

Regulations on Conducting Clinical Trials and Non-interventional studies and Labelling of Investigational Medicinal Products, and Procedure for Conducting Inspections on Compliance with the Requirements of Good Clinical Practice

*Issued pursuant to
Section 5, Clauses 6 and 15
of the Pharmacy Law*

I. General Provision

1. These Regulations determine the procedure for the conduct of clinical trials, including multi-centre trials, on medicinal products for human use in accordance with good clinical practice, procedure for the conduct of non-interventional studies and for labelling investigational medicinal products, and procedure for verifying the compliance of clinical trials with good clinical practice.
2. A trial subject is an individual who participates in a clinical trial either as a recipient of the investigational medicinal product or a part of the control group.
3. Investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated, or packaged) in a way different from the authorised form or when used to gain further information on the authorised form.
4. Investigator is a doctor, who, in accordance with the normative acts of medical treatment, is competent to independently engage in the practice of medical treatment and has a specialist practice in the field of the respective clinical trial.
5. Sponsor is a physical or legal entity which takes responsibility for the initiation, management or financing of a clinical trial.
6. Protocol is a document that describes the objective, design, methodology, statistical considerations and organisation of a trial, states subject inclusion and exclusion criteria, procedure for trial monitoring and publication policy.
7. Multi-centre clinical trial is clinical trial conducted according to a single protocol at more than one site and therefore by more than one investigator. The trial sites may be located in a single Member State, in a number of Member States, or in Member States and third countries.
8. Trials with gene or somatic cell therapy medicinal products may be conducted only at specialised medical centers located at clinical university hospitals.
9. The available non-clinical and clinical information of investigational medicinal product shall be adequate to support the proposed clinical trial.
10. The rights, safety and well being of the subject shall prevail over the interests of science and society.
11. Each individual involved in conducting a clinical trials shall be qualified (with regards to education, training and experience) to perform his tasks.
12. Clinical trial shall be scientifically sound and guided by ethical principles in all its aspects.
13. All clinical trials, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of good clinical practice.

14. Good clinical practice is a set of internationally recognised ethical and scientific quality requirements, which must be observed in designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.
15. All clinical trial information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of trial subject remains protected.

II. Obligations of Sponsor and Investigator

16. The investigator and sponsor shall consider these regulations, as well as normative acts of medical treatment and personal data protection with respect to commencing and conducting a clinical trial.
17. The investigator shall be responsible for the subject's medical care and all medical decisions made during the trial. The investigator shall be responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator who is responsible for the team is called the principal investigator.
18. The sponsor shall choose an investigator, basing its decision on investigator's qualification and experience. If necessary, the sponsor shall provide additional training to the investigator.
19. The investigators may participate in the first phase trials, only if they have previous experience in clinical trials of medicinal products.
20. The sponsor may delegate any or all of his trial-related functions to another physical or legal entity (hereinafter: contract research organisation). However, in such case, the sponsor shall remain responsible for ensuring that the conduct of the trial and the data generated by this trial comply with this regulation.
21. The investigator and the sponsor may be the same person.
22. The sponsor shall ensure that provisions have been made for insurance and indemnity to cover the liability of the investigator and sponsor. The sponsor is not responsible for a deliberate or accidental injury to a subject caused by the investigator or other individuals involved in the clinical trial.
23. The sponsor or a legal representative of the sponsor shall be registered in any of the Member States. If the sponsor or the legal representative of the sponsor is a physical person, it must be a resident of the European Union.
24. The sponsor shall supply the investigational medicinal product(s), which are manufactured and controlled in accordance with good manufacturing practice.
25. The sponsor shall be responsible for the quality of investigational medicinal product(s), for supplying the trial sites with the investigational medicinal product(s), as well as for the determination of storage conditions, storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor shall inform all the individuals involved in the clinical trials of these determinations. These individuals shall be responsible for observing the storage conditions.
26. The investigator shall be responsible for the accountability and storage of investigational medicinal product(s) at the trial site.
27. The sponsor shall supply the investigational medicinal product(s) and devices, if any, for product administration for free of charge.

III. Investigator's Brochure

28. Investigator's brochure is a compilation of the clinical and non-clinical data on the investigational medicinal product which are relevant to the study of the product in human subjects. The information in the investigator's brochure shall be presented in a concise, simple, objective, balanced and non-promotional form that enables a doctor or a potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial. These requirements apply also to any update of the investigator's brochure.
29. If the investigational medicinal product has a marketing authorisation in any Member State or any country within the European Economic Area, Summary of Product Characteristics may be used instead of the investigator's brochure.
30. The investigator's brochure shall be validated and updated by the sponsor at least once a year.

IV. Protection of Clinical Trial Subjects

31. A clinical trial may be undertaken only if:
 - 31.1. the opinion of Ethics Committee and clinical trial authorisation of the State Agency of Medicines state that the anticipated benefits for trial subject, other present or future patients and the society as a whole have been evaluated and they outweigh the foreseeable risks and the clinical trial may be continued only if compliance with this requirement is permanently monitored;
 - 31.2. the trial subject or, when the person is not able to give informed consent, his legal representative has freely given his written, dated and signed consent (hereinafter: informed consent) after being informed of the nature, significance, implications and risks of the clinical trial; if the individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases;
 - 31.3. the trial subject or, if the person is not able to give informed consent, his legal representative has had opportunity in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the clinical trial, and the conditions under which it is to be conducted and has also been informed of his rights to withdraw from the clinical trial at any time;
 - 31.4. the subject's personal data shall be protected according to the normative acts regarding personal data protection of a physical person;
 - 31.5. the informed consent shall include the subject's rights to withdraw from the clinical trial at any time by informing the sponsor or the investigator of the withdrawal of his informed consent without detriment on the quality of the health care provided to the subject;
 - 31.6. the informed consent document shall include provisions for insurance and indemnity to cover the liability of the investigator and sponsor.
32. In addition to regulations referred to in paragraph 31, a clinical trial on minors may be undertaken only if:
 - 32.1. the informed consent of at least one parent or legal representative has been obtained. Consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor;

- 32.2. staff with experience with minors has provided the minor with information regarding the trial, its risks and benefits according to its capacity of understanding. At least one parent or legal representative must confirm in written form that the minor has been informed according to its capacity of understanding of the nature of the clinical trial, its risks and benefits;
- 32.3. the explicit wish of a minor who is capable of forming an opinion and assessing this information referred to in paragraph 31.3 to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or principal investigator;
- 32.4. no incentives or financial inducements, except compensation covering expenses associated with the clinical trial (including transport expenses) and compensation in the event of injury or death attributable to the clinical trial, are given to the minor;
- 32.5. some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods. In addition such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors;
- 32.6. the scientific guidelines of the European Medicines Agency have been followed;
- 32.7. the clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage of the minor. Both the risk threshold and the degree of distress have to be specially defined and constantly monitored;
- 32.8. the Ethics Committee which is competent in the field of paediatrics or after a consultation with an expert in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol;
- 32.9. the interests of the patient always prevail over those of science and society.
33. In the case of other persons incapable of giving informed legal consent, all relevant requirements referred to in paragraph 31 listed for persons capable of giving such consent shall apply. In addition to these requirements, inclusion in clinical trials on incapacitated adults who have not given or have not refused informed consent before the onset of their incapacity shall be allowed only if:
 - 33.1. the informed consent of the legal representative has been obtained. Consent must represent subject's presumed will and may be revoked at any time, without detriment to the subject;
 - 33.2. the person not able to give informed consent has received information according to his/ her capacity of understanding regarding the clinical trial, the risks and benefits;
 - 33.3. the explicit wish of a subject who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;
 - 33.4. no incentives or financial inducements except compensation covering expenses associated with the clinical trial (for example, transport expenses) and compensation in the event of injury or death attributable to the clinical trial are given to the person not able to give informed consent;
 - 33.5. such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods and relates directly to a life-threatening or debilitating clinical condition from which the person concerned suffers;

- 33.6. the clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage. Both the risk threshold and the degree of distress have to be specially defined and constantly monitored;
- 33.7. the Ethics Committee, with expertise in the relevant disease and patient population concerned or after consultation with an expert in clinical, ethical and psychosocial problems in the field of the relevant disease and patient population concerned, has endorsed the protocol;
- 33.8. the interests of the patient always prevail over those of science and society;
- 33.9. there are grounds for expecting that participation in the clinical trial will produce a benefit to the patient outweighing the risks or produce no risk at all.
34. In emergency situation, if a person is not able to give informed consent, and the person does not have a legal representative or the legal representative is not available, the inclusion of the subject shall require measures described in the protocol for case of emergency.
35. In order for the subject to be able to receive objective information on a particular clinical trial the investigator shall provide the subject with contact information of the Ethics Committee (the one which has issued opinion on a particular clinical trial) and State Agency of Medicines.
36. Pregnant women or breast-feeding women shall not be enrolled in a clinical trial except in cases when otherwise it is not possible to conduct a clinical trial and when the foreseeable risks have been weighted against the anticipated benefit for the embryo, foetus or nursing infant.
37. A trial subject in need for an active therapy shall be enrolled in a placebo group only in the case when the requirements referred to in paragraphs 31, 32 and 33 are fulfilled and protocol provides a scientific and ethical justification.
38. In order to ensure the protection of personal data a unique identifier shall be assigned by the investigator to each trial subject and shall be used in lieu of the subject's name when reporting to the sponsor, the State Agency of Medicines and the Ethics Committee. The subject's name shall be revealed only upon request of institutions which according to the Medical Treatment Law are entitled to see information regarding a patient.
39. The investigator shall promptly inform the trial subject about conditions which may jeopardise the subject's life or health and which become known when conducting the clinical trial. The investigator shall record the information provided to the subject. In those cases, according to paragraph 31, the subject's written consent to continue his/her participation in the clinical trial is required.
40. If the clinical trial is prematurely terminated or suspended, the investigator shall promptly inform the trial subject and shall ensure appropriate therapy and follow up for the subject.

V. Ethics Committee

41. The Ethics Committee shall give its opinion, before a clinical trial commences, on any issue requested in order to protect the rights, safety and well-being of the trial subjects, and in order to provide public assurance of this protection. The Ethics Committee is an independent body working within a medical establishment or independently from a medical establishment.
42. The Ethics Committee shall consist of qualified and experienced professionals who are able to review the ethical and scientific aspects of the proposed clinical trial. The Minister of Health approves the composition of the Ethics Committee indefinitely.

43. The Ethics Committee shall consist of at least 9 members. The Ethics Committee shall include at least 2 professionals without medical education, as well as 2 members who are independent of the trial site (the location where trial-related activities are actually conducted) in its composition. The Ethics Committee shall include members of both sexes.
44. The Ethics Committee shall be entitled to invite non-member experts without rights to vote.
45. The Ethics Committee shall perform its functions according to the statutes approved by the Chairman of the Ethics Committee. These statutes are developed according to these regulations, principles of good clinical practice and normative acts on personal data protection.
46. The Ethics Committee shall have rights to vote if more than a half of its members are present at the meeting.
47. The Ethics Committee decision is approved by a majority vote after the members of the Ethics Committee have expressed their choice in an open vote.
48. The meetings and the opinions made by the Ethics Committee shall be recorded in minutes. The member, whose opinion is different from the final opinion of the Ethics Committee, shall be entitled to state his opinion in the annex to the minutes.
49. Only those members of the Ethics Committee who are independent of the investigator and the sponsor can vote and provide opinion on a trial-related matter.
50. The Ethics Committee shall retain all records for a period of at least 5 years after completion of the trial except cases when the normative acts stipulate a longer period of retaining records.
51. Information on the composition and qualifications of the members of the Ethics Committee and the statutes of the Ethics Committee shall be made available upon request from the investigator, sponsor, the State Agency of Medicines and the Ministry of Health.
52. The Ethics Committee shall submit its member list, contact information and information on the field of expertise and fees for reviewing the applications of the clinical trial to the Ministry of Health. The Ministry of Health shall publish this information on its web site.
53. Once a year (up to 1 February) the Ethics Committee shall submit the list of applications of the clinical trials and opinion made during the year to the State Agency of Medicines.
54. In order to receive the opinion by the Ethics Committee, the sponsor or the authorised person of the sponsor shall submit the following documents to the Ethics Committee:
 - 54.1. EudraCT number;
 - 54.2. an application form developed by the European Commission (available on the web site of the State Agency of Medicines) signed by the sponsor or the authorised person of the sponsor;
 - 54.3. protocol and its amendment(s), if any, signed by the sponsor and investigator;
 - 54.4. informed consent form, developed by the sponsor, in the official language. For the subjects who do not understand the official language to the extent which allows understand the content of the document, the informed consent form shall be developed in the language understandable to the subjects;
 - 54.5. other trial-related written information in the official language of the state intended for the subject. For the subjects who do not understand the official language to the extent which allows understand the content of the document, the written information shall be developed in the language understandable to the subjects;

- 54.6. subject recruitment procedures;
- 54.7. Investigator's Brochure or in the case referred to in paragraph 29 - Summary of Product Characteristics;
- 54.8. up-to-date curriculum vitae of the investigators and other individuals involved in the clinical trial, chosen by and working under the investigator (hereinafter: subinvestigators);
- 54.9. documentation on compensation, if any available, to trial subject for the participation in the clinical trial;
- 54.10. documentation certifying legal liability insurance of the sponsor and investigator as well as terms and conditions on compensation to trial subject in case of injury or death occurring due to clinical research;
- 54.11. agreement of the administration of the medical establishment allowing the conduction of the clinical trial;
- 54.12. sponsor's power of attorney if an authorised person of the sponsor submits the documents.
55. When reviewing the application for the initiation of a clinical trial and preparing the opinion, the Ethics Committee shall consider in particular:
 - 55.1. the relevance and objective of the clinical trial;
 - 55.2. whether the evaluation of the anticipated benefits and risks according to paragraph 31.1 is satisfactory and whether the conclusions are justified;
 - 55.3. the protocol;
 - 55.4. the suitability of the investigator and supporting staff;
 - 55.5. the investigator's brochure;
 - 55.6. the quality of the facilities;
 - 55.7. the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent as regards the specific restrictions laid down in paragraphs 31, 32 and 33;
 - 55.8. provision for indemnity or compensation in the event of injury or death attributable to a clinical trial;
 - 55.9. any insurance or indemnity to cover the liability of the investigator and sponsor;
 - 55.10. the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial subjects and the contract concerned signed by the sponsor and the clinical trial site;
 - 55.11. the arrangements for the recruitment of subjects.
56. The Ethics Committee no later than 30 days after the registration of an application containing all of the afore mentioned information will submit a written opinion to the applicant with a supplied justification for the opinion. The copy of the opinion shall be submitted to the State Agency of Medicines.

57. Within the period of evaluation of the application for an opinion, the Ethics Committee may send a single request for additional information. The period laid down in paragraph 56 shall be suspended until receipt of the additional information.
58. The Ethics Committee may extend the time period mentioned in paragraph 56 of these regulations, if the clinical trial involves medicinal products intended for gene therapy or somatic cell therapy or contain genetically modified organisms. The extension does not exceed beyond 180 days after the registration of the application. If the opinion regards xenogenic cell (alien cells with respect to the human organism) therapy, the time period for submitting the opinion has no limits;
59. For multi-centre clinical trials limited to the territory of Latvia, the Ethics Committee provides a single opinion for the concerned clinical trial. In the case of multi-centre clinical trials carried out in more than one Member State simultaneously, the Ethics Committee shall give a single opinion for the clinical trial in Latvia.
60. The opinion of the Ethics Committee may be disputed at the Central Medical Ethics Committee. The decision of the Central Medical Ethics Committee is not disputable.

V. Authorisation of the State Agency of Medicines

61. In order to receive authorisation from the State Agency of Medicines, the sponsor or the authorised person of the sponsor shall submit the following documents and information to the State Agency of Medicines:
 - 61.1. confirmation of the receipt of European Clinical Trial Database (EudraCT) number;
 - 61.2. application form developed by the European Commission (link available on the web site of European Commission http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-10/11_an1_14-2005_en.pdf), signed by the sponsor or the authorised person of the sponsor (XML file shall also be provided);
 - 61.3. the protocol and amendment(s), if any, signed by the sponsor and investigator;
 - 61.4. the list of all actual clinical trials involving the investigational medicinal product concerned;
 - 61.5. the Investigational Medicinal Product Dossier (IMPD), containing data on investigation medicinal products, including information on quality of test product and placebo (an inert form of medication without active substance and objectively without specific activity for the condition being treated) and data from previously conducted non-clinical and clinical studies, as well as risk-benefit profile with a critical analysis of non-clinical and clinical data of risks and benefits of the foreseen clinical trial, or a simplified IMPD, if the State Agency of Medicines reviews the investigational medicinal product repeatedly;
 - 61.6. the Summary of Product Characteristics for medicinal products authorised in the Member State;
 - 61.7. the list of the Member States where the application has been submitted as well as information on the authorisation status, if available;
 - 61.8. the copy of the manufacturing licence if the investigational medicinal product(s) are manufactured in the Member State or within the state of the European Economic Area;
 - 61.9. the documentation certifying that the manufacturing site is at least equivalent to the standards of good manufacturing practice of the European Union, as well as the copy of the import authorisation if the investigational medicinal product is manufactured in a third country;

- 61.10. the documentation certifying that the active substances are manufactured in accordance with the standards of the good manufacturing practice;
- 61.11. the informed consent form developed by the sponsor in the official language. For the subjects who do not understand the official language to the extent which allows understand the content of the document, the informed consent form shall be developed in the language understandable to the subjects.
- 61.12. other written trial-related information in official language intended for a subject. For the subjects who do not understand the official language to the extent which allows understand the content of the document, the information shall be developed in the language understandable to the subjects.
- 61.13. A written agreement from the administration of the medical establishment allowing the conduction of the clinical trial;
- 61.14. documentation certifying legal liability insurance of the sponsor and investigator as well as terms and conditions on compensation to trial subject in case of injury or death occurring due to clinical research;
- 61.15. documentation on compensation, if any available, to trial subject for the participation in the clinical trial;
- 61.16. the investigator's brochure or in the case referred to in the paragraph 29 – the Summary of Product Characteristics;
- 61.17. the sample of the investigational medicinal product(s) labelling in the official language;
- 61.18. the investigator's and subinvestigator's curriculum vitae;
- 61.19. written confirmation that the investigator has been trained to conduct clinical trials in accordance with the principles of good clinical practice and normative acts regarding conduction of clinical trials;
- 61.20. the sponsor's power of attorney if the documentation is submitted by a person authorised by the sponsor.
62. The applicant shall cover the review of clinical trial application according to the rates of public services of the State Agency of Medicines. If the clinical trial is not authorised the payment is not reimbursed.
63. The State Agency of Medicines shall have a maximum of 60 days from the date of receipt of a valid application (with all the information referred to in the paragraph 61) to review the application.
64. Within the period of examination of the application, the State Agency of Medicines may send a request for additional information. The period laid down in paragraph 63 shall be suspended until receipt of the additional information.
65. The State Agency of Medicines may extend the time period stated in paragraph 63 of these regulations, if the clinical trial involves medicinal products intended for gene therapy or somatic cell (any cell in an organism that is not a germ cell) therapy or contain genetically modified organisms. The extension does not exceed beyond 180 days after the registration of the application. In the case of xenogenic cell therapy, there shall be no time limit to the authorisation period.

66. Within the period referred to in paragraphs 63 and 64, the State Agency of Medicines shall make a decision for authorisation or prohibition of the clinical trial, if the requirements stated in these regulations are not met, and within 5 working days after the decision is made shall notify the sponsor of it in written form, providing justification for the decision. The authorisation shall not be issued until the payment referred to in paragraph 62 is made. The authorisation is issued for the duration of the clinical trial stated in the protocol.
67. Authorisation will not be issued for gene therapy trials that result in the modification of the subject's germ cell genetic information identity.
68. The authorization for a clinical trial involving medicinal products containing genetically modified organisms shall be issued by the State Agency of Medicines after an approval in accordance with the normative acts on restricted use and deliberate release of genetically modified organisms into the environment has been issued to the sponsor.
69. The decision of the State Agency of Medicines may be appealed in the Ministry of Health. The decision made by the Ministry of Health may be appealed in court.
70. For multi-centre clinical trials limited to the territory of Latvia, the State Agency of Medicines shall make a single decision for the concerned clinical trial. In the case of multi-centre clinical trials carried out in more than one Member State simultaneously, the State Agency of Medicines shall make a single decision for the clinical trial in Latvia.

VII. Commencement of a Clinical Trial

71. The sponsor shall commence a clinical trial after the Ethics Committee has issued a favorable opinion and the State Agency of Medicines has issued the authorisation for the clinical trial. The sponsor may submit the application simultaneously to the Ethics Committee and the State Agency of Medicines. Prior the commencement of a clinical trial the sponsor shall conclude an agreement with each of the medical establishments involved in a clinical trial stating responsibilities and duties of the parties involved with regard to conduct of a clinical trial (including clauses on intellectual property and confidentiality), financial requirements (including compensation to a medical establishment with regard to the utilisation of its human resources and facilities, as well as payment schedule).
72. If the State Agency of Medicines notifies the sponsor of grounds for non-acceptance of the clinical trial, the sponsor may, on one occasion only, amend the content of the request referred to in paragraph 61.2 in order to take into account the arguments stated in the justification of the decision. If the sponsor fails to amend the request accordingly the request shall be considered rejected and the clinical trial may not commence.

VIII. Conduct of a Clinical Trial

73. After the commencement of the clinical trial, the sponsor may make amendments to the application and its supplementary documents. If those amendments are likely to have a substantial impact on the safety of the trial subjects, the physical or mental integrity of trial subjects, the scientific value of the trial, the conduct of the trial, the quality or the safety of investigational medicinal product(s), the sponsor shall submit a notification of amendments to the State Agency of Medicines basing on a sample form for substantial amendments approved by the European Commission (link available on the web site of European Commission http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-10/11_an2_14-2005_en.pdf) and in written form shall notify the Ethics Committee concerned.

74. The Ethics Committee shall give an opinion and the State Agency of Medicines shall make a decision within 30 days after receiving the amendments referred to in paragraph 73 of these regulations.
75. If the opinion of the Ethics Committee is favourable and the State Agency of Medicines has made a positive decision, the sponsor shall proceed to conduct the clinical trial following the amended protocol.
76. If the opinion of the Ethics Committee is not favourable or the decision of State Agency of Medicines is negative, the sponsor may not implement the amendment to the protocol until the grounds for non-acceptance are taken into consideration. If the sponsor has not considered the grounds for non-acceptance, the amendment to the protocol is rejected.
77. If during the clinical trial new circumstances arise that relate to the conduct of the trial, the research or development of the investigational medicinal product and may affect the safety of the subject, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The sponsor shall immediately inform the State Agency of Medicines of these circumstances and safety measures taken and ensure that the Ethics Committee is also informed at the same time.
78. If the amendments to the protocol regard administrative issues, the sponsor shall notify the Ethics Committee and the State Agency of Medicines in written form. In this case the opinion of the Ethics Committee and the authorisation of the State Agency of Medicines are not necessary.
79. Within 90 days of the end of a clinical trial the sponsor shall notify the State Agency of Medicines and the Ethics Committee that the clinical trial in the territory of the Republic of Latvia has ended. The sponsor shall submit an application to the State Agency of Medicines basing it on the sample of the end of clinical trial notification form approved by the European Commission (link available on the web site of the European Commission http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-10/11_an3_14-2005_en.pdf). The sponsor shall inform the State Agency of Medicines of the number of subjects enrolled in the clinical trial in Latvia. If the trial has to be terminated prematurely, the sponsor shall inform the State Agency of Medicines and the Ethics Committee in written form within 15 days and shall explain the reasons for the termination.

IX. Exchange of Information

80. The State Agency of Medicines shall enter the following information in the European clinical trial database regarding each clinical trial proposed in the territory of Latvia:
 - 80.1. the application for authorisation of a clinical trial submitted to the State Agency of Medicines;
 - 80.2. any amendments made to the application or its supplementary documents according to guidelines provided by the State Agency of Medicines and paragraph 72 of these regulations;
 - 80.3. any amendments made to the protocol after commencing the clinical trial, as provided for in the paragraphs 73, 74 and 75 of these regulations;
 - 80.4. the favourable opinion of the Ethics Committee;
 - 80.5. the declaration of the end of the clinical trial in the Republic of Latvia;
 - 80.6. a reference to the inspection carried out on conformity with good clinical practice.

81. At the justified request of any Member State, the European Medicines Agency or the European Commission, the State Agency of Medicines shall supply additional information to the information referred to in paragraph 80 of these regulations.

X. Suspension of the Trial and Infringements

82. Where the State Agency of Medicines has objective grounds for considering that the conditions in the request for authorisation referred to in paragraph 61.2 are no longer met or has information raising doubts about the safety or scientific validity of the clinical trial, the State Agency of Medicines may suspend the clinical trial and shall notify the investigator and sponsor thereof.
83. Before the State Agency of Medicines reaches its decision concerning the case referred to in paragraph 80, it shall, except where there is imminent risk to the trial subject, ask the sponsor and/or investigator for their opinion, to be delivered within one week.
84. Where the State Agency of Medicines has objective grounds for considering that the sponsor or the investigator or any other person involved in the conduct of the clinical trial no longer meets that obligations laid down, it shall inform him thereof, indicating the course of action which he must take to remedy this state of affairs. The State Agency of Medicines shall inform the Ethics Committee, the other competent authorities and the European Commission of this course of action.
85. If the clinical trial causes serious risks to the subject and the sponsor and investigator do not take necessary measures in order to ensure the safety of subjects, the State Agency of Medicines has the right to prohibit the clinical trial.
86. The State Agency of Medicines shall inform the Ethics Committee concerned, other competent authorities, the European Medicines Agency and the European Commission of the decision to suspend or prohibit the clinical trial and the grounds for this decision.

XI. Manufacture, Import and Labelling of Investigational Medicinal Products

87. The requirements for manufacturing and importing investigational medicinal products are stipulated by the normative acts on the manufacture and control of medicinal products and on the import and distribution of medicinal products.
88. The secondary packaging of the investigational medicinal product or, if absent, the primary packaging must contain information in the official language of the state according to the European Commission guidelines published in the Rules Governing Medicinal Products in the European Union (*Eudralex*) and stated in section 25.² of the Pharmaceutical Law.

XII. The Trial Master File and Archiving

89. The trial master file is a set of essential documents, which enable both the conduct of a clinical trial and the evaluation of the quality of data produced in the trial. These documents shall show whether the investigator and the sponsor have complied with the principles and guidelines of good clinical practice and with the requirements of regulation on authorisation of medicinal products.
90. The trial master file shall provide the basis for the audit carried out by an independent auditor appointed by the sponsor and for the supervision and evaluation carried out by the State Agency of Medicines.
91. The content of essential documents shall be in accordance with the specificities of the phase of the clinical trial.

92. The sponsor and the investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion, except for documents referred to in paragraphs 93 and 94.
93. The investigator is responsible for retaining the list of subject identification codes for at least 15 years.
94. The sponsor is responsible for retaining the protocol, standard operational procedures, investigator's brochure, case report forms of each subject, clinical trial report, written opinions on the protocol and the progress of the clinical trial for at least five years after the authorisation of the investigational product.
95. The essential documents shall be retained for a longer period, where so required by the normative acts regarding handling of medical documentation or by an agreement between the sponsor and the investigator.
96. Essential documents shall be archived in a way that ensures that they are readily available, upon request from the State Agency of Medicines and Health Inspectorate according to the competency of the respective person and normative acts on personal data protection. Identification codes shall be available only to the authorities, which in accordance with the Medical Treatment Law are entitled to view information regarding a patient.
97. The medical files of the trial subjects shall be retained in accordance with the normative acts on procedures for handling medical documentation.
98. Any transfer of ownership of the data or of essential documents shall be documented. The new owner shall assume the responsibility for data retention and archiving in accordance with the paragraphs 92, 93, 94, 95, 96 and 97 of these regulations.
99. The sponsor shall appoint individual (individuals) who is responsible for archives.
100. Access to archives shall be restricted to the individuals referred to in paragraph 99 of these regulations.
101. The conditions for storage of essential documents must ensure that they remain complete and legible throughout the required period of retention and can be made available upon request of the institutions stated in paragraph 96 of these regulations.
102. Any alteration to records shall be traceable maintaining also the text which has been amended.

XIII. Procedure for Conducting Inspections on the Compliance of Clinical Trial with the Requirements of Good Clinical Practice

103. Inspection is an official review conducted by the State Agency of Medicines of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the State Agency of Medicines to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/ or contract research organisation's facilities, or at other establishments which the State Agency of Medicines sees fit to inspect.
104. In order to verify the compliance with the principles of good clinical practice, the State Agency of Medicines shall be entitled to inspect the trial-related facilities, in particular, the trial sites and any laboratory where trial related testing is performed.
105. The State Agency of Medicines shall observe the requirements of data protection with respect to the information obtained during the inspection of good clinical practice.

106. Inspection may be conducted by a qualified individual of the State Agency of Medicines who has:
107. 106.1. completed education at university level or appropriate experience in medicine, pharmacy, pharmacology, toxicology or other relevant fields;
108. 106.2. knowledge of principles and procedures for development of medicinal products and clinical research, knowledge of normative acts of the Republic of Latvia and European Union regarding conduct of clinical trials and granting of marketing authorisation of medicinal products.
109. 106.3. knowledge of the procedures and systems for recording clinical data and of the organisation and legislative regulation of the health care system.
110. The State Agency of Medicines shall maintain up-to-date records of the individuals having rights to conduct inspections, and their qualifications, training and experience, on regular basis. The State Agency of Medicines shall ensure that inspectors receive training, that their training needs are assessed regularly and that appropriate actions is taken to maintain and improve their skills.
111. The State Agency of Medicines shall ensure the individuals referred to in paragraph 105 with a documents setting out standard operating procedures and giving details of the duties, responsibilities and ongoing training requirements. The State Agency of Medicines shall update the documents on standard operating procedures and other information anticipated for the individuals referred to in paragraph 107.
112. The State Agency of Medicines shall provide the individuals referred to in paragraph 107 with a document (identification card) certifying that they are entitled to supervise and inspect the compliance of clinical trials with principles of good medical practice.
113. Each individual referred to in paragraph 107 shall sign a statement declaring any financial or other links to the parties to be inspected. That statement shall be taken into consideration by the State Agency of Medicines when the individual are to be assigned to a specific inspection.
114. Good clinical practice inspections may be conducted on the following occasions:
 - 111.1. before, during or after the conduct of a clinical trial;
 - 111.2. as part of the verification of applications for marketing authorisation.
112. If the good clinical practice inspection referred to in paragraph 111.2. includes a travel of a State Agency of Medicines' official to the trial site or a trial related institution, the applicant shall cover the official's expenditures for transport to and from destination, hotel (lodging), visa, travel health insurance and daily allowance according to normative acts regarding the procedure for compensating expenditures that have arisen due to business trips.
113. The State Agency of Medicines shall inform the European Medicines Agency about the inspection conducted. The inspections may be conducted on behalf of the European Union and other Member States recognise the results of the inspection. The State Agency of Medicines is entitled to request an inspection-related assistance from other member States.
114. After the inspection, the State Agency of Medicines shall prepare the inspection report. The inspection report shall be available to the sponsor at the same time ensuring necessary protection of the data. Upon a justified request the inspection report shall be made available to other Member States, the Ethics Committee and the European Medicines Agency.
115. Foreign competent authorities may also be entitled to conduct inspections. In order to conduct an inspection, the foreign competent authority informs the State Agency of Medicines on such inspection 30 days prior to the inspection. Representative of the State Agency of Medicines may take part in such an inspection.

116. In order to conduct inspection, all the involved parties shall ensure a direct access to the documentation at all trial-related sites to the State Agency of Medicines and foreign inspectors.
117. The Health Inspectorate shall be entitled to conduct an inspection of the clinical trial according to its competency. The State Agency of Medicines shall be informed of the results of the inspection.
118. If necessary, the State Agency of Medicines may involve experts in the inspection of the clinical trial whose qualification and experience correspond to the proposed clinical trial.

XIV. Notification of Adverse Events

119. The investigator shall immediately report to the sponsor about all untoward medical occurrences of the subject during the administration of an investigational medicinal product, but do not necessarily have a causal relationship with this treatment and at any dose result in death, is life-threatening, requires inpatient hospitalisation, prolongs an existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect (hereinafter: serious adverse events), except for those that the protocol or investigator's brochure does not identify as requiring immediate reporting. The immediate report shall be followed by a detailed written report to the sponsor. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to them.
120. Serious adverse events and or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported by the investigator in written form to the sponsor according to the reporting requirements and within the time periods specified in the protocol.
121. In case of subject's death, the investigator shall supply the sponsor and the Ethics Committee with any additional information requested.
122. The sponsor shall keep detailed records of all adverse events which are reported to him by the investigators and will evaluate the severity, causal relationship and expectedness of those adverse events. Upon request these records shall be submitted to competent institutions of the Member State where the clinical trial is conducted.

XV. Notification of Serious Adverse Reactions

123. The sponsor shall ensure that all suspected unexpected serious adverse reactions that are fatal or life-threatening are recorded. The sponsor shall enter the information about those reactions in the Eudravigilance Clinical Trials module of the EMEA Eudravigilance data base in any case no later than seven days after knowledge by the sponsor of such case. The sponsor shall enter all suspected unexpected serious adverse reactions that are fatal or life-threatening and occur in the trial sites in the territory of Latvia in the Eudravigilance Clinical Trials module of the EMEA Eudravigilance data base and shall state the addressee of State Agency of Medicines of the Republic of Latvia. The sponsor shall report all suspected unexpected serious adverse reactions that are fatal or life-threatening and occur in the trial sites in the territory of Latvia to the Ethics Committee. Sponsor shall communicate State Agency of Medicines and Ethics Committee relevant follow-up information within an additional eight days.
124. The sponsor shall enter all other suspected unexpected serious adverse reactions in the Eudravigilance Clinical Trials module of the EMEA Eudravigilance data base. The sponsor shall enter all other suspected unexpected serious adverse reactions occurring in the trial centres of Latvia in the Eudravigilance Clinical Trials module of the EMEA Eudravigilance data base and shall state the addressee of State Agency of Medicines of the Republic of Latvia in any case no later than fifteen days after knowledge by the sponsor of such case. The sponsor shall report all

other suspected unexpected serious adverse reactions to the Ethics Committee in any case no later than fifteen days after knowledge by the sponsor of such case.

125. The State Agency of Medicines shall ensure that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are recorded.
126. The sponsor shall periodically (the period depends on the specifics of the clinical trial and the number of adverse reaction) inform all investigators about all suspected serious unexpected adverse reactions.
127. Once a year, not later than 60 days after the end of the term stated in the protocol, throughout the clinical trial, the sponsor shall provide the State Agency of Medicines and the Ethics Committee with a listing of all suspected unexpected serious adverse reactions which have occurred over this period and a report of the subjects' safety. If the clinical trial duration is less than a year, the safety report may be submitted together with a declaration of the end of the trial.

XVI. Non-interventional Studies

128. Within non-interventional studies only those data obtained by the observer (a doctor) in his/her practice, based on the opinion of the health condition and treatment of a patient shall be collected. No additional diagnostic and control procedures are performed for the patients and only epidemiological methods shall be used for the data analysis.
129. Prior to a commencement of a non-interventional study a doctor or a representative of the manufacturer responsible for the coordination of the non-interventional study shall submit the following documentation to the State Agency of Medicines and the Ethics Committee:
 - 129.1. an application with the following information:
 - 129.1.1. trade name and non-proprietary name, pharmaceutical form and concentration of a medicinal product proposed for a non-interventional study;
 - 129.1.2. description of a non-interventional study (including inclusion criteria and methods of data analysis);
 - 129.1.3. a list of doctors participating in a non-interventional study, including name, surname and specialty;
 - 129.1.4. a list of medical establishments involved in a non-interventional study;
 - 129.1.5. proposed number of included patients;
 - 129.1.6. information whether the disease, treated with the medicinal product proposed for a non-interventional study, is included in the list of diseases subject to reimbursement;
 - 129.1.7. information whether medicinal product proposed for a non-interventional study is included in the list of medicinal products subject to reimbursement;
 - 129.1.8. duration of a non-interventional study, providing the starting and ending date;
 - 129.2. a sample of a document certifying the patient's permission for collection and processing of the medical treatment data;
 - 129.3. a sample of a data record form.

130. The applicant shall cover expenses for the review of a non-interventional study application according to the rates of public services of the State Agency of Medicines.
131. The non-interventional study can be initiated after the Ethics Committee has issued a favourable opinion and the State Agency of Medicines has not informed the applicant within a period of 30 days of grounds for non-acceptance.
132. The doctor shall report all adverse reactions observed in the non-interventional study to the State Agency of Medicines in accordance with the requirements of the normative acts regarding procedure for monitoring of adverse reactions.
133. Within 90 days since the end of a non-interventional study the doctor or a person referred to in paragraph 129 shall notify the State Agency of Medicines that the non-interventional study has ended and shall submit information on the number of patients enrolled and adverse reactions observed.
134. In the framework of their competence the State Agency of Medicines shall control and the Health Inspectorate shall inspect the compliance of the non-interventional studies of medicinal products with these regulations.
135. Persons involved in the non-interventional studies shall not reveal personal and clinical data of the patients, except in cases where these data are requested by the authorities that according to the Medical Treatment Law are entitled to view information regarding a patient. ‘

XVII. Closing Provisions

136. Acknowledge the February 28th 2006 Cabinet of Ministers Regulation No. 172 “Regulations Regarding the Conduct of Clinical Trials and Non-interventional Trials, the Procedures for the Labelling of Investigational Medicinal Products and the Procedures for Inspection of Conformity with the Requirements of Good Clinical Practice” (Latvijas Vēstnesis, 2006, No. 45; 2008, No. 10) as null and void.
137. These Regulations will come into force on April 1st 2010.

Informative Reference to European Union Directives

These Regulations contain legal norms arising from:

- 1) Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use;
- 2) Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice with regard to investigational medicinal products for human use, as well as requirements for manufacturing authorisation or importation of such products.

Prime Minister *V. Dombrovskis*

Minister for Internal Affairs, performing the duties of the Minister of Health *L. Mūrniece*