ANNEX

to Decision of the
Eurasian Economic Commission's
Council
No. _____ dated _____ ___, 20___

A M E N D M E N T S
to the Rules of Good Clinical Practice of the Eurasian Economic Union

1. The Rules shall be read as follows:

"APPROVED

by Decision of the
Eurasian Economic Commission's
Council
No. 79 dated November 3, 2016
(as amended by Decision of the
Eurasian Economic Commission's
Council
No. _____ dated _____ ___, 20___)

R U L E S
of Good Clinical Practice
of the Eurasian Economic Union

I. General provisions

These Rules represent an international ethic and scientific standard for planning and conducting studies involving humans as the trial subject, as well as for documenting and reporting such study results.

Compliance with the provisions of these Rules serves as a guarantee for the society that the trial subjects' rights, safety and well-being are in line with the principles stipulated in the Declaration of Helsinki adopted at the XVII World Health Association Session in 1964, and that the trial data are reliable.

The objective of these Rules is to establish a single procedure for conducting the medicinal product clinical trials/studies (hereinafter referred to as the Trials) which shall promote functioning of the common medicinal product market within the Eurasian Economic Union (hereinafter referred to as the Union), mutual recognition of the clinical trial data by the regulatory authorities of the Union Member States (hereinafter referred to as the Member States), as well as recognition of clinical studies/trials conducted on the Union territory and beyond it.

The enumeration used in the text of Section II of these Rules corresponds to the enumeration used in the international version of the Good Clinical Practice (GCP) in terms of all its subsections, except for Subsection 2 where the definitions are laid out in alphabetical order.

These Rules are developed on the basis of ICH GCP (Guideline for Good Clinical Practice), which is the Document E6 (R2) of the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Advances in technology and risk management processes open up new possibilities in improvement of the medicinal product clinical trial efficiency, allow focusing on more significant aspects. Advance in the area of documenting and reporting of the clinical studies data in terms of transition from the information hard copies to soft data format simplifies

implementation of up-to-date approaches. For instance, the centralized monitoring, at the present day, is able to provide more advantages and in more studies. The Rules have been supplemented to facilitate implementation of improved and more efficient approaches to planning, conduct, supervision, documenting and reporting of the clinical trial results, while maintaining the subject protection and the trial results reliability. To improve the clinical study quality and efficiency, requirements to electronic records and essential documents have been updated.

These Rules are related to the Union authorities' acts in the area of clinical studies (Guidelines for Clinical Studies in Special Populations: Geriatric Patients; General Issues of Clinical Studies; Guidelines for the Biostatistics Application Principles in Clinical Studies and Medicinal Product Clinical Studies in Paediatric Population).

Considering the importance of maintaining the regulatory documents of the Union in compliance with up-to-date international standards, the Rules have been supplemented on the basis of the last revision of the Guideline for Good Clinical Practice, ICH E6 (R2). All addenda introduced to the initial text of the Rules are marked with the 'Addendum' note facilitating their identification.

These Rules shall be followed at conducting any medicinal product clinical studies/trials, which data are to be submitted to the regulatory authorities (expert organizations) of the Member States.

The principles set forth by these Rules are also applicable to other clinical trials, which may affect the safety and well-being of a human involved as the trial subject.

These Rules are subject to revision on a regular basis considering the experience of their application in the Member States, as well as in case of any

changes in the international standards for conducting studies (followed by introducing the changes required).

II. Main Part

1. Terms and Definitions

For the purposes hereof, the concepts having the following meanings shall be used:

1.1. Audit is the systematic and independent inspection of the trial-related activities and documents conducted to confirm compliance of the activity, as well as procedures for data acquisition, analysis and reporting, with the protocol, sponsor's standard operating procedures, Good Clinical Practice and applicable regulatory requirements;

1.2. Well-Being of the Trial Subjects/Patients is the physical and mental health of the subjects involved in the trial;

1.3. Investigator's Brochure is the summary of clinical and non-clinical data on the investigational medicinal product related to its trial in human;

1.4. Study Design is the general trial plan, description of the trial method depending on the trial subject selecting and grouping, and data masking;

1.5. Contract is a dated and signed agreement between two or more parties, establishing arrangements related to the work scope and responsibility allocation during the trial, and financial issues, if necessary. The Contract basis shall be the study protocol;

1.6. Nonclinical Study means biomedical studies conducted without involving humans as trial subjects;

1.7. Audit Trail means the documents allowing to restore the events sequence;

1.8. Documentation means all records in any format (including hard copies, soft copies, data on magnetic or optical media, scanning images, X-ray films, electrocardiograms, etc.), which describe or record the study methods, organization and/or results, as well as factors effecting the trial and the actions taken;

1.9. Opinion (of the Independent Ethics Committee/Ethical Council) is the written document containing opinion and/or recommendations of the independent ethics committee concerning human participation in the trial;

1.10. Legally Acceptable Representative is a natural or juridical person or other legal entity having legal right to give a consent for participation in clinical study on behalf of the potential trial subject;

1.11. Subject Identification Code is the unique code assigned by the investigator to each trial subject to ensure confidentiality of his/her personal data and used instead of the trial subject name in the reports on adverse events and/or other trial-related data;

1.12. Case Report Form, CRF is the document in hard or soft copy or on optical medium intended for entering all information on each subject stipulated by the protocol and is subject to submission to the sponsor;

1.13. Inspection is the action of regulatory authority consisting in official inspection of documents, infrastructure, records, agreements on quality assurance and any other sources, which the regulatory authority considers as related to the trial and may be located at the trial site, sponsor's and/or clinical trial provider and other entities requiring inspection according to the regulatory authority's opinion;

1.14 Informed Consent is the process of volunteer confirmation by the subject of his/her consent for participation in a specific trial after obtaining information on all trial aspects significant for the decision making process.

The Informed Consent is documented through signing and dating the Informed Consent Form;

1.15 Investigator is a natural person responsible for the trial at the trial site.

If the trial is conducted at the trial site by a group of individuals, the Investigator (Chief Investigator) is the group manager;

1.16. Coordinating Investigator is the investigator responsible for coordination of investigator activities at all trial sites participating in a multicenter clinical trial;

1.17. Investigator/Institution is an investigator and/or institution depending on the context;

1.18. Trial Site is the site, where the trial is actually conducted.

1.19. Investigational Medicinal Product is the medicinal product investigated or used for comparison in the trial, including placebo, as well as authorized medicinal product (when its use method differs from the authorized one, as well as when it is used for a new indication or for obtaining new information on the authorized indication);

1.20. Clinical Trial/Study is any study involving human as the trial subject for revealing or confirmation of clinical and/or pharmacological effects of the investigational medicinal products and/or revealing adverse events caused by the investigational medicinal products, and/or study of their absorption, distribution, metabolism and elimination to assess their safety and/or efficacy. Terms "Clinical Trial" and "Clinical Study" are synonymous.

1.21. Contract Research Organization, CRO is a natural person or organization (commercial, scientific research or other), which executes one or more sponsor's responsibilities and functions related to conducting of a clinical trial under a contract with the sponsor;

1.22. Quality Control (QC) includes methods and activities constituting part of the quality assurance system and used for verification of compliance of the procedures performed during the trial with the requirements set for their quality;

1.23. Coordinating Committee is the committee, which may be established by the sponsor to coordinate conduct of a multicenter clinical trial;

1.24. Confidentiality is keeping privacy of information owned by the sponsor and allowing to identify a trial subject from unauthorized persons;

1.25. Multicentre Clinical Trial is a clinical trial performed under a single protocol at more than one trial site and by more than one investigator;

1.26. Monitoring is the activity consisting in monitoring the clinical trial progress, ensuring its conduct, data acquisition and reporting its results in accordance with the protocol, standard operating procedures, Good Clinical Practice and applicable regulatory requirements;

1.27. Good Clinical Practice, GCP is the code of ethical and scientific standards for planning, conducting, implementation, monitoring, audit, documenting, review and reporting of the clinical trial results, ensuring protection of rights, safety and well-being of the trial subjects and obtaining reliable and authentic data within the clinical trial;

1.28. Adverse Reaction – with reference to the pre-authorized clinical use of a new medicinal product or its use for new indications, especially, when therapeutic doses are not established – means all adverse reactions related to use of the medicinal product in any dose. The term "related to use of the medicinal product" means at least minimum possibility of presence of a causal link between the medicinal product and the adverse event, i.e. the relationship is not excluded. For the authorized medicinal products this term means all adverse reactions related to the use of the medicinal product in

regular doses for disease prevention, diagnosis or treatment, as well as for changing physiological functions;

1.29. Adverse Event is any unfavorable change in the health status of a patient or trial subject to whom the medicinal product has been administered, regardless of the causal link with its use. Adverse Event can be any unfavorable and unintentional change (e.g. abnormal laboratory findings), symptom or disease, the onset time of which does not exclude the causal link with the medicinal product use, whether the relationship with the medicinal product is present or not.

1.30. Independent Data-Monitoring Committee, IDMC (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee) is an independent committee, which may be established by the sponsor's initiative for periodic review of the clinical trial progress, safety data and/or main efficacy parameters, as well as for formulation of recommendations for the sponsor on the trial continuation, termination or alteration worthiness;

1.31. Independent Ethics Committee, IEC is an independent body (expert committee acting at the institutional, regional, domestic or international level) consisting of healthcare providers, as well as of persons outside the framework of medical science, which ensures protection of rights, safety and well-being of the trial subjects and acts for the society as guarantor of such protection, in particular, through review, approval of the trial protocol, candidacy for investigators, trial sites and materials and methods supposed to be used for obtaining and documenting the informed consent of the trial subjects. Legal status, membership functions and activities of the Independent Ethics Committees, as well as regulatory requirements applicable to them, may vary between the Member States, nevertheless, the NECs shall function in accordance with these Rules;

1.32. Impartial Witness is a natural person not implicated in the clinical trial conduct, who cannot be subjected to pressure of the clinical trial participants and who, if the trial subject or his/her legally acceptable representative can not or is not able to read, attends at obtaining informed consent, as well as reads the text of the informed consent and any other written materials submitted to the trial subject;

1.33. Unexpected Adverse Drug Reaction is adverse reaction, the nature or severity of which is consistent with the known information on the medicinal product (e.g. the investigator's for an unauthorized investigational medicinal product or with the medicinal product package insert/summary of product characteristics, in case of an authorized medicinal product);

1.34. Quality Assurance, QA is a set of systematic and consistent actions aimed at ensuring the compliance of the trial conducted, data acquisition, recording and representation with Good Clinical Practice and applicable regulatory requirements;

1.35. Approval (of the Institutional Review Board) is the opinion adopted by the Institutional Review Board (IRB) confirming the fact the clinical trial expert assessment and being permission for its conduct in this institution in accordance with the IRB instructions, regulatory documents of the medical institution, as well as Good Clinical Practice and applicable regulatory requirements;

1.36. Institution (Medical) is a healthcare institution irrespective of its organizational legal form, where a clinical trial is conducted;

1.37. Essential Documents are the documents, which in total or individually allow to assess the clinical trial progress and quality of the data obtained;

1.38. Monitoring Report is a written monitor's report for sponsor after each visit to the trial site and/or contact with investigators in accordance with the sponsor's standard operating procedures (SOPs);

1.39. Audit Report is a written sponsor's auditor opinion on the audit results;

1.40. Clinical Trial/Study Report is a written description of a clinical trial/study of any therapeutic, prophylactic or diagnostic drug involving a human as a subject, which consolidates clinical and statistical descriptions, data representation and analysis (see also Annex No. 1 hereto and Section 5 of Part 1 of Annex No. 1 to the Rules of Marketing Authorization and Expert Assessment of Medicinal Products for Human Use, approved by Decision No. 78 of the Eurasian Economic Commission's Council dated November 3, 2016 at supporting the marketing authorization application);

1.41. Source Documents (Original Medical Record) are the initial documents, data and records (e.g. medical records, clinical records, laboratory records, notes, trial subject diaries, medicines books, automatic device records, verified and certified copies and extracts, microfiches, photographic negatives, microfilms or magnetic media, X-ray films, any records related to the patient including those kept in a pharmacy, laboratories and instrumental examination units used in the clinical trial);

1.42. Source Data are all information on results of clinical observations, examinations and other activities contained in original medical records and their certified copies, which allow to restore the clinical trial progress and assess it. The Source Data are contained in source documents (their original or certified copies);

1.43. Protocol Amendment is the description of amendments or official protocol clarification executed in writing;

1.44. Comparator (Product) is the investigational or authorized medicinal product (active control) or placebo used for control in a clinical trial;

1.45. Applicable Regulatory Requirement(s) are the statements comprising the Union law and legislation of the Member States in the area of the medicinal product circulation regulating conduct of clinical trials;

1.46. Interim Clinical Trial/Study Report is the report on intermediate results and their assessment based on the data analysis performed in the course of a clinical trial;

1.47. Protocol is a document describing objectives, design, methodology, statistical methods and organization of the trial; Moreover, the Clinical Trial Protocol usually contents previously obtained data and the trial justification; however, this information may be represented in other documents referenced in the Clinical Trial Protocol. In terms of these Rules, the term 'Protocol' implies both all subsequent versions of the Clinical Trial Protocol and amendments to it;

1.48. Direct Access is the permission for check, analysis, verification and copying of any records and reports necessary for the clinical trial assessment. Persons having the Direct Access rights (i.e. representatives of national or foreign regulatory authorities, the sponsor's monitors and auditors) shall take all reasonable actions to comply with the applicable regulatory requirements concerning the information confidentiality allowing identification of the subjects and information owned by the sponsor;

1.49. Randomization is a process for distribution of the trial subjects in treatment groups or random control allowing to minimize the subjectivity;

1.50. Routine Clinical Practice means instance/equitype medical diagnosis and treatment procedures, technologies or arrangements performed for the given group of patients or the given healthcare standard;

1.51. Audit Certificate is the document drawn-up by auditor to confirm the fact of audit;

1.52. Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (serious ADR) is an unfavorable medical event caused death, imposes life threat, required inpatient hospitalization or its prolongation, caused persistent or significant disability or being congenital abnormality/malformation irrespective of the medicinal product dose (see also paragraph 1.2.1. of Annex No. 11 to these Rules);

1.53. Blinding/Masking is the method, which when applied ensures that one or several parties participating in the clinical trial do not know the treatment prescribed to the trial subject. Simple blind method implies unawareness of the treatment type prescribed to the trial subjects, while the double-blind method implies unawareness of the trial subjects, investigators, monitors and, in some cases, persons performing statistical data processing;

1.54. Compliance (in relation to clinical trials) is the compliance with all requirements related to clinical trials, Good Clinical Practice and other applicable regulatory requirements;

1.55. Subinvestigator is any member of the study personnel assigned by the investigator and performing important clinical trial procedures under his/her control at the trial site and/or taking important decisions related to the trial (e.g. clinical fellow, hospital physician, scientific researcher);

1.56. Sponsor is a natural or juridical person responsible for initiation, organization and financial support of the clinical trial;

1.57. Sponsor-Investigator is a person, who initiates and conducts a clinical trial independently or jointly with other persons, and under direct management of whom, the investigational medicinal product either prescribed, or handed over to the trial subject, or the latter takes it. The Sponsor-Investigator may be a natural person only. The Sponsor-

Investigator's responsibilities include both the sponsor's responsibilities and the investigator's responsibilities;

1.58. Standard Operating Procedures (SOPs) are written detailed instructions intended for reaching consistency at performing of a specific activity;

1.59. Subject (Trial Subject) is a natural person participating in a clinical trial in a group receiving the investigational medicinal product or in a control group;

1.60. Regulatory Authorities are the authorities having the right to perform regulatory functions. For the purposes of these Rules, the regulatory authorities include institutions authorized to review clinical data submitted to them, as well as to perform inspections. These authorities are also called competent authorities;

1.61. Vulnerable Subjects are the persons, whose wish to participate in the clinical trial may be excessively influenced by (reasonable or unreasonable) expectation of some or other profits associated with the participation in the trial or sanctions of higher-level persons in case of refusal from participation. The trial Vulnerable Persons include students of the higher and secondary medical, pharmacy and dentistry educational institutions, junior staff of clinics and laboratories, employees of pharmacy companies, military personnel and prisoners, as well as terminally ill patients, persons staying in care houses, low-income and jobless persons, medical emergency patients, ethnic minority representatives, vagrants, vagabonds, refugees, juveniles, persons under trusteeship or guardianship, as well as persons not able to give their consent.

1.62. Institutional Review Board (IRB) is an independent body including persons employed in medical science, science, as well as those unrelated to science, which ensures protection of rights, safety and well-being

of the trial subjects, including through review, approval of the trial protocol and amendments thereto, as well as materials and methods supposed to be used for obtaining and documenting the informed consent of the trial subjects.

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1.63. Certified Copy is a copy of original record (irrespective of the media type), which as certified (e.g. through dated signature or a validated copying process) contains the same information including data describing the context, contents and structure, as the original copy;

1.64. Monitoring Plan is a document describing the strategy, methods, responsibilities and requirements for the clinical trial monitoring;

1.65. Validation of Computerized Systems is the process for establishing and documenting of the fact that the requirements set forth for the computerized system by the user are permanently met starting from its design to decommissioning of the computerized system or transition to a new computerized system. Approach to validation of the computerized systems shall be based on risk assessment, which considers the computerized system purpose and its capability to impact on the trial subject protection and reliability of the clinical trial results.

2. Good Clinical Practice Principles

2.1. Clinical trials shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki adopted at the XVII World Health Association Session in 1964, and reflected in these Rules and the applicable regulatory requirements.

2.2. Prior to the trial initiation, foreseeable/predicted risks and inconveniences shall be assessed against the anticipated benefit for a trial

subject and society. The trial shall 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 of primary importance and shall prevail over interests of science and society.

2.4. The available (nonclinical and clinical) information on an investigational medicinal product shall be sufficient to support the proposed clinical trial.

2.5. Clinical trials shall be scientifically sound, and described in a clear, detailed clinical trial protocol (hereinafter referred to as the Protocol).

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

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

2.8. Each individual involved in conducting a trial shall have corresponding education, training and experience to perform his/her respective tasks.

2.9. Voluntary informed consent shall be obtained from every subject prior to his/her enrollment in the clinical trial.

2.10. All clinical trial information shall be recorded, transferred and stored in such a way to ensure its accurate reporting, interpretation and verification.

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This principle applies to all records referenced in these Rules, irrespective of the media type used.

2.11. The confidentiality of records that could identify subjects shall be ensured to respect the privacy and confidentiality rules in accordance with the applicable regulatory requirements.

2.12. Investigational medicinal products shall be manufactured and stored, as well as handled, in accordance with the Rules of Good Manufacturing Practice (GMP) of the Eurasian Economic Union approved by Decision of the Eurasian Economic Commission's Council No. 77 dated November 3, 2016. The investigational medicinal products shall be used in accordance with the approved protocol.

2.13. Systems with procedures that assure the quality of every aspect of the clinical trial shall be implemented.

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Aspects of the clinical trial that are essential to ensure the trial subject protection and reliability of trial results shall be the focus of such systems.

3. Institutional Review Board/ Independent Ethics Committee (IRB/IEC)

3.1. Responsibilities.

3.1.1. The institutional review board/independent ethics committee shall safeguard the rights, safety and well-being of all trial subjects. Special attention shall be paid to trials that may include vulnerable subjects.

3.1.2. The IRB/IEC shall obtain the following documents for review:

trial protocols/protocol amendments;

written informed consent form and consent form updates that the investigator proposes for use in the trial;

description of the activities aimed to subject recruitment for the trial (e.g. advertisements);

written information to be provided to the trial subjects;

investigator's brochure;

available (known) safety information;

information on payments and compensation available to the trial subjects;

investigator’s current curriculum vitae and/or other documentation evidencing the qualifications;

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

The IRB/IEC shall review the issue on conduct of the proposed clinical trial within the reasonable time and provide its opinion in writing, clearly identifying the trial, the documents reviewed and the dates for the following possible decisions:

approval/favorable opinion for the trial conduct;

request to amend the submitted documentation prior to its approval/favorable opinion for the trial conduct;

disapproval/negative opinion for the trial conduct;

termination/suspension of any prior approval/favorable opinion for the trial conduct.

3.1.3. The IRB/IEC shall assess compliance of the investigator's qualifications for the proposed trial on the basis of the current curriculum vitae and/or any other relevant documentation requested by the IRB/IEC.

3.1.4. The IRB/IEC shall conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to the trial 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 hereof 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 trial 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 paragraphs 4.8.12 and

4.8.14 hereof), the IRB/IEC shall make sure that the submitted protocol and/or other document(s) adequately addresses relevant ethical considerations and meets applicable regulatory requirements for such clinical trials.

3.1.7. Where the protocol indicates that obtaining of the consent of the trial subject or the subject's legally acceptable representative is not possible (see paragraph 4.8.15 hereof) prior to the subject inclusion in the trial (e.g. in emergency situations), the IRB/IEC shall make sure that the submitted protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such clinical trials.

3.1.8. The IRB/IEC shall 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 the subjects shall be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9. The IRB/IEC shall ensure that information regarding payment to subjects, including the ways, 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 shall be specified.

3.2. Composition, Functions and Operations.

3.2.1. The IRB/IEC shall include a reasonable number of members, who collectively have the qualifications and experience required to review and assess the scientific, medical and ethics aspects of the proposed trial.

It is recommended that the IRB/IEC shall include:

a) at least five members;

b) at least one member who is not specialized in the area of scientific research (activities);

c) at least one member who is independent of the medical institution/trial site, where the trial is conducted;

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial shall vote/provide opinion on a trial-related matter. The IRB/IEC shall maintain its list of members indicating their qualifications.

3.2.2. The IRB/IEC shall perform its functions according to documented operating procedures, shall document its activities, and shall maintain minutes of its meetings. Its activities shall comply with these Rules and with the applicable regulatory requirements of the Member State legislation.

3.2.3. The IRB/IEC shall 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 the IRB/IEC members who directly participate in the trial documentation review and discussion may vote/provide their opinion and/or advise.

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

3.2.6. The IRB/IEC may involve independent experts in special areas for assistance.

3.3. Procedures.

The IRB/IEC shall establish, document in writing and follow its procedures regulating the following:

3.3.1. 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 the trial documentation.

3.3.4. Determining the frequency of continuing review of the trial documentation.

3.3.5. Providing, according to the applicable regulatory requirements, expedited review and approval/favorable opinion of minor changes in ongoing trials that already have the approval/favorable opinion of the IRB/IEC.

3.3.6. Unacceptability of inclusion of any subject in a trial before the IRB/IEC issues its written approval/favorable opinion of the trial.

3.3.7. Unacceptability of any deviations from or changes of the protocol, if they are initiated without prior written IRB/IEC approval/favorable opinion of the appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the changes concern only administrative or logistical aspects of the trial (e.g. change of monitors, telephone numbers) in accordance with paragraph 4.5.2 of these Rules.

3.3.8. Responsibility of the investigator to promptly report to the IRB/IEC on:

a) deviations from or changes in the protocol to eliminate immediate hazards to the trial subjects in accordance with paragraphs 3.3.7, 4.5.2 and 4.5.4 hereof;

b) changes increasing the risk to subjects and/or affecting significantly the conduct of the trial in accordance with paragraph 4.10.2 hereof;

c) all serious and unexpected adverse drug reactions;

d) new data that may indicate increasing risk for the trial subjects or adversely affect the trial course.

3.3.9. The IRB/IEC responsibility to promptly notify the investigator/institution in writing of:

a) Its trial-related decisions/opinions;

b) the reasons for its decisions/opinions;

c) procedures for appeal of its decisions/opinions.

3.4. Documentation.

The IRB/IEC shall retain all relevant records (e.g. written procedures, membership lists, lists of occupations/affiliations of members, documents submitted for review, minutes of meetings and correspondence) for a period of at least 3 years after completion of the trial and provide them to the regulatory authorities upon their request. Investigators, the sponsor or regulatory authorities may request the IRB/IEC to provide its written procedures and membership lists.

4. Investigator

4.1. Investigator's Qualifications and Responsibilities.

4.1.1. The investigator shall have adequate qualification, education, training and experience to assume responsibility for the proper conduct of the clinical trial. The investigator's qualifications shall meet the applicable regulatory requirements and evidenced through their up-to-date curriculum vitae and/or other relevant documentation, as may be requested by the sponsor, the IRB/IEC and/or the regulatory authorities.

4.1.2. The investigator shall be thoroughly familiar with the appropriate use of the investigational medicinal product, as described in the protocol, in the current investigator's brochure, in the summary of product characteristics and in other information sources provided by the sponsor.

4.1.3. The investigator shall be aware of and comply with these Rules and the applicable regulatory requirements.

4.1.4. The investigator/institution shall assist in monitoring and auditing by the sponsor, and in inspecting by the appropriate regulatory authorities.

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

4.2. Adequate Resources.

4.2.1. The investigator shall be able to demonstrate (e.g. basing on retrospective data) a potential for recruiting the required number of suitable trial subjects within the determined recruitment period.

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

4.2.3. The investigator shall have available an adequate number of qualified staff and physical resources (facilities, equipment) during the trial to conduct the trial properly and safely.

4.2.4. The investigator shall ensure that all persons involved in a clinical trial are adequately informed about the protocol, the investigational medicinal product, and their trial-related duties and functions.

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4.2.5. The investigator is responsible for supervising any individual or party to whom the investigator delegates any trial-related duties and functions conducted at the trial site.

4.2.6. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution shall:

Make sure (get documentary proof) that this individual or party is adequately qualified to perform those trial-related duties and functions;

Implement the procedures to ensure the complete execution of the trial-related duties and functions performed and the integrity of any data generated.

4.3. Medical Care of Trial Subjects.

4.3.1. The physician, who is an investigator or a subinvestigator for the trial, shall be responsible for all trial-related medical decisions.

4.3.2. During and following subject's participation in a trial, the investigator/institution shall ensure that adequate medical care is provided to the trial subject for any trial-related adverse events, including clinically significant abnormal laboratory findings. The investigator/institution shall inform a subject when medical care is needed for intercurrent illnesses 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 the trial subject is not obliged to give his/her reasons for withdrawing prematurely from the trial, the investigator shall make a reasonable effort to ascertain the reasons, while fully respecting the trial subject's rights.

4.4. Communication with an IRB/IEC.

4.4.1. Prior to a trial, the investigator/institution shall have written and dated approval/favorable 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 the trial subjects.

4.4.2. Along with other documents, the investigator/institution shall provide the IRB/IEC with the last revision of the investigator's brochure. If

the investigator's brochure is updated during the trial, the investigator/institution shall submit a copy of the updated investigator’s brochure to the IRB/IEC.

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

4.5. Compliance with the Protocol.

4.5.1. The investigator/institution shall conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authorities and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor shall sign the protocol or a separate contract to confirm agreement.

4.5.2. The investigator shall not implement any deviation from or changes of the protocol without the sponsor's consent and prior review and documented approval/favorable opinion from the IRB/IEC of the amendment, except where necessary to eliminate immediate hazard to trial subjects, or when the changes involve only logistical or administrative aspects of the trial (e.g. change in monitors, change of telephone numbers).

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

4.5.4. The investigator may implement a protocol deviation to eliminate immediate hazard to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and, if appropriate, the proposed protocol amendments shall be submitted to:

a) the IRB/IEC for review and approval/favorable opinion;

b) the sponsor for agreement;

c) the regulatory authorities, if required.

4.6. Investigational Medicinal Products.

4.6.1. Responsibility for investigational medicinal products accountability at the trial sites rests with the investigator/institution.

4.6.2. Where allowed/required, the investigator/institution may/shall assign some or all of the investigator's/institution’s duties for investigational medicinal products accountability at the trial sites 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 pharmacist or another appropriate individual, who is designated by the investigator/institution, shall keep 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 products. These records shall include dates, quantities, batch/lot numbers, expiration dates (if applicable) and the unique code numbers assigned to the investigational medicinal products and trial subjects. Investigators shall maintain records confirming that the trial subjects have been provided with the doses specified by the protocol and with the quantities in accordance with the total amount of the investigational medicinal products received from the sponsor.

4.6.4. The investigational medicinal products shall be stored as specified by the sponsor (see paragraphs 5.13.2 and 5.14.3 hereof) and in accordance with applicable regulatory requirements.

4.6.5. The investigator shall ensure that the investigational medicinal products are used only in accordance with the approved protocol.

4.6.6. The investigator or individual designated by the investigator/institution shall explain the correct use of the investigational medicinal products to each trial subject and shall check, at intervals appropriate for the trial, that each trial subject is following the instructions properly.

4.7. Randomization Procedures and Unblinding.

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

4.8. Informed Consent of Trial Subjects.

4.8.1. In obtaining and documenting informed consent, the investigator shall comply with the applicable regulatory requirements and shall adhere to these Rules and to the ethical principles having their origin in the WMA Declaration of Helsinki. Prior to the trial initiation, the investigator shall have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to the subjects.

4.8.2. The written informed consent form and any other written information to be provided to the subjects should be revised whenever important new information becomes available that may be relevant to the subject’s consent. Any revised written informed consent form and other written information to be provided to the subjects shall receive the IRB/IEC's approval/favorable opinion in advance of their use in the trial. The subject or the subject’s legally acceptable representative shall 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 fact of communication of such information shall be documented.

4.8.3. Neither the investigator nor other individuals involved in the trial shall coerce or unduly influence a subject to participate or to continue to participate in the trial.

4.8.4. None of the oral and written information concerning the trial, including the written informed consent form/patient information sheet, shall contain any wordings 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 individual designated by the investigator shall 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 about the trial and the approval/favorable 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, shall contain as little medical jargon as practical and shall 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 individual designated by the investigator shall provide the subject or the subject's legally acceptable representative with 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 shall 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 subject or the subject's legally acceptable representative and the person who conducted the informed consent discussion shall sign and personally date the written informed consent form.

4.8.9. If a subject or his/her legally acceptable representative is unable to read, an impartial witness shall be present during the entire informed

consent discussion. After the written informed consent form and any other written information to be provided to the 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 shall 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 has been accurately explained to and apparently understood by the subject or the subject's legally acceptable representative and that informed consent has been 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/patient information sheet and any other written information to be provided to the subjects shall include explanations of the following:

a) the trial has investigational nature;

b) objective of the trial;

c) trial treatment options and the probability of random assignment to each treatment group;

d) trial procedures to be followed, including all invasive procedures;

e) subject's responsibilities;

f) trial aspects having investigational nature;

g) foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or neonate;

h) expected benefits. When there is no intended clinical benefit to the subject, the subject shall be made aware of this;

i) apart of the procedures provided for in the trial, alternative procedures or courses of treatment that may be available to the subject and their important potential benefits and risks;

j) compensation and/or treatment available to the subject in the event of trial- related injury;

k) anticipated payment, if any, to the subject for participating in the trial;

l) anticipated expenses, if any, of the subject for participating in the trial;

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

n) the monitors, auditors, IRB/IEC and regulatory authorities 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 applicable laws and regulations and, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access;

o) the records identifying the subject will be kept confidential and may be disclosed only to the extent permitted by the legislation of the Member States. If the results of the trial are to be published, the subject’s identity will remain confidential;

p) 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;

q) the persons to contact for further information regarding the trial and the rights of trial subjects and whom to contact in the event of a trial-related injury;

r) possible circumstances and/or reasons under which the subject's participation in the trial may be terminated;

s) expected duration of the subject's participation in the trial;

t) 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 shall 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 shall receive copies of all signed and dated consent form updates and copies of any amendments to the written information provided to the subjects.

4.8.12. When a clinical trial 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 shall be informed on the trial to the extent compatible with the subject’s understanding and, if capable of doing so, the subject shall sign and personally date the written informed consent form.

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

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

a) the trial objectives cannot be met through the trial in subjects who can give their informed consent personally;

b) foreseeable risks to the subjects are low;

c) the negative impact on the subject’s well-being is minimized and insignificant;

d) the trial is not prohibited by the legislation;

e) the approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects and the written approval/favorable opinion covers this aspect.

Such trials (unless justified) shall be conducted in patients with a disease, which the investigational medicinal product is intended to treat. Subjects in such trials shall be kept under particularly close supervision and their participation shall be terminated if there is any reason to believe that they are experiencing undue discomfort.

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) shall be requested. When prior consent of the subject is not possible and the subject’s legally acceptable representative is not available, enrollment of the subject shall require measures described in the protocol and/or elsewhere, with documented approval/favorable 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 shall be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see paragraph 4.8.10 hereof) shall be requested.

4.9. Documentation and Reports.

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4.9.0. The investigator/institution shall keep adequate and accurate source documents and trial records that include all pertinent observations on each of the site’s trial subject. Source data shall be legible, accurate, complete, be recorded in the course of observations and, thus, shall be

attributable. Changes to source data shall be traceable, shall not obscure the original entry and shall be explained if necessary (e.g. via an audit trail).

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 in the CRF, that are derived from source documents, shall be consistent with the source documents or the discrepancies shall be explained.

4.9.3. Any change or correction to a CRF shall be dated, signed and explained (if necessary) and shall not obscure the original entry (i.e. audit trail shall be maintained). This applies to both written and electronic changes or corrections (see paragraph 5.18.4 (n) hereof). The sponsor shall provide guidance to investigators and/or the investigators' designated representatives on making such corrections. The sponsor shall 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 shall retain records of the changes and corrections.

4.9.4. The investigator/institution shall maintain the trial documents as specified in Subsection 8 of this Section and as required by the applicable regulatory requirements. The investigator/institution shall take measures to prevent accidental or premature destruction of these documents.

4.9.5. Essential documents shall be retained for at least 2 years after the last approval of the marketing application in the Member State and until there are no pending or contemplated marketing applications, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. These documents shall be retained for a longer period however if required by the applicable regulatory

requirements or by a contract 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 in accordance with paragraph 5.5.12 hereof.

4.9.6. The financial aspects of the trial shall be documented in a contract between the sponsor and the investigator/institution.

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

4.10. Trial Progress Reports.

4.10.1. The investigator shall 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 shall promptly provide written reports to the sponsor, the IRB/IEC (in accordance with paragraph 3.3.8 hereof) 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) shall 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 shall be followed promptly by detailed, written reports. The immediate and follow-up reports shall 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 shall also comply with the applicable requirements specified in Annex No. 11 to these Rules determining the procedure for reporting of unexpected serious adverse drug reactions to the regulatory authorities and the IRB/IEC.

4.11.2. All adverse events and/or laboratory abnormalities identified in the protocol as critical to safety assessment shall be reported to the sponsor according to the AE reporting requirements and within the terms specified by the sponsor in the protocol.

4.11.3. When reporting deaths, the investigator shall 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 shall promptly inform the trial subjects, shall assure appropriate therapy and follow-up for the subjects and, where required by the applicable regulatory requirements, shall inform the regulatory authorities. In addition:

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

4.12.2. If the sponsor terminates or suspends a trial (in accordance with paragraph 5.21 hereof), the investigator shall promptly inform the institution where applicable and the investigator/institution shall promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the trial termination or suspension.

4.12.3. If the IRB/IEC terminates or suspends its approval/favorable opinion of the trial (in accordance with paragraphs 3.1.2 and 3.3.9 hereof), the investigator shall inform the institution where applicable and the investigator/institution shall promptly notify the sponsor and provide the

sponsor with a detailed written explanation of the trial termination or suspension.

4.13. Final Investigator's Report.

Upon completion of the trial, the investigator (where applicable) shall inform the institution; the investigator/institution shall provide the IRB/IEC with a summary of the trial's outcome and the regulatory authorities with any reports required (including in the form of a message).

5. Sponsor

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5.0 Quality Management

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors shall focus on trial activities essential to ensuring the clinical trial subject safety and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential/necessary to decision making.

The methods used to assure and control the quality of the trial shall be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor shall ensure that all aspects of the trial are operationally feasible and shall avoid unnecessary complexity, procedures and data collection. Protocols, case report forms and other operational documents shall be clear, concise and consistent.

The quality management system shall use a risk-based approach as described in paragraphs 5.0.1 through 5.0.7 of these Rules.

5.0.1. Critical Process and Data Identification

During protocol development, the sponsor shall identify those processes and data that are critical to ensure trial subject protection and the reliability of trial results.

5.0.2. Risk Identification

The sponsor shall identify risks to critical processes and data of the clinical trial. Risks shall be considered at both the system level (e.g. standard operating procedures, computerized systems, personnel) and clinical trial level (e.g. trial design, data acquisition, informed consent process).

5.0.3 Risk Assessment

The sponsor shall assess the identified risks, against existing risk controls by considering:

a) the likelihood of errors occurring;

b) the extent to which such errors would be detectable;

c) the impact of such errors on the trial subject protection and reliability of trial results.

5.0.4. Risk Control

The sponsor shall decide which risks to reduce and/or which risks to accept. The measures used to reduce risk to acceptable level shall be proportionate to the significance of the risk. The risk mitigation activities may be incorporated in the protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures and training in processes and procedures.

Predefined quality tolerance limits shall be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact the trial subject safety or reliability of results. Detection of deviations

from the predefined quality tolerance limits shall trigger the assessment to determine if any action is needed.

5.0.5. Risk Communication

The sponsor shall document quality management activities. The sponsor shall communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during the clinical trial execution.

5.0.6. Risk Review

The sponsor shall periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

5.0.7 Risk Reporting

The sponsor shall describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (see paragraph 9.6. of Annex No. 1 to these Rules).

5.1. Quality Assurance and Quality Control.

5.1.1. The sponsor is responsible for implementing and maintaining quality assurance and quality control systems along with adopted written SOPs to ensure that trials are conducted and data are documented and reported in compliance with the protocol, these Rules and the applicable regulatory requirements.

5.1.2. The sponsor is responsible for securing consent of all involved parties to grant direct access (in accordance with paragraph 1.49 hereof) to all trial related sites, source data/documents and reports for the purpose of monitoring and auditing by the sponsor and inspection by domestic and foreign regulatory authorities.

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

5.1.4. Contracts made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, shall be in writing, as part of the protocol or as an independent document.

5.2. Contract Research Organization.

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

5.2.2. Any trial-related duty and function that is transferred to and assumed by a contract research organization shall be documented.

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The sponsor shall ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to any third party by the sponsor’s contracted contract research organizations.

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

5.2.4. All references to a sponsor in these Rules also apply to a contract research organization to the extent that a contract research organization has assumed the trial related duties and functions of the sponsor.

5.3. Medical Expertise.

The sponsor shall designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or

problems. If necessary, outside consultants may be appointed for this purpose.

5.4. Trial Design.

5.4.1. The sponsor shall involve 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 analyzing and preparing interim and final clinical trial reports.

5.4.2. The sponsor shall consider requirements of Subsection 6 of this Section and Annex No. 11 hereto.

5.5. Trial Management, Data Handling and Record Keeping

5.5.1. The sponsor must involve 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 make a decision on establishing an independent data-monitoring committee (IDMC) to review the clinical trial progress, including the safety data and the critical efficacy parameters and to recommend to the sponsor whether to continue, stop or modify the trial. The IDMC shall 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 shall:

a) ensure and document that the electronic data processing systems conform to the sponsor’s established requirements for completeness, accuracy, reliability and consistent intended performance (i.e. validation).

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The sponsor shall base its approach to validation of such systems on a risk assessment that takes into consideration the intended use of the system

and the potential of the system to affect trial subject protection and reliability of trial results.

The approach to validation of such electronic systems for handling study data and/or electronic systems for remote access to data shall be carried out by the sponsor based on a risk assessment, taking into account the intended use of the system and its potential impact on the protection of trial subjects and reliability of the clinical trial results;

The approach to validating such systems shall be based on a risk assessment, taking into account the intended use of the system and its potential impact on the protection of trial subjects and reliability of the clinical trial results.

b) have SOPs for using such systems.

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The SOPs shall cover system setup, installation and operation. The SOPs shall describe system validation and functionality testing, data acquisition and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning and decommissioning. The responsibilities of the sponsor, investigator and other parties with respect to the use of these computerized systems shall be clear and the users shall be provided with training in their use.

c) 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 the previously entered data (i.e. maintain an audit trail);

d) maintain a security system that prevents unauthorized access to the data;

e) maintain a list of individuals authorised to make data changes (in accordance with paragraphs 4.1.5 and 4.9.3 hereof);

f) maintain adequate backup of the data;

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

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ensure the integrity of the data including any data that describe the context, content and structure. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.

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

5.5.5. The sponsor shall use an unambiguous subject identification code (in accordance with paragraph 1.11 hereof) that allows identification of all the data reported for each subject.

5.5.6. The sponsor, or other owners of the data, shall retain all of the sponsor-specific essential documents pertaining to the trial (in accordance with Subsection 8 of this Section).

5.5.7. The sponsor shall retain all sponsor-specific essential documents on the trial in compliance with the applicable regulatory requirements of the legislation of the Member States, where the product is approved and/or where the sponsor intends to apply for approvals.

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

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

5.5.10. Any transfer of ownership of the data shall be reported to the appropriate authorities, as required by the applicable regulatory requirements.

5.5.11. The sponsor-specific essential documents shall be retained until at least 2 years have elapsed after the last approval of the drug marketing authorisation application in a Member State and until there are no pending or contemplated marketing authorisation applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. These documents shall be retained for a longer period, if required by the applicable regulatory requirements or if needed by the sponsor.

5.5.12. The sponsor shall inform the investigators/institutions in writing of the need for record retention and shall notify the investigators/institutions 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 investigators/institutions. Each investigator shall have qualification, experience and adequate resources (see paragraphs 4.1 and 4.2 hereof) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigators are to be utilized in multicentre trials, their organization and/or selection are the sponsor's responsibility.

5.6.2. Before signing a contract with an investigator/institution to conduct a trial, the sponsor shall provide the investigator/institution with the protocol and an up-to-date investigator's brochure and shall provide sufficient

time for the investigator/institution to review the protocol and the information provided.

5.6.3. The sponsor shall obtain the investigator's/institution's consent for:

a) conducting the trial in compliance with these Rules and the applicable regulatory requirements (see paragraph 4.1.3 hereof) and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC (see paragraph 4.5.1 hereof);

b) compliance with procedures for data recording/reporting;

c) monitoring, auditing and inspection (see paragraph 4.1.4 hereof);

d) retaining the trial-related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see paragraphs 4.9.4 and 5.5.12 hereof). The sponsor and the investigator/institution shall sign the protocol, or an alternative document, to confirm this consent.

5.7. Allocation of Responsibilities.

Prior to initiating a trial, the sponsor shall 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 requirements, the sponsor shall provide insurance or shall 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 of the investigator or the investigator's personnel.

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

5.8.3. When trial subjects receive compensation, the method and manner of compensation shall comply with applicable regulatory requirements.

5.9. Financing.

The financial aspects of the trial shall be documented in the contract between the sponsor and the investigator/institution.

5.10. Notification/Submission to Regulatory Authorities.

Before initiating the clinical trials, the sponsor (or the sponsor jointly with the investigator, if required by the applicable regulatory requirements) shall submit any required applications to the appropriate authorities for review, acceptance and/or permission (as required by the applicable regulatory requirements) to begin the trials. Any notification/submission shall be dated and contain sufficient information to identify the protocol.

5.11. Confirmation of Review by IRB/IEC

5.11.1. The sponsor shall obtain from the investigator/institution:

a) the name and address of the investigator's/institution’s IRB/IEC;

b) a statement obtained from the IRB/IEC that it is organized and operates according to these Rules and the applicable legislation of the Member State;

c) documented IRB/IEC approval/favorable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent forms 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/favorable opinion upon changes in any aspect of the trial, such as amendments to the protocol, written informed consent form and any other written information to be

provided to subjects and/or other procedures, the sponsor shall obtain from the investigator/institution a copy of the amendments made and the date approval/favorable opinion has been given by the IRB/IEC.

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

5.12. Information on Investigational Medicinal Products

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

5.12.2. The sponsor shall 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 Medicinal Products

5.13.1. The sponsor shall ensure that the investigational medicinal products (including active comparators and placebo, if applicable) is characterized as appropriate to the stage of the product development, is manufactured in accordance with any applicable GMP requirements and is coded and labelled in a manner that ensures the blinding, if applicable. In addition, the labelling shall comply with applicable regulatory requirements.

5.13.2. The sponsor shall determine, for the investigational medicinal products, acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures and devices for the product infusion, if any. The sponsor shall inform all involved parties

(e.g. monitors, investigators, pharmacists, storage managers) of these requirements.

5.13.3. The investigational medicinal products shall be packaged to prevent contamination and their intactness/suitability during transport and storage.

5.13.4. In blinded trials, the coding system for the investigational medicinal products shall include a mechanism that permits rapid identification of the products in case of a medical emergency, but does not permit undetectable breaks of the blinding.

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

5.14. Supplying and Handling Investigational Medicinal Products

5.14.1. The sponsor is responsible for supplying the investigators/institutions with the investigational medicinal products.

5.14.2. The sponsor shall not supply an investigator/institution with the investigational medicinal products until the sponsor obtains all required documentation (e.g. approval/favorable opinion from IRB/IEC and regulatory authorities).

5.14.3. The sponsor shall ensure that written procedures include instructions that the investigator/institution shall follow for the handling and storage of investigational medicinal products for the trial and documentation thereof. The procedures shall address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects and return of unused investigational medicinal products to the sponsor (or alternative

disposition if authorized by the sponsor and in compliance with the applicable regulatory requirements).

5.14.4. The sponsor shall:

a) ensure timely delivery of investigational medicinal products to the investigators;

b) document the shipment, receipt, disposition, return and destruction of the investigational medicinal products (see Subsection 8 of this Section);

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

d) maintain a system for the disposition (or alternative disposal) of unused investigational medicinal products and for the documentation of this disposition (or alternative disposal).

5.14.5. The sponsor shall:

a) take steps to ensure that the investigational medicinal products are stable over the period of use;

b) have sufficient quantities of the investigational medicinal products used in the trials to reconfirm specifications, shall this become necessary and maintain records of batch sample analyses and characteristics. Depending on the stability, the samples shall be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirements, whichever represents the longer retention period.

5.15. Access to Trial Documentation

5.15.1. The sponsor shall envisage in the protocol or other written agreement that the investigators/institutions are obliged to provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review and regulatory inspection.

5.15.2. The sponsor shall 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 medicinal products.

5.16.2. The sponsor shall promptly notify all concerned investigators/institutions and the regulatory authorities of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favorable opinion to continue the trial.

5.17. Adverse Drug Reaction Reporting.

5.17.1. The sponsor shall expedite the reporting to all concerned investigators/institutions, to the IRBs/IECs, where required, and to the regulatory authorities of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2. Such expedited reports shall comply with the applicable regulatory requirements and Annex No. 11 to these Rules.

5.17.3. The sponsor shall submit for review to the regulatory authorities all safety information updates and periodic safety reports for the investigational medicinal product, as required by applicable regulatory requirements and Annex No. 1 to these Rules.

5.18. Monitoring.

5.18.1. Purpose.

The purposes of trial monitoring are to verify that:

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

b) the reported trial data are accurate, complete and verifiable from source documents;

c) the trial is conducted in compliance with the currently approved protocol/amendments, with these Rules and with the applicable regulatory requirements.

5.18.2. Selection and Qualifications of Monitors.

a) Monitors shall be appointed by the sponsor;

b) Monitors shall be appropriately trained and shall have the scientific and/or clinical knowledge needed to monitor the trial adequately. Monitor's qualifications shall be documented.

c) Monitors shall be thoroughly familiar with the investigational medicinal products, the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, these Rules and the applicable regulatory requirements.

5.18.3. Extent and Nature of Monitoring.

The sponsor shall ensure that the trials are adequately monitored. The sponsor shall determine the appropriate extent and nature of monitoring basing on the trial objective, purpose, methodology, complexity, blinding, size and the trial endpoints. 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 these Rules. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

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The sponsor shall develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this Section is intended to permit varied approaches that improve the monitoring effectiveness and efficiency. The

sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring only. The sponsor shall document the rationale for the chosen monitoring strategy (e.g. in the monitoring plan).

On-site monitoring is performed at the sites, where the clinical trial is being conducted. Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g. data managers, biostatisticians).

Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.

Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:

a) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations;

b) examine data trends such as the range, consistency and variability of data within and across sites;

c) evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems;

d) analyze site characteristics and performance metrics;

e) select sites and/or processes for targeted on-site monitoring.

5.18.4. Monitor's Responsibilities.

The monitors in accordance with the sponsor’s requirements shall ensure that the trial is conducted and documented properly. For that purpose, when relevant and necessary to the specific trial and the trial site, the monitor performs the following activities:

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 paragraphs 4.1, 4.2 and 5.6 hereof) and remains adequate throughout the trial period, that facilities, including laboratories, equipment and staff, are adequate to conduct the trial safely and properly and remains adequate throughout the trial period.

c) verifying, for the investigational medicinal products:

that the storage conditions and periods are acceptable and that supplies are sufficient throughout the trial;

that the investigational medicinal products are supplied only to subjects who are eligible to receive it and at the protocol specified doses;

that subjects are provided with necessary instruction on properly using, handling, storing and returning the investigational medicinal products;

that the receipt, use and return of the investigational medicinal products at the trial sites are controlled and documented adequately;

that the disposition of unused investigational medicinal products at the trial sites complies with applicable regulatory requirements and is in accordance with the sponsor;

d) verifying that the investigator follows the approved protocol and all approved amendments, 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 version of the investigator's brochure, all documents and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirements;

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 unauthorized individuals;

i) verifying that the investigator complies with subject selection criteria at their inclusion in the trial;

j) reporting the subject recruitment rate;

k) verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained, as well as the procedure for maintaining such documents;

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) verifying the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically shall 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 in 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 in the CRFs;

all withdrawals and dropouts of enrolled subjects from the trial are reported and explained in the CRFs;

n) informing the investigator of any CRF entry error, omission, or illegibility. The monitor shall ensure that appropriate corrections, additions, or deletions made are dated, explained (if necessary) and signed by the investigator or by a member of the investigator's trial staff who is authorized to sign the CRF changes for the investigator. This authorization shall be documented;

o) determining whether all adverse events (AEs) are appropriately reported within the time periods required by these Rules, the protocol, the IRB/IEC, the sponsor and the applicable regulatory requirements;

p) determining whether the investigator is maintaining the essential documents (in accordance with Subsection 8 of this Section).

r) communicating deviations from the protocol, SOPs, these Rules 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 shall 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. Monitoring Report.

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

b) reports shall include the date, site, name of the monitor and name of the investigator or another individual contacted.

c) reports shall 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, these Rules and regulatory authorities.

d) the review and follow-up of the monitoring report with the sponsor shall be documented by the sponsor’s designated representative.

ADDENDUM

e) reports of on-site and/or centralized monitoring shall be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up. Results of monitoring activities shall be documented in sufficient detail to allow verification of compliance with the monitoring plan. Reporting of centralized monitoring activities shall be regular and may be independent from site monitoring visits.

ADDENDUM

5.18.7. Monitoring Plan

The sponsor shall develop a monitoring plan that is tailored to the specific trial subject protection and data integrity risks of the trial. The plan shall describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used and the rationale for their use. The plan shall also emphasize the monitoring of critical data and processes. Particular attention shall be given to those aspects that are not routine clinical practice and require additional training of the personnel. The monitoring plan shall reference the applicable policies and procedures of the sponsor.

5.19. Audit.

If or when sponsors perform audits, as part of implementing quality assurance, they shall 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, shall be to evaluate trial

compliance with the protocol, SOPs, these Rules and the applicable regulatory requirements.

5.19.2. Selection and Qualification of Auditors.

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

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

5.19.3. Auditing Procedures.

a) The sponsor shall ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures determining the audit object, audit methods, audit frequency, as well as the audit report form and contents.

b) When developing a trial audit plan and procedures, the sponsor shall consider 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 problems.

c) The observations and findings of the auditors shall be documented.

d) To preserve the independence and value of the audit function, the regulatory authorities shall not routinely request the audit reports. Regulatory authorities may seek access to an audit report on a case by case basis when evidence of serious non-compliance with these Rules exists, or in the course of legal proceedings.

e) When required by applicable legislation of the Member State, the sponsor shall provide an audit certificate.

5.20. Noncompliance.

5.20.1. Noncompliance with the protocol, SOPs, these Rules and/or applicable regulatory requirements by an investigator/institution, or by

members of the sponsor's personnel shall lead to prompt action by the sponsor to secure compliance.

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If noncompliance of any requirements specified in indent 1 of this paragraph, that significantly affects or has the potential to significantly affect the trial subject protection or reliability of trial results, is discovered, the sponsor shall perform a root cause analysis and implement appropriate corrective and preventive actions.

5.20.2. If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor shall terminate the investigator's/institution’s participation in the trial. When an investigator's/institution’s participation is terminated due to noncompliance, the sponsor shall notify promptly the regulatory authorities.

5.21. Premature Termination or Suspension of a Trial.

If a trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators/institutions and the regulatory authorities of the termination or suspension and the reasons for the termination or suspension. The IRB/IEC shall also be informed promptly and provided with the reasons for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirements.

5.22. Clinical Trial/Study Report.

Whether a trial is completed as per the protocol or prematurely terminated, the sponsor shall ensure that the clinical trial reports are prepared and provided to the regulatory authorities as required by the applicable regulatory requirements under the form provided in Annex No. 1 to these Rules. The sponsor shall also ensure that the clinical trial reports in marketing authorization applications meet the requirements of

Annex No. 1 and the Rules of Marketing Authorization and Assessment of Medicinal Products for Human Use.

5.23. Multicenter Trials.

For multicenter trials, the sponsor shall 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 authorities and given approval/favorable opinion by the IRB/IEC.

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

5.23.3. The responsibilities of coordinating investigators and the other participating investigators shall be documented prior to the start of the trial.

5.23.4. All investigators shall be instructed on following the protocol, complying with the uniform set of standards for the assessment of clinical and laboratory findings and on completing the CRFs.

5.23.5. Communication between investigators shall be facilitated.

6. Clinical Trial Protocol and Protocol Amendments

The contents of a trial protocol shall generally have the following structure. However, site specific information may be provided on separate protocol pages, 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 amendments shall also bear the amendment numbers and dates.

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

6.1.3. Names and positions of the persons authorized to sign the protocol and the protocol amendments for the sponsor.

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

6.1.5. Names and positions of the investigators who are responsible for conducting the trial and the addresses and telephone numbers of the trial sites.

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

6.1.7. Names and addresses of the clinical laboratories and other medical and/or technical departments and/or institutions involved in the trial.

6.2. Background Information.

6.2.1. Name and description of the investigational medicinal products.

6.2.2. Summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the specific 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 periods.

6.2.5. A statement that the clinical trial will be conducted in compliance with the protocol, these Rules and the applicable regulatory requirements.

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 justification of the trial and the credibility of the data obtained in the trial depend substantially on the trial design. The trial design description shall include the following:

6.4.1. A specific statement of the primary endpoints and the secondary endpoints (if any) to be assessed 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 the schematic diagram of the trial design, procedures and stages.

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

a) randomization;

b) blinding/masking.

6.4.4. The description of the trial treatments, the dosing and dosage regimen of the investigational medicinal products (includes the description of the dosage form, packaging and labelling of the investigational medicinal products).

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

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

6.4.7. The accountability procedures for the investigational medicinal products, including the placebos and comparators (if any).

6.4.8. Keeping the trial treatment randomization codes and procedures for their breaking.

6.4.9. The list of all 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 medicinal product treatment/trial treatment) and procedures specifying:

a) when and how to withdraw subjects from the investigational medicinal product treatment/trial treatment;

b) type and timing of the data to be collected for the withdrawn subjects;

c) whether and how subjects are to be replaced, if it is envisaged;

d) follow-up for subjects withdrawn from the investigational medicinal product treatment/trial treatment.

6.6. Treatment of Subjects.

6.6.1. The treatments to be administered, including the names of all the medicinal products, doses, dosing regimens, routes/modes of administration and the treatment periods, including the follow-up periods for subjects for each investigational medicinal product treatment/trial treatment group/arm of the trial.

6.6.2. The medicinal products/treatment types permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3. Procedures for monitoring the trial subject compliance.

6.7. Assessment of Efficacy.

6.7.1. List of the efficacy parameters.

6.7.2. Methods and timing for assessing, recording and analyzing the efficacy parameters.

6.8. Safety Assessment.

6.8.1. List of safety parameters.

6.8.2. Methods and timing for assessing, recording and analyzing the safety parameters.

6.8.3. Requirements for reports, procedures for recording and reporting the adverse events and intercurrent diseases.

6.8.4. Type and duration of the follow-up of subjects after occurrence of the adverse events.

6.9. Clinical Trial Statistics Considerations.

6.9.1. Description of the statistical methods to be applied, including timing of any planned interim analysis.

6.9.2. Number of subjects planned to be enrolled. For multicenter trials, the number of subjects to be enrolled at each trial site shall be identified. Justification of the sampling size, including clarifications or calculations to justify the trial statistical power and the trial clinical reasonability.

6.9.3. The level of significance to be used.

6.9.4. Criteria for the termination of the trial.

6.9.5. Procedures for accounting for missing, unusable and spurious data.

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

6.9.7. Selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

6.10. Direct Access to Source Data/Documents.

The sponsor shall ensure in the protocol or in another written agreement that the investigators/institutions are not to obscure trial-related monitoring, audits, IRB/IEC review and regulatory inspections and provide direct access to source data/documents.

6.11. Quality Control and Quality Assurance.

6.12. Ethical Considerations.

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. Clinical Trial Results Publications.

Publication policy, if not addressed in a separate contract.

6.16. Annexes to the protocol.

7. Investigator’s Brochure

7.1. Introduction.

The investigator's brochure is a compilation of the clinical and non-clinical data on the investigational medicinal products that are relevant to the study of the products in human subjects. The purpose of the investigator's brochure is to provide the investigators and other persons 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, modes of administration and safety monitoring procedures. The investigator's brochure also provides insight to support the clinical management of the trial subjects during the clinical trial course. The information shall 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

worthiness of the proposed trial. For this reason, a medical expert shall generally participate in development of an investigator's brochure, but the contents of the investigator's brochure shall be approved by the specialist in the disciplines that generated the described data.

These Rules delineate the minimum information that shall be included in investigator's brochure and provide recommendations for its layout. It is expected that the nature and extent of information available will change with the stage of development of the investigational medicinal product. If the investigational medicinal product is marketed and its pharmacology is widely understood by medical practitioners, the investigator's brochure may be less detailed. Where permitted by the regulatory authorities, a basic product information documents, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive and detailed information on all aspects of the investigational medicinal 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 investigator's brochure specific to that new use shall be prepared. The investigator's brochure shall be reviewed at least annually and revised as necessary in compliance with a sponsor's standard procedures. More frequent revision may be appropriate depending on the stage of development and the generation of the relevant new information. However, in accordance with the Good Clinical Practice principles, such relevant new information may be so important that it shall be communicated to the investigators and, if required, to the IRB/IEC and/or regulatory authorities before it is included in the new revision of the investigator's brochure.

Generally, the sponsor is responsible for ensuring that the up-to-date investigator's brochure is made available to the investigators and the

investigators are responsible for providing the up-to-date investigator's brochure to the responsible IRB/IEC.

In the case of an investigator sponsored trial, the sponsor-investigator shall consider the possibility to obtain the brochure from the commercial manufacturer. If the investigational medicinal product is provided by the sponsor-investigator, then he/she shall provide the necessary information to the personnel involved in the trial. In cases where preparation of a formal investigator's brochure is impractical, the sponsor-investigator shall provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information envisaged by these Rules.

7.2. General Considerations.

The investigator's brochure shall include:

7.2.1. Title Page.

This shall indicate the sponsor's name, the identity of each investigational medicinal product (i.e. trial number, chemical or approved generic name and trade names where legally permissible and desired by the sponsor) and the date of the investigator's brochure revision. The investigator's brochure version number and the reference to the number and date of the version it supersedes shall be provided.

7.2.2. Confidentiality Statement.

The sponsor may wish to include in the investigator's brochure a statement instructing the investigator/recipients to treat the investigator's brochure 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 investigator's brochure shall contain the following sections, each of which (if applicable) should contain the list of literature references:

7.3.1. Table of Contents.

7.3.2. Summary.

A brief summary (preferably not exceeding two pages) shall 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 medicinal product.

7.3.3. Introduction.

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

7.3.4. Physical, Chemical and Pharmaceutical Properties and Dosage Form

The description of the investigational medicinal product substances (including the chemical and/or structural formula(e)) shall be provided and a brief summary of the relevant physical, chemical and pharmaceutical properties shall be given.

To ensure appropriate safety measures to be taken in the course of the trial, a description of the formulation of the dosage form to be used, including excipients, shall be provided and justified, if required. Instructions for the storage and handling of the dosage forms shall also be provided.

Any structural similarities to other known compounds shall be mentioned.

7.3.5. Nonclinical Studies.

Introduction.

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic and metabolism studies of the investigational medicinal product shall be provided in a summary form. This summary shall address the methods used, the results and discussion of the relevance of the findings to the investigated therapeutic and the possible unfavorable and unintended effects in humans. The information provided may include the following, as appropriate, if known/available:

animal 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;

dose response of effects;

time to onset of effects;

reversibility of effects;

duration of the effects.

Tabular format/listings shall be used whenever possible to enhance the clarity of the presentation. The following sections shall contain 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 required, the effective and nontoxic dose findings in the same animal species shall be compared (i.e. the therapeutic index shall be determined). The relevance of this information to the proposed human dosing shall be addressed. Whenever possible, comparisons shall be made in terms of blood/tissue levels rather than on a mg/kg basis.

a) Nonclinical pharmacology.

This section shall include a summary of the pharmacological properties of the investigational medicinal product and, where appropriate, its significant metabolites studied in animals. Such a summary shall incorporate studies that assess the possible therapeutic potency (e.g. efficacy models, ligand-receptor interaction and specificity) as well as those that assess safety (e.g. special studies to assess pharmacological effects other than the intended therapeutic effects).

b) Pharmacokinetics and product metabolism in animals.

This section shall include a summary of the pharmacokinetics and biological transformation and disposition of the investigational medicinal product in all species studied. The discussion of the findings shall address the absorption and the local and systemic bioavailability of the investigational medicinal product and its metabolites and their relationship to the pharmacological and toxicological findings in animal species.

c) Toxicology.

This section shall include a brief description of the toxic effects of the investigational medicinal product revealed in the studies in various animal species. Where possible, the following structure of the table of contents for this section shall be followed:

single dose toxicity;

repeated-dose toxicity;

carcinogenicity;

special studies (for example, local irritant effect, sensitizing effect study);

reproductive toxicity;

genotoxicity (mutagenicity).

7.3.6. Effects in Humans.

Introduction.

The known effects of the investigational medicinal product in humans shall be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities shall be thoroughly discussed in this section. Where possible, a summary of each completed clinical trial shall be provided. Information shall also be provided regarding results of any use of the investigational medicinal product other than from clinical trials (e.g. data obtained during the product post-authorization use).

a) Pharmacokinetics and product metabolism in humans.

This section shall contain a summary of information on the pharmacokinetics of the investigational medicinal product, including the following, if available:

pharmacokinetics (including metabolism, as appropriate and absorption, plasma protein binding, distribution and elimination);

bioavailability of the investigational medicinal product (absolute, where possible and/or relative) using a reference dosage form as comparator;

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 pharmacokinetics studies in various groups performed within clinical trials).

b) Safety and efficacy.

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

The investigator's brochure shall provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the investigational medicinal product and with the related products. The precautions or special monitoring to be done as part of the investigational use of the products shall be also described.

c) Post-authorization experience.

The investigator's brochure shall identify countries where the investigational medicinal product has been marketed or authorized. Any significant information arising from the marketed use shall be summarized (e.g. dosage forms, dosages, routes of administration and adverse product reactions). The investigator's brochure shall also identify all the countries where the investigational medicinal product did not receive approval/authorization for marketing or was withdrawn from marketing/authorization.

7.3.7. Summary of Data and Guidance for the Investigator.

This section shall provide an overall discussion of the non-clinical and clinical data and shall summarize the information from various sources on different aspects of the investigational medicinal products, wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on the related products shall 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 shall be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological and clinical information on the investigational medicinal products. Guidance shall 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 medicinal product.

8. List of Essential Documents for a Clinical Trial

8.1. Introduction.

The clinical trial essential documents are the documents, which individually and collectively permit evaluation of the trial conduct and the quality of the data obtained. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the Good Clinical Practice principles 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 trial management 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 authorities 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 is provided below. 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 (in accordance with paragraph 8.2 of these Rules);

2) during the clinical conduct of the trial (in accordance with paragraph 8.3 of these Rules);

3) after completion or termination of the trial (in accordance with paragraph 8.4 of these Rules);

The indicated below subparagraphs of Subsection 8 of this Section contain the purpose of each document and whether it shall be filed in either the investigator/institution and/or sponsor files. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files shall be generated at the beginning of the trial, both at the investigator/institution’s site and at the sponsor's office. The final trial close-out 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 these Rules may be subject to and shall be available for audit by the sponsor's auditor and inspection by the regulatory authorities.

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The sponsor and investigator/institution shall maintain the record of the locations of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) shall provide for document identification, version history, search and retrieval.

Essential documents for the trial shall be supplemented or may be reduced where justified (in advance of trial initiation) basing on the importance and relevance of the specific documents to the trial.

The sponsor shall ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor shall not have exclusive control of those data.

When a copy is used to replace an original document (e.g. source documents, CRF), the copy shall fulfill the requirements for certified copies.

The investigator/institution shall have control of all essential documents and records generated by the investigator/institution before, during and after the trial.

8.2. Before the Clinical Phase of the Trial Commences

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

Document name	Purpose	Located in Files of	
		the Investigator/ Institution	the Sponsor
8.2.1. Investigator's Brochure	to document that relevant and current scientific information	X	X

Document name	Purpose	Located in Files of	
		the Investigator/ Institution	the Sponsor
	about the investigational medicinal product has been provided to the investigator		
8.2.2. Clinical trial planning documents: signed protocol and its amendments (if any) and sample CRF	to document investigator and sponsor agreement to the protocol/amendments and CRF	X	X
8.2.3. Information provided to trial subject	to document the informed consent, to document that subjects will be given the appropriate written information (content and wording) to support their ability to give fully informed consent. To document that recruitment measures are appropriate and not coercive		
informed consent form (including all applicable explanatory materials)		X	X
any other written information		X	X
advertisement for subject recruitment (if used)		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 subjects for trial-related injury will be available	X	X
8.2.6. Signed agreement between involved parties, e.g.:	to document the parties rights, responsibilities and relations between the		
investigator/institution and the sponsor		X	X
between the investigator/institution and the contract research organization		X	X (where required)
between the sponsor and the contract research organization			X

Document name	Purpose	Located in Files of	
		the Investigator/ Institution	the Sponsor
between the investigator/institution and the regulatory authorities (where required)		X	X
8.2.7. Dated, documented approval/favorable opinion of the IRB/IEC of the following documents:	to document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. identify the version number and date of the documents		
protocol and any amendments, CRF (where required)		X	X
informed consent forms			
any other written information to be provided to the subjects			
advertisement for subject recruitment (if used)			
trial subject compensation (if any)			
any other permitted/approved documents			
8.2.8. Composition of the IRB/IEC, Ethics Committee (EC)	to document that the IRB/IEC is constituted in agreement with these Rules	X	X (where required)
8.2.9. Regulatory authorities authorization/approval/ notification of protocol (where required)	to document appropriate authorization/approval/notification by the regulatory authorities has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirements	X (where required)	X (where required)
8.2.10. Current version of a curriculum vitae and other relevant documents evidencing	to document qualifications and eligibility to conduct the trial and/or provide medical supervision of subjects	X	X

Document name	Purpose	Located in Files of	
		the Investigator/ Institution	the Sponsor
qualifications of investigators and sub-investigators			
8.2.11. Normal values/ranges for medical/ laboratory/technical procedures and/or tests included in the protocol	to document normal values and/or ranges of the tests	X	X
8.2.12. Medical/laboratory/technical procedures and/or tests, – certification, accreditation, established quality control and/or external quality assessment, other validation methods (where required)	to document competence of a facility to perform required tests and support reliability of results	X (where required)	X
8.2.13. Sample of labels on the investigational medicinal product packages	to document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
8.2.14. Instructions for handling of investigational medicinal products and trial-related materials (if not included in the protocol or the investigator's brochure)	to document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational medicinal products and trial-related materials	X	X
8.2.15. Shipping records for investigational medicinal products and trial-related materials	to document shipment dates, batch numbers and method of shipment of investigational medicinal products and trial-related materials. Allows tracking of product batch, monitor the shipping conditions and accountability	X	X
8.2.16. Certificates of analysis of investigational medicinal products shipped	to document identity, purity of the investigational medicinal products and active substance assay (dosage) in them		X

Document name	Purpose	Located in Files of	
		the Investigator/ Institution	the Sponsor
8.2.17. Decoding procedures for blinded trials	to document the procedure for emergency identification of the masked investigational medicinal product without unmasking the rest subjects	X	X (third party if applicable)
8.2.18. Randomization list	to document method of the trial subjects randomization		X (third party if applicable)
8.2.19. Pre-trial monitoring report	to document the trial site acceptability of a specific trial (may be combined with item 8.2.20 of this Table)		X
8.2.20. Trial initiation monitoring report	to document that the investigator and the investigator's personnel involved in the trial are familiar with the trial procedures (may be combined with item 8.2.19 of this Table)	X	X

8.3. During the Clinical Conduct of the Trial

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

Document name	Purpose	Located in Files of	
		the Investigator/ Institution	the Sponsor
8.3.1. Investigator's brochure updates	to document that the investigator/institution is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2. Any revision to: the protocol/amendments and CRF, informed consent	to document revisions of these trial-related documents that take effect	X	X

Document name	Purpose	Located in Files of	
		the Investigator/ Institution	the Sponsor
form, any other written information provided to subjects, advertisement for subject recruitment (if used)	during trial		
8.3.3. Dated, documented approval/favorable opinion of the IRB/IEC of the following documents: protocol amendments, updates of: informed consent form, information materials to be provided to the subjects advertisement for subject recruitment (if used) any other documents given approval/favorable opinion continuing review of trial (where required)	to document that the amendments and/or revisions have been subject to IRB/IEC review and are given approval/favorable opinion. Identify the version number and date of the documents.	X	X
8.3.4. Regulatory authorities authorizations/approvals/notifi cations, where required, for:	to document compliance with applicable regulatory requirements	X (where required)	X
8.3.5. Current version of a curriculum vitae for new investigators and/or subinvestigators	see item 8.2.10 of this Table	X	X
8.3.6. Updates to normal values/ranges for medical/ laboratory/ technical procedures/tests included in the protocol	to document normal values and ranges that are revised during the trial (see item 8.2.11 of this Table)	X	X
8.3.7. Updates of medical/laboratory/ technical procedures/tests, certification, accreditation, established quality control and/or external quality assessment, other validation (where required)	to document that tests remain adequate throughout the trial period (see item 8.2.12 of this Table)	X (where required)	X

Document name	Purpose	Located in Files of	
		the Investigator/ Institution	the Sponsor
8.3.8. Documentation of investigational medicinal products and trial-related materials shipment	see item 8.2.15 of this Table	X	X
8.3.9. Certificates of analysis for new batches of investigational medicinal products	see item 8.2.16 of this Table		X
8.3.10. Monitoring visit reports	to document site visits by and findings of the monitor		X
8.3.11. Trial-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 reporting	X	X
8.3.12. Signed informed consent forms/patient information sheet	to document that consent is obtained in accordance with these Rules and protocol and dated prior to participation of each subject in trial. Moreover, to document direct access permission (see item 8.2.3 of this Table)	X	
8.3.13. Source documents	to document the existence of the subject and substantiate integrity of trial data collected. To include the original documents related to the trial, medical treatment and history of a subject	X	
8.3.14. Signed, dated and completed CRFs	to document that the investigator or authorized member of the investigator's personnel confirms the observations recorded	X (copy)	X (original)
8.3.15. CRF correction documenting	to document all changes/additions or	X (copy)	X (original)

Document name	Purpose	Located in Files of	
		the Investigator/ Institution	the Sponsor
	corrections made to a CRF after initial data were recorded		
8.3.16. Investigator's notification of serious adverse events to the sponsor and the related reports	Investigator's notification of serious adverse events to the sponsor and the related reports in accordance with paragraph 4.11 of these Rules	X	X
8.3.17. Notification by the sponsor and/or investigator/institution, where applicable, to regulatory authorities and IRBs/IECs of unexpected serious adverse drug reactions and of other safety information	notification the sponsor and/or investigator/institution, where applicable, to regulatory authorities and IRBs/IECs of unexpected serious adverse drug reactions in accordance with subparagraphs 5.17 and 4.11.1 of these Rules and of other safety information in accordance with subparagraphs 5.16.2 and 4.11.2 of these Rules	X (where required)	X
8.3.18. Notification by the sponsor to investigators of safety information	notification by the sponsor to investigators of safety information in accordance with paragraph 5.16.2 of these Rules	X	X
8.3.19. Interim or annual reports to the IRB/IEC and regulatory authorities	interim or annual reports provided to the IRB/IEC in accordance with paragraph 4.10 of these Rules and to authorities in accordance with paragraph 5.17.3 of these Rules	X	X (where required)
8.3.20. Subject screening log	to document identification of subjects who passed the pre-trial screening	X	X (where required)
8.3.21. Subject identification code list	to document that investigator/institution keeps a confidential list of	X	

Document name	Purpose	Located in Files of	
		the Investigator/ Institution	the Sponsor
	names of all subjects allocated to trial numbers on enrolling in the trial. Allows the investigator/institution to reveal identity of any subject		
8.3.22. Subject enrollment log	to document chronological enrollment of subjects by trial identification numbers	X	
8.3.23. Investigational medicinal products accountability at the trial site	to document that investigational medicinal products have been used according to the protocol	X	X
8.3.24. Signature sheet	to document signatures and initials of all persons authorized to make entries and/or corrections in 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 Subsections 8.2 and 8.3 of these Rules shall be in the file together with the following documents:

Document name	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
8.4.1. Investigational medicinal products accountability at the trial site/medical institution	to document that investigational medicinal products have been used	X	X

Document name	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
	according to the protocol. To documents the final accounting of investigational medicinal products received at the trial site/medical institution, dispensed to the trial subjects, returned by the trial subjects and returned to the sponsor		
8.4.2. Documentation of the investigational medicinal product destruction	to document the fact of destruction of unused investigational medicinal products by the sponsor or at the trial site/medical institution	X (if destroyed at site)	X
8.4.3. Final subject identification code list	to permit identification of all subjects enrolled in the trial in case the follow-up is required. The list shall be kept in a confidential manner and for agreed upon time	X	
8.4.4. Audit certificate (if available)	to document the fact of audit performed		X
8.4.5. Final trial close-out monitoring report	to document that all activities required for the 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	to be returned to the 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 authorities (if applicable)	to document completion of the trial	X	

Document name	Purpose	Located in Files of	
		Investigator/ Institution	Sponsor
8.4.8. Clinical trial report	to document the trial results and their interpretation	X (if applicable)	X

2. In the first sentence of paragraph 9.4.3 of Annex No. 1 to the Rules indicated, replace the word "institutions" with phrase "medical institutions".

3. Annex No. 11 shall be read as follows:

"Annex No. 11
to the Rules of the
Good Clinical Practice of the Eurasian
Economic Union)

PROCEDURE
for presentation of safety information
during clinical trials

1. Sponsor's Responsibilities on Provision of Safety Information during Clinical Trial

1.1. Arrangement of the system of written standard procedures

The sponsor is responsible for establishing a system of written standard procedures to ensure the required level of quality standards in the performance of the functions on documenting, data acquisition, validation, assessment, archiving, reporting and follow-up reporting of identified adverse drug reactions during the clinical trials.

1.2. Submission of information on unexpected serious adverse drug reactions to the regulatory authority of the Member State of the Eurasian Economic Union (hereinafter referred to as the Member States, the Union).

1.2.1. The sponsor shall provide information on all unexpected serious adverse drug reactions to the investigational medicinal product identified in the course of clinical trials approved for conduct in the Member State, where the clinical trial of the investigational medicinal product is being conducted,

without delay, but not later than 7 calendar days from the date of receipt of the information on identification of the unexpected serious adverse drug reaction, when it has caused death or imposed life threat;

not later than 15 calendar days from the date of receipt of the information on identification of the unexpected serious adverse drug reaction for the rest unexpected serious adverse drug reactions.

The decision on expediency of urgent reporting (expedited reporting) in other situations (e.g. in cases of medically important events not imposing immediate threat to the patient's life, causing death or hospitalization, but putting the patient at risk or requiring intervention to prevent one of the outcomes in the definition) shall be based on medical and scientific judgment. Such cases shall usually also be considered serious adverse events.

1.2.2. In the absence of complete information as of the date of submission of the expedited report on death or the life-threatening condition development, the sponsor shall take measures to provide complete information in the form of additional expedited report on the identified unexpected serious adverse drug reaction no later than within 8 calendar days from the date of the initial report submission.

1.2.3. If the sponsor receives new relevant information regarding the identified unexpected serious adverse drug reaction, this information shall be provided in the form of the follow-up report within 15 calendar days from the date of its receipt.

1.2.4. Requirements for reporting the unexpected serious adverse drug reactions apply to the investigational medicinal product, including the

comparator product. These requirements do not apply to placebo, except for the cases of unexpected serious adverse reactions, for which the causal link with the placebo has been established.

1.2.5. The period for reporting the information specified in paragraphs 1.2.1 through 1.2.3 of this Annex shall start from the date of obtaining permission to conduct the clinical trial in the Member State and shall end after the last visit of the last trial subject in the Member State, where the clinical trial of the investigational medicinal product is being conducted.

1.3. Requirements for reporting an unexpected serious adverse drug reaction.

1.3.1. The minimum required information on the unexpected serious adverse drug reaction.

The minimum information for submission of the initial expedited report on an identified unexpected serious adverse drug reaction within the specified terms shall include:

indication of the suspected investigational medicinal product, identification code of the trial subject who developed the adverse drug reaction;

description of the adverse drug reaction or its outcome determined as serious and unexpected and for which the causal link with the investigational medicinal product is supposed;

result of the causal link assessment;

source of information on the adverse drug reaction, identification number of the adverse drug reaction report assigned by the sponsor;

trial protocol number.

1.3.2. Complete information on the unexpected serious adverse drug reaction.

The subsequent collection and reporting of complete information on the case of the unexpected serious adverse drug reaction should be ensured; it shall comply with the requirements of the International Conference on Harmonization Guideline E2B on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports.

1.4. Reference safety information.

1.4.1. The reference safety information of the unauthorized investigational medicinal product.

The current version of the investigator's brochure as of the date the serious adverse drug reaction identification shall be used to determine the predictability of the serious adverse drug reaction to the investigational medicinal product identified during the clinical trial.

1.4.2. The reference safety information of the authorized investigational medicinal product.

The current version of the summary of product characteristics or its equivalent in other countries or the effective version investigator's brochure as of the date of identification of the serious adverse drug reaction shall be used to determine the predictability of the serious adverse drug reaction to the investigational medicinal product authorized in the country, where the serious adverse drug reaction is identified, during the clinical trial.

1.5. Sponsor notification of other safety information.

The sponsor shall submit to the regulatory authority of the Member State, investigators and the IRB/IEC of the relevant trial sites other safety information that may change the benefit-risk assessment of the investigational medicinal product or serve the basis for changes in the recommendations for its prescription and the basis for revising the possibility of continuing the trial within 15 calendar days from the date of receipt of other safety information on:

a) clinically relevant excess of the expected frequency and change in the nature of the expected serious adverse drug reactions;

b) unexpected serious adverse drug reactions that developed in a patient after completion of his/her participation in the clinical trial;

c) new data related to the clinical trial or development of the investigational medicinal product that may affect the patient safety, including:

serious adverse events related to the trial procedure, basing on which amendments to the trial protocol are required;

lack of efficacy of the investigational medicinal product used for the life-threatening health condition;

new important safety data obtained in the course of recently completed studies in animals (identified carcinogenicity and effects similar in severity and importance);

premature termination or suspension of the trial in another country/-ies due to change in the safety assessment of the similar investigational medicinal product;

other safety data that change the benefit-risk ratio for the trial subjects;

d) recommendations of the independent data monitoring committee regarding the investigational medicinal product safety evaluation.

The sponsor may submit the other safety information to the IRB/IEC of the respective trial sites within the above specified terms through transmission of this information by the investigator to the IRB/IEC of the respective trial site.

1.6. Sponsor's safety notification form.

1.6.1. The sponsor's safety notification form on the unexpected serious adverse drug reactions to the regulatory authorities of the Union Member States.

The sponsor shall submit the information on the unexpected serious adverse drug reactions in the form of the adverse drug reaction notification in accordance with paragraph 1.2 of this Annex. The notifications format shall comply with the International Conference on Harmonization Guideline E2B on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports. When compiling the contents of the individual notification, the terminology of the Medical Dictionary for Regulatory Activities (MedDRA) shall be used. At that, the lower-level terms (LLT) shall be used in the notification.

1.6.2. The sponsor's safety notification form on the unexpected serious adverse drug reactions to investigators and the IRB/IEC.

1.6.2.1. Information on the unexpected serious adverse drug reaction shall be preferably submitted in the form of a summarized list of adverse drug reactions for the period, the duration of which is to be determined by the safety profile of the investigational medicinal product and the number of the unexpected serious adverse drug reactions identified. This list shall be accompanied by the current safety profile assessment summary for the specified period. In cases where the submission of the summarized information is impractical, or if required, it is acceptable to submit such information in the form of the expedited report on the unexpected serious adverse drug reaction.

1.6.2.2. The sponsor may notify the respective trial site IRB/IEC on the unexpected serious adverse drug reaction through transmission this information by the investigator of the respective trial site to the IRB/IEC of the respective trial site in accordance with paragraphs 3.3.8 and 4.10.2 of these Rules.

1.6.2.3 The period for notification as indicated in paragraphs 1.6.2.1 through 1.6.2.2 of this Annex starts not later than the trial site opening and

ends after the last visit of the last trial subject to the trial site, where the clinical trial is being conducted.

1.6.3. Form of the sponsor notification on other safety information.

The sponsor shall notify the other safety information in accordance with paragraph 1.5 of this Annex in writing, indicating the name of the clinical trial, number of the trial protocol and summary of the new safety information.

1.7. Scope of the requirement for reporting the unexpected serious adverse drug reactions.

Requirements of subparagraphs 1.2 through 1.4. and 1.6 of this Annex apply to all unexpected serious adverse drug reactions identified in trial sites located within the Union and other countries where the sponsor or its partner is conducting the clinical trial approved within the Member State territory, as well as in clinical trials with the same active substance irrespective the dosage form, dosage, dosing regimen and indications for use.

1.8. Serious adverse drug reactions not related to the investigational medicinal product.

The sponsor should submit the information on serious adverse drug reactions identified during the clinical trial, for which the relationship is determined with authorized medicinal products that are not investigational medicinal products and prescribed as concomitant therapy, in the absence of the interaction with the investigational medicinal product, to the regulatory authorities of the Member States.

1.9. Randomization decoding.

1.9.1. Requirements for randomization decoding in the event of unexpected serious adverse drug reaction.

The randomization decoding in the event of report on the adverse event estimated as the unexpected serious adverse drug reaction shall be performed

only for the trial subject developed this adverse drug reaction. The sponsor shall fulfill the requirement under subparagraph 1.2 of this Annex for expedited reporting on the identified unexpected serious adverse drug reaction to the regulatory authority of the Member State considering the randomization decoding results. At that, the sponsor shall maintain blinding for such cases for persons responsible for continuing the clinical trial (such as managers, monitors, investigators), as well as persons responsible for analyzing data and interpreting the results after the trial is completed, such as the biometrics department personnel. Information on adverse drug reactions with the randomization decoding of trial subjects may be available only to persons responsible for fulfilling the requirements for reporting the adverse drug reactions to the regulatory authorities of the Member States, to the IRB/IEC and independent data monitoring committees, or to other persons responsible for performing ongoing safety assessments during the clinical trial. For investigators, the randomization decoding during the clinical trial shall be performed only if it is deemed necessary to ensure the safety of the trial subject.

1.9.2. The randomization decoding results shall be reflected properly in the databases of the sponsor and the regulatory authorities of the Member States. The safety information update in the investigator's brochure shall be based on the analysis of the decoded treatment data.

1.9.3. Special populations.

When conducting clinical trials in population with high rate of complications and mortality, in cases where the endpoints for evaluating efficacy can be both serious and unexpected adverse drug reactions, or when death or other serious unfavorable outcome can be the endpoint for the investigational medicinal product efficacy assessment, the reliability of the clinical trial results may be compromised due to systematic randomization

decoding. In such or similar cases, the sponsor should determine the serious events associated with the underlying disease not subject to the systematic randomization decoding and expedited reporting to the regulatory authority of the Member State upon obtaining the clinical trial protocol approval and in coordination with the regulatory authority of the Union Member State. In these cases, it is mandatory to appoint and maintain an independent data monitoring committee in order to continuously assess and analyze the safety data of the ongoing clinical trial and determine recommendations for the sponsor regarding the possibility of continuing the clinical trial, amending the study protocol or stopping the clinical trial.

1.9.4. Annual safety reporting.

During the entire period of the clinical trial, the sponsor shall annually submit to the regulatory authority of the Member State, where the clinical trial of the medicinal product is being conducted, a periodic report (periodic reports) on the developed medicinal product safety, the contents of which shall meet the requirements specified in Annex No. 12 to the Rules of Good Clinical Practice of the Eurasian Economic Union approved by Decision of the Eurasian Economic Commission's Council No. 79 dated November 3, 2016. It is not mandatory to submit periodic reports on the developed medicinal product safety in clinical trials with duration of less than one year.

The sponsor shall submit either periodic report on the developed medicinal product safety or brief summary of the main report content to the IRB/IEC. In the latter case, the sponsor shall provide the structured list of serious adverse drug reactions as per Annex No. 12 to the Rules of Good Clinical Practice of the Eurasian Economic Union under the IRB/IEC request.

2. Investigator's Responsibilities for Reporting Adverse Events Identified in the Clinical Trial to the Sponsor

The Investigator shall immediately, within 24 hours of the date of identification or receipt of information on the identification, provide to the sponsor the information concerning serious adverse events other than those indicated in the protocol or another document (e.g. in the investigator's brochure) as not subject to immediate reporting.

Following the expedited report on the serious adverse event, the investigator shall provide the sponsor with the detailed report containing full information on the serious adverse event allowing the sponsor to assess the need to reconsider the benefit-risk ratio of the clinical trial.

The Investigator shall provide the sponsor with information on adverse events and laboratory abnormalities that are indicated in the trial protocol as critical for safety assessment within the terms specified in the clinical trial protocol.”

4. In Annex No. 12 to these Rules:

a) in the tenth indent of Section 1, replace the phrase "basic prescribing information" with the phrase "summary of product characteristics";

b) in Subsection 3.5, replace the phrase "basic prescribing information" with the phrase "summary of product characteristics";

c) in Section 4:

in the section title, replace the words “and the content” with the words “content and form of submission”;

in the sixteenth indent of Subsection 4.6, replace the phrase "basic prescribing information" with the phrase "summary of product characteristics";

the last sentence of Subsection 4.14 shall be amended as follows: “The safety data in this Section shall include the results of use both in accordance with the summary of product characteristics or basic prescribing information and not in accordance with the summary of product characteristics or basic prescribing information, results of prescription errors, cases of overdose, addiction, use in special groups of patients (e.g. in pregnant women).”;

in the second sentence of Subsection 4.22, replace the phrase "basic prescribing information" with the phrase "summary of product characteristics".

d) add Subsection 4.25 with the following contents:

"4.25. Periodic Safety Update Report
on an Investigational Medicinal Product

The periodic safety update report on the investigational medicinal product shall be submitted electronically with the possibility of text search in Russian or English with the obligatory translation into Russian of the following sections: summary and conclusion/-s. At the request of the Member State’s regulatory authority, the applicant is obliged to submit other sections of the periodic safety update report translated into Russian within 30 calendar days from the date of receipt of such a request.

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