well as integrated evaluation of all new relevant clinical, non-clinical, and epidemiologic information obtained during the reporting period relative to previous knowledge of the investigational drug. For drug products with a marketing approval, this assessment should consider clinically relevant data from post-marketing experience. It should not repeat information presented in previous sections of the report, but should provide an interpretation of the new safety information and its implications for the study population and the development programme. Separate assessments can be provided for therapeutic area, route of administration, formulation and/or indication (if applicable).

4.21.1. Risk assessment

Risk assessment should specifically focus on the interpretation of data on identified emerging safety issues or significant new safety information. The assessment of the following safety profile aspects should be provided (if applicable):

a) emerging safety profile aspects:

– details on adverse events or reactions;

– laboratory findings related to the investigational drug;

– risk factors;

– relationship of adverse events to dose and treatment duration;

– reversibility of complications;

– factors useful to predict and to prevent adverse reactions.

b) important changes to characterization of previously documented adverse reactions (e.g., increase in anticipated frequency or severity, worsening of outcomes, establishment of risk groups);

c) symptoms, complaints, laboratory findings specific for these new or previously identified clinically significant toxicities, e.g., hepatic and cardiac toxicity (including Q-T elongation and special QT/QTc findings), myelotoxicity, lung and renal toxicity, immunogenicity as well as hypersensitivity reactions;

d) fatal outcomes of adverse events;

e) termination of a clinical study due to adverse reactions including laboratory findings or examination results;

f) drug interactions and other forms of interactions;

g) important safety-related data from non-clinical studies;

h) manufacturing aspects that have the potential to affect safety profile;

i) lack of efficacy involving additional risks for clinical trial subjects;

j) additional risk for specific populations such as elderly patients, children, patients with liver or kidney failure or other (e.g., subjects with low or high metabolism);

k) pregnancy and lactation exposure and its outcomes;

l) safety aspects of long-term use;

m) data on clinically significant medication errors;

n) data on patient non-compliance with treatment;

o) experience of overdose and its treatment;

p) occurrences of misuse and abuse;

q) safety aspects associated with procedures required by the protocol (e.g., bronchoscopy, biopsy, insertion of central line catheter) or with the conduct or design of a particular study (e.g., inadequate subject monitoring, excessive period without active treatment); and potential risk of significant new safety data identified with another drug in the same class.

4.21.2. Assessment of benefit-risk balance

This sub-section should provide a brief statement on the balance between cumulative risks that have been identified from safety data and anticipated efficacy (benefits). It should note the change in the benefit-risk balance since the previous DSUR. This section is not intended to be a detailed benefit-risk assessment of the investigational drug.

4.22. Summary of important risks

This section should provide a list of important identified and potential risks. These include, e.g., risks that might lead to precautions, warnings, or contraindications in labelling. Such risks might include, for example, toxicities or safety issues known to be associated with a particular molecular structure based on non-clinical or clinical data. Each risk should be re-evaluated annually and re-summarized, based on the current state of knowledge, with particular emphasis on new safety data arising during the reporting period. The level of detail provided is likely to be dependent on phase of drug development: for example, summaries covering drugs in early development might include information on individual cases, in later development, as more knowledge and perspective are gained, the information on each risk might be less detailed.

Risks that have been fully addressed or resolved should remain in the summary and be briefly described (e.g., findings from toxicology studies or early clinical trials that were not confirmed by later clinical data.

The information can be provided in either narrative or tabular format.

4.23. Conclusions

The conclusion should briefly describe any changes to the previous knowledge of efficacy and safety resulting from information gained since the last DSUR. The conclusion should outline actions that have been or will be taken to address emerging safety issues in the clinical development programme.

4.24. Appendices to the report

The DSUR should be accompanied by the following appendices:

1. Investigator's Brochure
2. Cumulative Table of Important Regulatory Requests;
3. Status of Ongoing and Completed Clinical Trials;
4. Cumulative Summary Tabulations of Demographic Data;
5. Line Listings of Serious Adverse Reactions Identified during the Reporting Period;
6. Cumulative Summary Tabulation of Serious Adverse Events;
7. Synopsis (if applicable).

The DSUR could also be accompanied by the following Appendices:

- cumulative summary tabulation of serious adverse reactions;
- list of subjects who died during the reporting period;
- List of subjects who dropped out of studies during the reporting period;
- significant Phase I protocol modifications
- significant manufacturing changes;
- description of the general investigation plan for the coming year.

Examples of tables for clinical trial listings

Table 1

Status of ongoing and completed clinical trials

Overview of ongoing clinical trials _____
(investigational product)

Identification number of a clinical trial	Phase	Country	Study name	Study design	Dosage regimen	Study population	First patient first visit	Planned enrollment	Exposure of study subjects

_____

* Based on cumulative number of study subjects as of_____and randomization schedule
(date)

Table 2

Overview of clinical trials completed during the reporting period_____
(investigational product)

Identification number of a clinical trial	Phase	Country	Study name	Study design	Dosage regimen	Study population	Subject exposure by treatment arms (male/female)

Table 3

Estimated number of subjects exposed to investigational product (estimated cumulative exposure) calculated based on the actual data from completed clinical trials as well as calculated based on the randomization schedule from ongoing clinical trials

Treatment	Number of subjects
Drug product	
Active comparator	
Placebo	

Table 4

Estimate of the total number of subjects exposed to the investigational product (estimated cumulative exposure from completed clinical trial data by age and sex*

Number of subjects			
Age group	Males	Females	Total

* Data from completed clinical trials as of _____ .
(date)

Table 5

Estimate of the total number of subjects exposed to the investigational product (estimated cumulative exposure) from completed clinical trial data by racial group

Racial group	Number of study subjects
Asian	
Black	
Caucasian	
Other	
Unknown	
Total	

Table 6

Examples of cumulative tabulations of serious adverse reactions (SARs)

Line listing of serious adverse reactions

Clinical trial ID number*	SAR** report ID number* (study subject ID number*†)	Country Age Sex	SAR description	Outcome	Date of adverse reaction onset*** time between administration and onset of the reaction‡	Suspected drug (investigational product)	Daily dose Route of administration Formulation	Date of treatment start and the date of treatment completion Duration of treatment	Comments
1	2	3	4	5	6	7	8	9	10

*ID number – identification number
**Study (centre, patient)
***Only for initial SAR reports

Table 7

Examples of cumulative tabulations of serious adverse reactions

Cumulative table on serious adverse events

System Organ Class	Total number up to December 31, 2015			
Preferred Term	(Name of the investigational product)	Blinded drug product	Active comparator	Placebo
Studies	18	4	7	2
Increase in alanine transaminase activity	9	2	4	1
Increase in aspartate transaminase activity	9	2	3	1
Nervous system disorders	2	2	4	7
Syncopal condition	2	2	4	7