Conditions and Procedure for Conducting Clinical Trials of Medicinal Products

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This Regulation is established on the basis of subsection 88 (4) and subsection 90 (8) of the Medicinal Products Act (RT I 2005, 2, 4).

§ 1. General provisions

(1) The Regulation establishes the list of information and documents to be submitted for conducting a clinical trial of a medicinal product (hereinafter trial), the requirements for the investigational medicinal product and the conditions and procedure for submission of application for a trial, the recruitment and notification of trial subjects, the measures taken for the protection of the trial subjects, the commencement of a trial, the making of amendments in the trial protocol and in the conducting of a trial, collection of data relating to the conducting of the trial, the storage of the specified data and termination of a trial.

(2) The requirements of this Regulation apply to the conducting of a clinical trial of a veterinary medicinal product in so far as these are applicable taking into account the specific character of the clinical trial of a veterinary medicinal product and unless otherwise established in this Regulation.

(3) A trial shall be conducted in accordance with the requirements of good clinical practice (hereinafter good clinical practice) adopted by the European Commission on the basis of Article 1(3) of the Directive 2001/20/EC of the European Parliament and of the Council 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 (OJ No. L 121, 01.05.2001, pp. 34–44).

§ 2. Information and documents submitted to the Agency of Medicines for conduct of trial

(1) In order to conduct a trial, the sponsor of the trial or his or her representative shall submit a written application and the following information and documents to the Agency of Medicines at least two months before the commencement of the planned trial:
   1) trial protocol with valid amendments;
   2) information concerning the pharmaceutical and chemical characteristics and pharmaco-toxicological characteristics of the investigational medicinal product;
   3) results of clinical trials conducted with the investigational medicinal product;
   4) insurance policy or an certified copy thereof;
   5) if the applicant is not a sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor;
   6) informed consent form and subject information leaflet;
   7) outline of active trials with the same IMP;
   8) examples of the label in Estonian;
   9) viral safety trials (if applicable);
   10) applicable authorisations to cover medicinal products and trials with special characteristics (e.g. genetically modified organisms, radiopharmaceutical medicinal products) (if available);
   11) transmissible spongiform encephalopathy (TSE) certificate (if applicable);
12) information on restricted use or release of genetically modified organisms (if applicable and if such information exists);
13) certification of GMP status of active biological substance;
14) copy of the manufacturer authorization of the medicinal product if the investigational medicinal product is manufactured in EU;
15) certification of the OP that the manufacturing site works in compliance with good manufacturing practice (GMP) established in the European Union;
16) certificate of analysis for the test product if additives are not prescribed in specifications or if non-prescribed additives are established (not present in the specification).

(2) All information and documents specified in subsection (1) shall be appended to the application if:
1) the investigational medicinal product does not have a valid marketing authorisation in Estonia;
2) the effect of the medicinal product is tested for indications which have not been approved upon issue of the marketing authorisation or on patients with whom the medicinal product has not been previously used;
3) the effect of the medicinal product is investigated in a dose or manner of administration which has not been previously investigated;
4) if narcotic drugs or psychotropic substances, contraceptive or radiopharmaceutical preparations are being investigated;
5) trial subjects are not patients.

(3) In cases not listed in subsection (2), an application for a trial to be conducted and the information and documents specified in clauses (1) 1), 5) and 6) shall be submitted to the Agency of Medicines.

(4) In order to conduct a clinical trial of a veterinary medicinal product, an application and the information and documents specified in subsection (1) shall be submitted to the Agency of Medicines, taking into account the provisions of subsections (2) and (3).


(5) The approval of the ethics committee of clinical trials (hereinafter ethics committee) may be submitted to the Agency of Medicines also after the submission of the application, indicating the date of obtaining the approval.

(6) Confirmation of the payment of the state fee which shall set out the date of making the payment, the amount paid and the bank account number from which the payment was made, or a document certifying payment of the state fee shall be appended to the application for conducting a trial.

§ 3. Submission of application for conducting trial

(1) An application for trial shall be submitted in the format set out in Annex 1 and Annex 2 to the Regulation on paper in A4 format and the information set out in Annex 1 shall be submitted additionally electronically on CD-ROM in XML format. The documentation of a trial of veterinary medicinal products shall be submitted on paper in A4 format in the format set out in Annex 3 to the Regulation.

(2) An application for trial and the appended documents shall be submitted in a single copy in Estonian or in English.

§ 4. Tasks of the Agency of Medicines upon submission of application for conduct of trial

(1) On the receipt of an application for a trial, except for a clinical trial of a veterinary medicinal product, the Agency of Medicines shall enter the following information in the EudraCT database which is available only to the competent authorities of the member states of the European Economic Area (hereinafter Member States), the European Medicines Agency and the European Commission.
1) application for trial;
2) all amendments made to the application;
3) all amendments made to the trial protocol;
4) positive opinion of the ethics committee;
5) notification of termination of the clinical trial;
6) reference indicating how compliance with good clinical practice has been verified.

(2) At the reasoned request of a Member State, the European Medicines Agency or the European Commission, the Agency of Medicines shall give information concerning the clinical trial in question in addition to the information contained in the EudraCT database.

(3) In the event of a clinical trial of a veterinary medicinal product, the Agency of Medicines shall forward a copy of the application together with the documents to the Ministry of Agriculture for obtaining approval.

§ 5. Recruitment of trial subjects and notification of trial subjects

(1) Subjects may be recruited to the trial only in a manner approved by the ethics committee. The informational materials used in the recruitment of subjects shall set out clearly that a scientific research is going to be conducted and that the trial may involve risk to the health of the subject.
(2) Recruitment of subjects in a clinical trial of a veterinary medicinal product shall be approved by the Ministry of Agriculture.

(3) Trial activities may be commenced only after notification of trial subjects of all circumstances of the trial and obtaining written consent of the subjects. The consent shall be documented in two original copies which shall be signed by the trial subject or his or her legal representative, indicating the date of signing, and by the person who notified the trial subject. One original copy shall be given to the trial subject, the other shall remain with the person who conducts the trial.

(4) The provisions of section 91 of the Medicinal Products Act shall be observed in giving the consent to participate in the trial.

(5) A trial subject or his or her legal representative has the right to obtain explanations from the investigator or a member of the trial team concerning the objectives, risks and inconveniences of the trial and the conditions under which it is conducted. The trial subject or his or her legal representative shall be informed of the right to terminate participation in the trial by withdrawal of the consent for trial at any time without any sanctions.

(6) Upon inclusion of an animal in a clinical trial of a veterinary medicinal product, the owner of the animal shall be notified of all circumstances of the trial.

(7) A trial subject or his or her legal representative, in the event of a clinical trial conducted on an animal, the owner of the animal shall be provided with contact details from where he or she can obtain additional information.

(8) The trial subject or his or her legal representative shall be informed that officials of competent state agencies of Estonia and foreign states and the representatives appointed by the sponsor of the trial shall be granted access to the medical information related to the trial as necessary in accordance with currently valid legislation for the performance of supervision or other inspection of the conduct of the trial. The trial subject or his or her legal representative shall grant consent to the access to the specified information by granting the written consent specified in subsection (3).

(9) The investigation materials which enable the identification of the person of the trial subject are confidential and they may be forwarded to third persons or access may be granted thereto only under the conditions prescribed by the Personal Data Protection Act (RT I 2003, 26, 158; 32, correction notice; 2004, 30, 208).

(10) The sponsor of the trial and persons conducting the trial shall ensure the rights of trial subjects to physical and mental integrity, inviolability of private life and the protection of information concerning him or her.

§ 6. Investigational medicinal product

(1) The medicinal products used in a trial shall be prepared pursuant to the requirements of the Medicinal Products Act and legislation established on the basis thereof.

(2) The batch of the investigational medicinal product shall be released by a competent person and a certificate of the release of the production batch for use, with the signature of the competent person, is required.

(3) The competent person shall prove that each production batch has been manufactured in compliance with good manufacturing practice.

(4) The following information shall be set out on the package of a medicinal product used in a trial:
   1) the name, address and telephone number of the representative of the manufacturer of the medicinal product, the contract research organisation or the co-ordinating investigator;
   2) the identification code or name of the medicinal product (in case of an open trial), pharmaceutical form, manner of administration, quantity of medicinal product, strength of medicinal product in case of open trial;
   3) batch number or code;
   4) identification number of the trial subject or the treatment;
   5) instruction for use (may be replaced by a reference to the package leaflet or additional materials);
   6) notation “exclusively for use in clinical trials”;
   7) name of the principal investigator if this is not set out in coded form in other clauses;
   8) the reference code of the trial which allows identification of trial site, the person conducting the trial and the sponsor of the trial if this is not set out in other clauses;
   9) storage conditions of medicinal product;
   10) date of expiry (month/year);
   11) the notation “Keep out of reach of children”, unless the medicinal product is used only in the conditions of the provision in-patient health services.

(5) The information set out in clauses (4) 2), 5), 6), 9) and 11) shall be in Estonian on the outer packaging or, in the absence thereof, on the inner packaging of the medicinal product.
(6) The information set out in clauses (4) 3), 4), 7) and 8) may be submitted as a code or codes which the person specified in clause 1) can open immediately.

(7) If the information specified in clauses (4) 1)-11) is set out on the outer packaging, the inner packaging shall set out the information specified in clauses 1), 2), 3), 4), 6) and 8). In such case, the address and telephone number may be left unspecified in clause 1); the manner of administration, except in case of liquid and injectable pharmaceutical forms, may be left unspecified in clause 2).

(8) If the inner packaging contains a blister or ampoule or other small packaging on which it is impossible to set out the information specified in subsection (7), it shall set out the information which enables identification of the medicinal product and the information set out in clauses (4) 1), 3) and 4) and in the case of liquid and injectable pharmaceutical forms also the manner of administration.

(9) In case of change of the expiry date of the medicinal product in the course of the trial, an additional label shall be placed on the packaging which sets out the new expiry date and the original batch number. The additional label may cover the original date of expiry but shall display the original batch number. When adding an additional label, good manufacturing practice shall be adhered to.

(10) Investigational medicinal products may be imported from a Member State and from countries outside of the European Economic Area by persons who hold an activity licence for wholesale trade in medicinal products ensuring that the investigational medicinal product has been released for use in the European Economic Area by a competent person with appropriate training.

(11) An application for authorisation for import of an investigational medicinal product shall be submitted to the Agency of Medicines after receiving consent for conducting the trial.

(12) The principal investigator is responsible for the storage of and maintenance of records on the investigational medicinal product at the trial site.

(13) The investigational medicinal products which were not used shall be destroyed on site, delivered for destruction to a waste treatment facility who holds a corresponding activity licence or returned to the manufacturer. All the specified activities shall be documented.

§ 7. Commencement of trial

(1) Before commencement of a trial, a list of persons participating in the trial specified in subsections 89 (1) and (2) of the Medicinal Products Act shall be prepared.

(2) A co-ordinating investigator shall be appointed from among the persons conducting the trial who shall coordinate the conducting of the trial in the trial site and shall ensure the exchange of information with the Agency of Medicines and the ethics committee and, in case of veterinary medicinal products, with the Ministry of Agriculture. If the trial is conducted in several trial sites, a co-ordinating investigator shall be appointed in each of them.

§ 8. Protection of trial subjects

(1) A trial may be conducted only if the estimated clinical benefit and the benefit for public health justifies the risks taken and the compliance with this requirement is continuously monitored during the trial.

(2) It is not permitted to conduct gene therapy trials resulting in the change of original genetic identity of the trial subject.

(3) A trial on persons with restricted active legal capacity is permitted only if the patient group directly benefits from the trial and only if the trial is essential for proving the data which have been obtained from clinical trials on persons who are capable of giving informed consent or by other scientific methods. In addition, the trial should be directly related to the clinical condition of the person with restricted active legal capacity or to such nature of the trial as allows it to be conducted only on person with restricted active legal capacity.

(4) Depending on the trial, a doctor, dentist or veterinarian with appropriate qualifications shall be responsible for medical care provided to the trial subjects and medical decisions made in the interests of the trial subjects.

§ 9. Amendments to trial protocol and conducting of trial

(1) Upon conducting a trial, the trial protocol shall be closely observed which describes the scientific background and objective of the trial, the trial plan, selection of trial subjects, use of the investigational medicinal product and other treatment of trial subjects, evaluation of the efficacy and safety of the medicinal product, the methods of collecting, storing and processing of data, the statistical methods used, the system for ensuring the quality and for inspection of the trial, the ethical aspects of the trial, the financing and insurance cover of the trial and the principles of publishing of the results of the trial.

(2) A doctor, dentist or veterinarian conducting a trial and a manufacturer of medicinal products or a representative thereof participating in the conduct of a trial shall notify the Agency of Medicines and, in the case
of a trial of a veterinary medicinal product, the Ministry of Agriculture in advance of amendments to the trial
protocol and to the conducting of the trial. In the case of a trial of medicinal products for human use, the ethics
committee shall be notified at the same time. If amendments to the trial protocol are necessary to ensure the
safety of trial subjects the amendments shall be communicated immediately.

(3) In order to make amendments to the trial protocol and conducting of the trial, the approval of the Agency of
Medicines and the ethics committee, in the case of a veterinary medicinal product, the approval of the Agency of
Medicines and the Ministry of Agriculture is required.

(4) For the notification of the Agency of Medicines and for application for consent for making amendments,
an application shall be submitted in the format set out in Annex 4 to the Regulation on paper in A4 format and
additionally electronically on CD-ROM in XML format; in the case of a clinical trial of a veterinary medicinal
product, notification shall be given in writing in free form. The ethics committee and the Ministry of Agriculture
shall be notified in writing in free form.

(5) The Agency of Medicines and the ethics committee shall grant their consent not later than within 35 days
as of receipt of the application for amendment of the trial protocol and of conducting of the trial. Upon refusal
to consent to amendments, the Agency of Medicines, the ethics committee or the Ministry of Agriculture may
submit their amendment proposals.

(6) If consent is obtained, the conducting of the clinical trial may be continued in accordance with the amended
trial protocol or the amendment made to the trial. Upon refusal to consent to the amendments submitted, the
sponsor of the trial shall adapt the trial protocol or the amendment to the trial according to the amendment
proposals submitted by the agencies specified in subsection (3) and the ethics committee or withdraw its
amendment proposals.

§ 10. Reporting serious unexpected adverse events occurring in clinical trials

(1) In addition to the Agency of Medicines, the sponsor of the clinical trial shall also notify in writing the
ethics committee who granted consent to the trial of serious unexpected adverse events occurring with the
investigational medicinal product and the reference medicinal product in Estonia within the established terms
and in the established form pursuant to the procedure established on the basis of subsection 90 (8) of the
Medicinal Products Act.

(2) The sponsor of the clinical trial shall submit a report in writing once a year on serious adverse reactions of
the investigational medicinal product occurring in any country.

§ 11. Collection and storage of data relating to the conducting of trial

(1) The persons conducting the trial and the sponsor or the representative of the sponsor shall ensure the
completeness and accuracy of the information collected in the course of the trial, the possibility of comparison
of this information with original sources, the functioning of the quality control system and the protection of the
personal data of the trial subjects.

(2) The principal investigator shall ensure the preservation of essential information collected in the course of
the trial, including source information for at least fifteen years after the end of the trial.

(3) The sponsor and the persons conducting the trial shall ensure the preservation of all information concerning
the investigational medicinal product for the time of validity of the marketing authorisation of the medicinal
product or for at least five years after the termination of the use of the medicinal product for research purposes
unless the sponsor or his or her representative and the person conducting the trial have agreed otherwise.

§ 12. Termination of trial

(1) The sponsor of the trial, the principal investigator or the manufacturer of the investigational medicinal
product shall terminate the trial immediately if in his or her opinion the danger to the life and health of the
subjects is too serious.

(2) If the Agency of Medicines decides to suspend or terminate the trial on the basis of section 98 of the
Medicinal Products Act it shall promptly notify, together with the reasons, the competent authorities of other
Member States, the ethics committee, the European Medicines Agency and the European Commission, in the
case of a trial of a veterinary medicinal product also the Ministry of Agriculture.

(3) If the trial is prematurely terminated the co-ordinating investigator shall notify within fifteen calendar days
in writing the Agency of Medicines and the ethics committee and in the case of a trial of a veterinary medicinal
product, the Agency of Medicines and the Ministry of Agriculture, and shall provide an explanation on the
reason for termination of the trial.
(4) If the trial is terminated as planned, the principal investigator shall notify the agencies specified in subsection (3) and the ethics committee thereof within 90 calendar days.

(5) The Agency of Medicines shall be notified of the termination of the trial in the format set out in Annex 5 to the Regulation in A4 format and additionally electronically in XML format on CD-ROM; termination of a trial of a veterinary medicinal product shall be communicated on paper in A4 format.

(6) The sponsor of the trial shall submit a trial report to the Agency of Medicines after the termination of the trial.

§ 13. Entry into force of Regulation

This Regulation enters into force on 1 March 2005.


Annex 1
Annex 2
Annex 3
Annex 4
Annex 5