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Finnish Medicines Agency Administrative Regulation

CLINICAL TRIALS ON MEDICINAL PRODUCTS

Unofficial translation

Legal bases

Medicines Act, sections 87 and 15a

Medical Research Act, section 10i

Target groups

Those performing clinical trials

Entry into force

This Administrative Regulation will enter into force on 1 January 2020 and will remain so until further notice.

Regulation(s) repealed

Regulation 2/2012

This regulation implements

Directive 2001/20/EC of the European Parliament and of the Council (32001L0020, OJ L 121, 1.5.2001, p. 34–44) and Directive 2005/28/EC of the European Parliament and of the Council (32005L0028, OJ L 91, 9.4.2005, p. 13–19)

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1. GENERAL

Pursuant to sections 15a and 87 of the Medicines Act (395/1987) and section 10i of the Medical Research Act (488/1999), the Finnish Medicines Agency (Fimea) hereby issues the following provisions to be complied with in clinical trials concerning medicinal products on human subjects.

Finnish legislation in force must be observed when conducting the above-mentioned clinical trials.

Regard shall be had to the following in particular:

Medical Research Act (488/1999) and Medical Research Decree (986/1999) and the subsidiary regulations issued in pursuance thereof

Medicines Act (395/1987)

Act on the Status and Rights of Patients (785/1992)

Data Protection Act (1050/2018)

Gene Technology Act (377/1995) and Decree (928/2004)

Patient Injuries Act (585/1986)

Act on the Medical Use of Human Organs, Tissues and Cells (101/2001)

This Regulation nationally implements Directive 2001/20/EC of the European Parliament and of the Council on the conduct of clinical trials on medicinal products for human use and, concerning its application, Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. This Regulation does not concern Article 6 of Commission Directive 2005/28/EC. The manufacturing practices to be observed in the production of investigational medicinal products and the role of the Qualified Person (QP) are set out in the Fimea administrative regulation on Good Manufacturing Practice (GMP).

The EU has issued guidelines on the observance of good clinical trial practice (Good Clinical Practice ICH E6(R2)).

The EU has issued a guideline on the observance of good manufacturing practice concerning the manufacture and quality control of medicinal products (EU GMP Volume 4 Good Manufacturing Practice). Annex 13 to the guideline (Investigational Medicinal Products) concerns investigational medicinal products in particular.

As well as having regard to these provisions, attention should also be paid to the Declaration of Helsinki of the World Medical Assembly.

Appendix 3 contains a list of internet addresses providing norms, guidelines and recommendations.

2. DEFINITIONS AND GLOSSARY

ATMP (Advanced Therapy Medicinal Product)

An advanced therapy medicinal product (ATMP) is a gene therapy medicinal product, a somatic cell therapy product or a tissue engineered product.

CIOMS

Council for International Organizations of Medical Sciences

EMA

The European Medicines Agency

EudraCT number

Identification number of a clinical trial in the European EudraCT database obtained by the sponsor

EudraVigilance

An EMA-maintained network and database for processing, evaluation and exchange of information on adverse reactions to medicinal products in the European Economic Area. EudraVigilance CT (Clinical Trial Module) deals with clinical trials on medicinal products.

Gene therapy medicinal product

A gene therapy medicinal product means a biological medicinal product which has the following characteristics: it contains an active substance which contains or consists a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence. Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains or to the product of genetic expression of this sequence.

Good Manufacturing Practice, GMP

Good manufacturing practice means the arrangements and procedures in pharmaceutical manufacturing and its quality control to ensure that the medicinal products meet all the requirements imposed on them as far as manufacturing is concerned.

Adverse event

An adverse event is any untoward medical occurrence presenting itself in a trial subject which need not necessarily derive from the said product.

Serious adverse event, SAE

A serious adverse event is any untoward medical occurrence or effect that results in death, is life-threatening requires hospitalisation or prolongation of existing inpatients' hospitalisation, results in persistent or significant disability or incapacity or is a congenital anomaly or birth defect.

Adverse reaction

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function; a noxious and unintended response to a medicinal product regardless of dose when there is a possible causal connection to the medicinal product.

Unexpected adverse reaction

An adverse reaction, the nature or severity of which is not consistent with the information provided in the summary of product characteristics, or investigator's brochure for an unapproved investigational product.

Serious adverse reaction, SAR

Any untoward medical occurrence or effect that results in death, is life-threatening, requires hospitalisation or prolongation of existing inpatients' hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Suspected unexpected serious adverse reaction, SUSAR

A serious adverse reaction that is also unexpected.

Interventional clinical trial

A trial which intervenes with the inviolability of the trial subject for the purpose of the investigation. For example, the administration of an investigational medical product to the trial subject or use of some extra means of intervention (i.e. samples, tests or questionnaires) that would not otherwise be used. Short survey forms are not considered interventions. See also: non-interventional clinical trial

Clinical trial

An interventional clinical trial conducted with human subjects in order to discover the effects of medicinal products in human subjects (effectiveness or safety, i.e. pharmacodynamics) or their pharmacokinetics in the human organism (absorption, distribution, metabolism or excretion), or both.

Non-interventional clinical trial

A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is wholly independent of the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of the data.

Post-authorisation safety study (PASS)

A post-authorisation safety study may be a clinical trial or a non-interventional clinical trial depending on the study design.

Tissue Engineered Product (TEP)

A tissue engineered product means a product that contains or consists of engineered cells or tissues and is presented as having properties for or used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue. A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells and tissues may be viable or non-viable. Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be included from this definition. Cells or tissues must be considered engineered if they have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved or if the cells or tissues are not intended to be used for the same essential function or functions in the recipient as the donor.

Medicinal product

A product or substance intended to be used internally or externally to cure, alleviate or prevent a disease or its symptoms in a human or animal subject. 'Medicinal product' also means any substance or combination of substances as referred to above that may be used internally or externally to determine the state of health of a person or the cause of a disease or to restore, improve or change his physiological functions through pharmacological, immunological or metabolic means. In the event of uncertainty, in cases where the product, having regard to all its properties, may correspond to the definition of medicinal product and of other preparation appearing in legislation and the instruments of the European Union, the provisions concerning medicinal products shall primarily apply (See also: investigational medicinal product).

MedDRA (Medical Dictionary for Regulatory Activities)

MedDRA is a clinically validated international medical terminology used by the European Medicines Agency (EMA) in the classification of adverse events and reactions.

Multi-centre trial

A clinical trial conducted according to a single protocol but at more than one trial site.

Transgenic micro-organism

The genetic material of a transgenic micro-organism has been altered in a way that does not occur naturally by mating and/or natural recombination. Micro-organism means any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including viruses and viroids as well as cultures of animal and plant cells and cultures of human cells and tissue cultures.

Substantial amendment

A substantial amendment is one that may affect the safety or physical or mental wellbeing of the subjects, or the scientific value of the trial, or that significantly changes the quality or safety of any IMP used in the trial, or is in some other way significant.

Independent data-monitoring committee, IDMC

An independent group of experts independent of the sponsor and the investigator which regularly monitors the progress of the trial. The group monitors the progress, safety data and critical result variables of the trial and may if necessary recommend its continuation, modification or suspension.

Somatic cell therapy medicinal product (SCTMP)

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics: contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor. It is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

Informed consent form

A document given to the trial subject which contains an explanation of the trial subject's rights, the purpose and nature of the trial and procedures to be used therein and any associated risks and disadvantages, and which is signed by the giver and recipient of the consent (further information in the Medical Research Decree 986/1999, 313/2004). The document may be independent or comprise the trial subject information leaflet (or patient information leaflet) and consent form.

Inspection

An official inspection performed by a competent supervisory authority for medicines, such as Fimea, of documents, premises, equipment, quality assurance system and any other circumstances which the authority considers relevant to the clinical trial and the checking of which said authority considers necessary.

Sponsor

An individual, company, institution or organisation that takes responsibility for the initiation, management or financing of a clinical trial. If an outside party participates in the trial only by financing it, the investigator and the sponsor can agree between themselves that the investigator is also the sponsor. The investigator himself is regarded as the sponsor in the case of trials where there is no outside sponsor.

Investigator

An authorised physician or dentist with the appropriate professional and scientific qualification who is responsible for performance of the clinical trial at the trial site. If a trial group is conducting a trial at some trial site, the term 'investigator' refers to the physician or dentist acting as the leader of the group.

Person responsible for the trial

An authorised physician or dentist with the appropriate professional and scientific qualifications in Finland who is responsible for the trial. He must ensure that the personnel conducting the trial are competent, the equipment and devices sufficient and the conditions safe. He must also ensure that legally imposed requirements, international obligations affecting the status of the trial subject, and rules and regulations relating to the trial are taken into consideration in its performance. He must suspend the trial as soon as the safety of a trial subject so requires and immediately perform any safety measures needed for protection of the trial subjects.

Investigator's Brochure

A compilation of the preclinical, clinical and non-clinical data on the investigational medicinal product which are relevant to the study of the product in human subjects. 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 an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial. The sponsor shall validate and update the investigator's brochure annually.

Commencement and end of trial

A trial is deemed to have commenced when the first trial subject signs a consent document. A trial is deemed to have ended when its entire clinical phase is over in respect of the last trial subject.

Investigational medicinal product, IMP

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 for an unauthorised indication, or when used to gain further information about the authorised form.

Investigational medicinal product dossier, IMPD

Information on an investigational medicinal product which must be appended to the trial notification. The scope of the information depends on whether the medicinal product has marketing authorisation (Appendix 2).

Trial site

The location where the trial subjects are studied.

Protocol

A document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments;

Trial subject

An individual who participates in a clinical trial as either a recipient of the investigational medicinal product or as a control. A trial subject may be a patient or a healthy volunteer.

3. GENERAL PREREQUISITES FOR CLINICAL TRIALS ON MEDICINAL PRODUCTS

Medical research in Finland is governed by the Medical Research Act (488/1999). The Act covers all medical research intervening with the inviolability of a human being, human embryo or foetus, including clinical trials on medicinal products in human subjects, which are also covered by the provisions of the Medicines Act (395/1987).

Medical research must respect the inviolability of human dignity. According to section 5 of the Medical Research Act, the interests and well-being of trial subjects must always come before the interests of science and society. Every effort must be made to prevent any risks to and adverse effects on the subjects. The trial must be conducted in accordance with the principles of good clinical practice (Appendix 1) and the principles of the Declaration of Helsinki. A trial must be medically justifiable.

According to section 6 of the Medical Research Act, trial subjects must be given sufficient information about the trial and the rights of the subject. An informed written consent must be obtained from prospective subjects prior to their participation in a trial. Even after giving this consent, a trial subject is free to withdraw from the research at any time without providing reasons for so doing or, for example, in the case of people who are sick, without risking their continued care.

According to section 5 of the Medical Research Act, each clinical trial on a medicinal product must have a sponsor and in Finland, a person responsible for the trial, who must be a physician or a dentist with appropriate professional and scientific qualifications. The person responsible for the trial must ensure the availability of competent and appropriately instructed research staff, sufficient equipment and appliances, and otherwise safe circumstances for the conduct of the trial. In addition, the person responsible for the trial must ensure adherence to legal provisions relating to the trial and to the requirements of international obligations or guidelines concerning the status of trial subjects.

An Independent Data-Monitoring Committee (IDMC) must, as necessary, be set up to monitor long-term trials conducted with large numbers of patients and trials relating to new, potentially dangerous, treatments. This Committee monitors trial progress, safety data and critical result variables, and may if necessary recommend continuation, modification or suspension of the trial.

The detailed division of duties between the investigator and the sponsor can be agreed on separately. The investigator himself is regarded as the sponsor in trials where there is no outside sponsor.

In addition to being notified of the commencement of a clinical trial, Fimea must be notified of any substantial amendments to be made to the protocol (section 87a of the Medicines Act), any serious adverse reactions occurring during a trial (section 10g of the Medical Research Act), and the termination of a trial, and must also be provided with a summary of the trial results (section 10h of the Medical Research Act). In addition, Fimea must be provided with an annual account of the safety of persons participating in a clinical trial in accordance with section 10g of the Medical Research Act. The Agency conducts inspections of clinical trials and can order their suspension when necessary.

4. MEDICINAL PRODUCTS USED IN CLINICAL TRIALS

Information about investigational medicinal products

The trial group must have at its disposal sufficient pharmacological, toxicological, pharmaceutical/chemical and biological data on the medicinal products used in clinical trials and this

data must be appended to the notification concerning a clinical trial on a medicinal product (Appendix 2).

The responsibility for the adequacy of data relating to medicinal products is primarily borne by the sponsor, who must provide the physician or dentist who will be conducting the trial with all the data on said products and with any other relevant information.

If the sponsor is not a legal person, the person who is responsible for the clinical trial is also responsible for the adequacy and reliability of the data on the medicinal product or the trial substance.

For medicinal products with marketing authorisation as referred to in section 21 of the Medicines Act, it is generally sufficient to refer to the material submitted in connection with the marketing authorisation application (Appendix 2).

The release of vaccines and plasma-derived medicinal products for use in clinical trials in Finland is overseen by Fimea (further information in Appendix 2).

Labelling, supply and record-keeping of investigational medicinal products

If necessary, the investigational medicinal products must be labelled in both official languages of Finland. If the patient is not given the package but instead the medicine is administered at the trial site, the labelling can be in English only. Packages which are used for clinical trials, including placebo packages, must be marked 'Kliiniseen tutkimukseen' /'För klinisk prövning' [For clinical trial].

The labelling of an investigational medicinal product shall indicate the following information as instructed in EU GMP Volume 4 Good Manufacturing Practice, Annex 13, Investigational Medicinal Products:

- the trial code, batch number or other means of identification, the manufacturer and/or sponsor, the name of the investigator and the patient identifier, the pharmaceutical form, the method and/or route of administration, the number of doses, the instructions for storage (if special storage instructions are necessary), the expiry date and, if necessary, the technical handling instructions.

Repackaging or relabelling in which the packaging of an investigational medicinal product is altered or its labelling is altered or covered are considered as manufacture of an investigational medicinal product within the meaning of section 3 of Annex 2. A justified change of the shelf life is not considered as manufacture within the meaning of section 3 of Annex 2.

When an investigational medicinal product is supplied to the trial subject, information concerning the trial subject and the study visit can be added to the label of the investigational medicinal product concerned.

According to section 88 of the Medicines Act, the investigator may be supplied with investigational medicinal products for a clinical trial by a pharmaceutical manufacturer, a unit manufacturing medicinal products for clinical trials, a wholesale distributor, a hospital pharmacy or a pharmacy operating in Finland. If a pharmacy, hospital pharmacy or medical centre is responsible for the storage of investigational medicinal products, the head of the unit concerned may acknowledge receipt of the products.

The sponsor must keep a record stating the delivery, receipt, use, return and destruction of investigational medicinal products.

The investigator is responsible for the record of medicinal products at the trial site stating their delivery, receipt, use, return and destruction.

The trial subject must be provided with investigational medicinal products and any equipment needed for their use without charge, unless there is justifiable reason for acting otherwise.

5. NOTIFICATION CONCERNING THE CLINICAL TRIAL ON A MEDICINAL PRODUCT

Fimea must be notified of clinical trials on medicinal products that intervene with the inviolability of the trial subject in order to investigate the effects or properties of a medicinal product, regardless of whether the investigational medicinal product has marketing authorisation as referred to in section 21 of the Medicines Act. Provisions on the notification requirement and processing times are laid down in section 87 of the Medicines Act.

Fimea must only be notified of interventional trials. No notification is needed for non-interventional trials (For a definition, please refer to Section 2 Definitions and Glossary). In the event of any uncertainty, Fimea will decide whether a notification for a clinical trial on medicinal products should be submitted.

An administrative fee, set in the Decree of the Ministry of Social Affairs and Health on fees levied by the Finnish Medicines Agency, is payable for notifications and marketing authorisation applications. Fee exemptions may be available in certain circumstances. A single fee is payable for multi-centre trials. Further information is available on the Fimea website.

6. DOCUMENTS TO BE APPENDED TO THE NOTIFICATION

The following documents must be appended to the notification filed with Fimea:

1. Covering letter. The sponsor or an authorised representative compiles and signs a covering letter which accompanies the notification. The signature can also be electronic. The heading of the covering letter must include the EudraCT number, the sponsor protocol number, the name of the trial protocol and the name of the person responsible for the trial in Finland. The body of the letter must contain a brief description of the trial, focusing on its special features (e.g. specific groups of patients, the first time the medicinal product is administered to human subjects, exceptional features of the medicinal product, exceptional trial arrangement, etc.) In addition, the covering letter shall list the documents accompanying the notification.
2. List of trial sites and investigators (physicians and dentists). The list must include the address of the trial site, the investigators at each trial site, and their degrees and areas of specialisation, if this information was not provided in the notification form.
3. The curriculum vitae (CV) of the person responsible for the trial in Finland.
4. Notification form. The signed EudraCT notification form shall be submitted to Fimea. (See Chapter 7. Notification form.)
5. More detailed payment instructions for the notification or application fee are provided on the Fimea website. A waiver of processing fee may be requested in respect of a notification relating to a clinical trial on a medicinal product conducted by an individual investigator, a trial team, a university institute, a university hospital clinic or the National Institute for Health and Welfare without outside financing or with financing by a non-profit corporation. In these cases, the notification concerning a trial must be accompanied by an informal statement to the effect that the investigation will not receive any outside financing. Medicinal products received free of charge for the purpose of the investigation are not deemed outside financing.
6. A brief description of any unusual division of duties and responsibilities between the sponsor and the person responsible for the clinical trial, in the event that some of the sponsor's duties have been transferred to the person responsible for the clinical trial.
7. A trial protocol signed by the person responsible for the clinical trial in Finland (the signature can also be electronic).

8. A consent document, which may comprise a separate information leaflet and consent form. The informed consent of a trial subject is subject to the provisions of the Medical Research Act (488/1999) and the content of the consent document to the provisions of the Medical Research Decree (986/1999, 313/2004, 65/2016). In the event that changes are made to the consent document after its submission to Fimea based on, for example, the requirements imposed by an ethics committee, the revised consent document shall be submitted to Fimea for information.
9. The investigator's brochure, if one has been compiled. The sponsor is required to validate and update the investigator's brochure annually. If the investigational medicinal product has been granted marketing authorisation in Finland, the Summary of Product Characteristics (SPC) currently in effect will be sufficient.
10. Evidence that the manufacture of the investigational medicinal products conforms to good manufacturing practice (GMP).
11. Data on previous trials on human subjects
12. Data on the pharmaceutical, chemical and biological properties of the medicinal product.
13. Data on the pharmacology and pre-clinical toxicology of the medicinal product. In the case of a clinical trial on a medicinal product that has been granted marketing authorisation, or whose application for marketing authorisation is pending at Fimea, reference to the material submitted in connection with the application for marketing authorisation is usually sufficient as regards items 9–12. If trials on an investigational medicinal product have been conducted in Finland earlier, reference may be made to the material accompanying the earlier trial notification, provided that no substantial changes have occurred. (See Appendix 2.)

For communication relating to a clinical trial on medicinal products, a foreign sponsor must have a representative in Finland who is responsible for communication with Fimea.

7. CLINICAL TRIAL APPLICATION FORM

In the case of a clinical trial on a medicinal product, the sponsor or the sponsor's legal representative in the European Union must submit to Fimea a notification on or a request for authorisation of a clinical trial on a medicinal product before the commencement of the trial as provided under section 87 of the Medicines Act. If the person submitting the notification is not the sponsor or his legal representative, the notification must be accompanied by a letter in which the sponsor authorises the party submitting the notification to act on his behalf.

Notification of a clinical trial shall be made using the Clinical Trial Application Form (<https://eudract.ema.europa.eu/eudract-web/index.faces>) available on the EMA EudraCT database website (<http://eudract.ema.europa.eu/>). In the event that a EudraCT number has already been obtained for notification to be made to the competent authority of another State, the same number shall be used. Instructions on completing the form are available on the Fimea and EMA websites.

Fimea verifies the information and transfers it to the European EudraCT database for use by the authorities. More detailed instructions are provided on the Fimea website.

8. TRIAL PROTOCOL

The trial protocol or the documents appended to the notification must include the following information:

1. General administrative information, i.e. the full name of the clinical trial, the abbreviated name of the trial, sponsor's protocol number, the version number and date of the protocol, and the names of the sponsor and the person responsible of the trial in Finland.
2. The purpose of the investigation and the justification for its conduct.

3. A description of the research method (controlled, uncontrolled), structure of the trial (e.g. parallel groups, cross-over), randomisation (the method and procedure), and blinding (e.g. double blind, single blind).
4. A list of the trial sites, investigators (physicians or dentists) and their degrees and specialist qualifications, if not separately listed.
5. A description of the patients. The inclusion and exclusion criteria.
6. The estimated number of patients to be included in the trial, and its justification. Whether the patient material is sufficient from the standpoint of the investigation.
7. The estimated schedule of the trial.
8. The method of administration, dose and dosing schedule of the investigational medicinal product and the comparator, and the treatment period.
9. The control groups and control treatment (placebo, other treatment, etc.).
10. Other concurrent therapy, if any.
11. Assessment of efficacy. Result variables, primary result variable, description and evaluation of measurement methods. Measurement schedule.
12. Assessment of trial safety and related laboratory and other tests.
13. Reporting and assessing of adverse events and reactions. A description of the recording of adverse events and reactions and of any systematic follow-up questionnaire on adverse events.
14. Precautions for emergencies and criteria for opening the trial code and suspending the trial.
15. Any adverse effects in patients' relatives, nursing staff and the surroundings which may be caused by the investigational medicinal product and by the trial, and measures to prevent these.
16. Processing and recording of the data on persons participating in a trial. Compilation of personal data files and processing of related personal information.
17. Information on quality assurance methods.
18. Measures used to ensure the authenticity of the collected data and observance of good clinical trial practice.
19. Analysis of the results. A description of the research methods and statistical methods. Processing of data on subjects who have interrupted the trial.
20. Information on the advance information to be given to trial subjects/patients and on the method for obtaining the informed consent of trial subjects.
21. Ethical aspects relating to the trial.
22. The arrangements for the treatment of patients after the trial (such as gradual discontinuation of the investigational medicinal product, possible replacement by other medication, etc.). An account of the arrangements for the treatment of patients showing good results from the medicinal product investigated.
23. A description of how amendments to the trial protocol are recorded and reported to Fimea and the Ethics Committee.

24. Appendices to the protocol.

25. An account of the manner in which the trial and its results will be published.

The person responsible for the trial in Finland must date and sign the protocol.

Some of the above information may be incorporated in the documents appended to the trial protocol, such as the Investigator's Brochure.

9. AMENDMENTS TO THE TRIAL PROTOCOL

The sponsor must ensure that Fimea is notified in writing of any substantial amendments that may be made to a trial protocol or its appendices submitted earlier under Section 87a of the Medicines Act. If Fimea does not request any further information on the amendment notification within 35 days of receiving it, the Agency has accepted the amendment. The sponsor must, however, obtain the positive opinion of the Ethics Committee on the amendment(s) before implementation.

Any changes in investigators or trial centres must also be reported to Fimea.

Substantial amendment is notified in writing using the Substantial Amendment Notification Form available on the European Commission website at <http://ec.europa.eu/health/documents/eudralex/vol-10/>. The completed form is submitted to Fimea.

If a new version of the trial protocol or its appendices is later submitted to Fimea, all changes from the earlier version must be clearly itemised.

10. REPORTING ADVERSE EVENTS AND REACTIONS

The investigator and sponsor must report the occurrence of any adverse events and reactions during clinical trials in Finland as provided in sections 10e and 10f of the Medical Research Act (488/1999). Fimea need not be notified of adverse reactions occurring in clinical trials not conducted in Finland.

According to section 10g of the Medical Research Act, the sponsor must keep detailed records of all serious adverse events and all adverse events defined as significant in the trial protocol which are reported to him by the investigator. The sponsor must report all serious unexpected adverse reactions which are fatal or life-threatening as quickly as possible, however no later than within seven days of the sponsor being informed of such an adverse reaction. Any additional relevant information on such an adverse reaction must be reported within eight days of submission of the first notification.

Serious unexpected adverse reactions which are not life-threatening or fatal must be reported as soon as possible and in any case within 15 days of the sponsor first being informed thereof.

Registration with EMA's EudraVigilance is mandatory for commercial sponsors. Registration instructions are available at the EudraVigilance website (<http://eudravigilance.ema.europa.eu/highres.htm>). Registered sponsors must submit electronic notifications to EudraVigilance. Unexpected serious adverse reactions occurring both in Finland and abroad must be reported to the European Medicines Agency (recipient identifier EVCTMPROD). Specific instructions have been issued by the European Commission in the document titled "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use" ('CT-3').

If the sponsor is not registered with EudraVigilance, a report must be made in writing to Fimea. The report may not be submitted by fax or email. It can be made in the form of a free-form letter or with the CIOMS-I form (available at <http://www.cioms.ch/>) or a corresponding form. The report must show at least:

- EudraCT number of the trial or the number provided by Fimea if the trial has been notified prior to June 1, 2004;

- information on whether the event has been reported to Fimea earlier (whether this is a follow-up report);
- name of the investigational medicinal product which is suspected to have caused the reaction. If the pharmacotherapy has been blinded (masked), the code must be broken if no other method has been justified in the trial protocol;
- diagnosis of the trial subjects or information that healthy volunteers are treated;
- adverse reaction observed, preferably also the MedDRA code of the reaction;
- start date and end date;
- outcome (recovered, recovering, not yet recovered, permanent disability, fatal, unknown)
- trial subject's identification number;
- trial subject's age (in the case of infants under 12 months to an accuracy of one month, and in the case of infants under one-month old to an accuracy of one day);
- trial subject's gender;
- the name of the person who reported the adverse reaction; and
- the country where the adverse reaction was identified (=Finland).

According to section 10g of the Medical Research Act, once a year, the sponsor must provide Fimea with a list of all suspected serious adverse reactions which have occurred during the period in question. At the same time, the sponsor must supply a brief report of the safety of persons participating in the clinical trial. The report shall take into account all facts relating to the trial, not only the safety of the investigational medical product. This requirement remains in force throughout the period the clinical trial is ongoing in Finland.

The sponsor must without delay inform the investigators and Fimea of any significant new observations relating to the safety of the investigational medicinal product.

11. COMMENCEMENT, SUSPENSION AND ENDING OF A TRIAL

According to section 3 of the Medical Research Act, before commencement, a favourable opinion of the clinical trial must be obtained from the relevant Ethics Committee. If the Ethics Committee has proposed changes to the trial, the amended documents such as the trial protocol, its appendices and patient consent must be submitted to Fimea in the form approved by the Ethics Committee prior to commencement of the trial. A trial notification or request for authorisation may be submitted to Fimea regardless of the stage of processing by the Ethics Committee.

Fimea examines the notification or request for authorisation concerning a clinical trial on medicinal products and its appendices. If on preliminary examination the notification is found to be deficient, the Agency requests supplementation of the notification before processing it. The sponsor is sent an announcement of the receipt of a valid notification or request for authorisation; this states the date of commencement of processing and the number assigned to the investigation by Fimea. This number and the EudraCT number must be used as a reference in any correspondence or other communication regarding the trial.

If Fimea cannot approve the conduct of the trial, the sponsor is asked for further clarification. If such clarification is requested, the request is made in writing within 60 days of the commencement of processing to the party submitting the notification. On the basis of the request for clarification from Fimea, the sponsor may amend its trial protocol to rectify the deficiencies observed. If the amendments are not made or the amendments are not in line with the request for clarification, the trial may not commence. If no clarification is requested, the trial may commence without specific permission from Fimea when 60 days have elapsed from commencement of the processing.

According to section 87 of the Medicines Act, the Fimea processing period is 90 days if the clinical trial involves medicinal products for gene therapy, somatic cell therapy or medicinal products containing genetically modified organisms. Written authorisation from Fimea is required before such clinical trial can commence. Fimea can extend the processing period by a further 90 days if issuance of a statement requires extensive further clarifications. No fixed time limit applies to decisions to authorise trials involving xenogenic cell therapy.

If the trial is not initiated, Fimea must be notified of the decision and the reasons for it in writing within 90 days. If the trial has been interrupted, Fimea must be notified of the interruption and the reasons for within 15 days using the EudraCT form "Notification of amendment". The same form must be used to notify of re-commencement of the trial.

Clinical trial is deemed to have ended when the last patient has completed the clinical stage of the trial. According to section 10h of the Medical Research Act, Fimea must be notified of the end of the trial within 90 days. In the event that a clinical trial is terminated early, a notification must be submitted to Fimea within 15 days of the termination. In the event that a multinational trial ends in Finland earlier than at the other trial sites, a separate notification is required. Notification concerning the end or early termination of the trial must be made in writing using the EudraCT form "Declaration of the end of a trial" available on the European Commission website (<http://ec.europa.eu/health/documents/eudralex/vol-10/>).

12. REPORT ON THE TRIAL RESULTS

According to section 10h of the Medical Research Act, the sponsor or the person responsible for the trial must provide Fimea with a report on the results of the trial not later than one year after it ends. If the trial subjects have included persons under the age of 18 and if the sponsor is the marketing authorisation holder for the investigational medicinal product, the report must be submitted within six months. The report should be submitted in the form of a summary, a synopsis, published article or in some other similar way in writing. An extensive trial report containing complete research data only needs to be supplied at the request of Fimea.

Even if a Final Report on the trial results has been submitted to Fimea as an attachment of an application for marketing authorisation, a summary of the trial results must nonetheless be sent separately to the Clinical Trials Unit.

Additionally, the results shall be submitted to the EU register of clinical trials. The sponsor shall register in the EudraCT database of the European Medicines Agency as a supplier of results:

<https://eudract.ema.europa.eu/results-web/>

More detailed information is available in the European Commission guidance on the publication of the results of clinical trials at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf

13. INSPECTIONS AND SUPERVISION

According to section 87b of the Medicines Act, Fimea is the supervisory authority for clinical trials on medicinal products. The Agency must, when it so requests, be provided with any clarifications that it requires to perform this supervision. Notwithstanding the rules on confidentiality, the Agency has the right to inspect any aspect necessary, including the trial site, trial documents and the patient documents concerning trial subjects.

If another country's competent authority intends to inspect the trial site and the trial documents in Finland, the sponsor must report the inspection to Fimea by letter within seven days of the sponsor being informed of the intended inspection.

14. TRIAL DOCUMENTATION AND ITS STORAGE

The original trial documents must be stored for at least 15 years from the end of the trial. The keeping of patient files is governed by the relevant general provisions and regulations.

15. GRANTING OF WAIVERS

Fimea may for particular reasons grant waivers from the above provisions.

16. GUIDANCE AND INFORMATION

Guidance and information on the practical application of this Regulation is available upon request from Fimea.

17. ENTRY INTO FORCE

This administrative regulation enters into force on 1 January 2020.

Director General Eija Pelkonen

Head of Unit Jukka Sallinen

DISTRIBUTION

Pharma Industry Finland
National Institute for Health and Welfare
Finnish Red Cross Blood Transfusion Service
Hospital pharmacies and medical centres
Hospital districts
National Committee on Medical Research Ethics (TUKIJA)
National Supervisory Authority for Welfare and Health (Valvira)
Ministry of Social Affairs and Health
Finnish Medical Association

APPENDIX 1. THE PRINCIPLES OF GOOD CLINICAL PRACTICE

According to Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

1. The rights, safety and well being of the trial subjects shall prevail over the interests of science and society.
2. Each individual involved in conducting a trial shall be qualified by education, training, and experience to perform his or her tasks.
3. Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects.
4. The necessary procedures to secure the quality of every aspect of the trials shall be complied with.
5. The available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial.
6. Clinical trials shall be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association in 1996.
7. The protocol referred to in point (h) of Article 2 of Directive 2001/20/EC shall provide for the definition of inclusion and exclusion of subjects participating in a clinical trial, monitoring and publication policy.
8. The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.
9. 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 the trial subjects remains protected.

APPENDIX 2. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)

Pharmaceutical, chemical and biological data on the investigational medicinal products, together with toxicological, pharmacological and clinical data on them, must be appended to the notification concerning a clinical trial if the investigational medicinal product does not have marketing authorisation as referred to in Section 21 of the Medicines Act or the investigational medicinal product characteristics have been changed compared with the manufactured/pharmaceutical form that has marketing authorisation.

Where relevant, the information must follow the "Detailed guidance for the request for authorisation of a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial" (CT-1) issued by the European Commission. The extent of the information depends on the stage of the investigation. When a clinical trial moves from one phase to another, the sponsor may be required to provide more information.

If the data on the investigational medicinal product have been submitted to Fimea as an appendix to a previous trial notification, or if the product has marketing authorisation in Finland, only supplementary information on the trial need be appended to the trial notification (simplified IMPD). Examples of the information which needs to be provided are shown in Tables 1 and 2.

Table 1. Supplementary IMPD documentation

Types of previous assessment	Quality data	Non-clinical data	Clinical data
<p>The IMP has an MA in any EU Member State or ICH country and is used in the trial</p> <ul style="list-style-type: none"> • within the conditions of the SPC • outside the conditions of the SPC • after modification (e.g. blinding) 	SPC		
	SPC	If appropriate	If appropriate
	P + A	SPC	SPC
<p>Another pharmaceutical form or strength of the IMP has an MA in any EU Member State or ICH country and IMP is supplied by the MA holder.</p>	SPC + P + A	Yes	Yes
<p>IMP has no MA in any EU Member State or ICH country but the active substance is part of a medicinal product with an MA in an EU Member State and</p> <ul style="list-style-type: none"> • is supplied by the same manufacturer • is supplied by another manufacturer 	SPC + P + A	Yes	Yes
	SPC + S + P + A	Yes	Yes
<p>The IMP is subject to a previous CTA and authorised in the Member State concerned and has not been modified, and</p> <ul style="list-style-type: none"> • No new data available since the latest amendment to the CTA • New data is available since the last amendment to the CTA • Is used under different conditions 	Reference to previous submission		
	New data	New data	New data
	If appropriate	If appropriate	If appropriate

(S= Data relating to active substance, P = Data relating to the IMP, A = Appendices to the current version of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials*).

*CHMP/QWP/185401/2004 final (http://ec.europa.eu/health/files/eudralex/vol-10/18540104en_en.pdf)

Table 2. IMPD in cases of placebo

IMPD in for placebo	Quality data	Non-clinical data	Clinical data
The IMP is a placebo	P + A	No	No
The IMP is a placebo and the placebo has the same composition as the tested IMP, is manufactured by the same manufacturer, and is not sterile	No	No	No
The IMP is a placebo and has been submitted in a previous CTA in the Member State concerned	No	No	No

(S= Data relating to active substance, P = Data relating to the IMP, A = Appendices to the current version of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials*).

*CHMP/QWP/185401/2004 final (http://ec.europa.eu/health/files/eudralex/vol-10/18540104en_en.pdf)

1. Pharmaceutical, chemical and biological data

Pharmaceutical and chemical data is to be presented in accordance with the CHMP guidelines as set out in CHMP/QWP/185401/2004, Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials. For biological IMPs, please observe guideline CHMP/BWP/534898/2008, Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials.

The quality requirements for the active ingredient and final product must always be provided. In addition, analysis results from one or several batches must be included. Investigations into the shelf-life of the active ingredient and the final product must also be provided.

In case of products containing substances of biological origin, the starting materials should also be specified. In the information relating to substances of biological origin, special attention should be paid to the manufacturing process for the active ingredient and to ensuring its virus and prion safety.

If a placebo or some other reference product is used in the trial, an adequate account must be provided of its manufacture, composition, appearance and taste. Tables 1 and 2 contain more detailed instructions. Attention must also be paid to other relevant guidelines provided by the European Commission, CPMP and ICH.

Changes in a medicinal product being used for a trial already in progress which substantially affect the kinetics, manufacture or shelf-life of the medicinal product must be reported without delay.

If the pharmaceutical, chemical and/or biological characteristics of the medicinal product have changed compared with the characteristics of the medicinal product used in animal tests or in earlier clinical trials, the nature of this change must be explained and the reason for the change stated.

2. Toxicological, pharmacological and clinical data

Before Phase I clinical trials, Fimea must be provided information in accordance with the following guidelines:

- ICH Topic M 3 (R2) Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (CPMP/ICH/286/95, revised 2009)
- ICH guideline M3 (R2) - questions and answers (EMA/CHMP/ICH/507008/2011)
- ICH Topic S 7 A Safety Pharmacology Studies for Human Pharmaceuticals (CPMP/ICH/539/00)

- ICH Topic S 7 B The nonclinical Evaluation of the Potential for delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (CPMP/ICH/423/02)
- Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products EMEA/CHMP/GTWP/125459/2006

In addition, note should be taken of other relevant guidelines issued by the European Commission, CPMP and ICH, including:

- Guideline on strategies to identify and mitigate risks for first-inhuman clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07)
- ICH Topic S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008)

Relevant data from earlier clinical trials in human subjects must be submitted to Fimea before Phase II, III and IV trials. Specifically, the instructions given in "ICH Topic E 8. General Considerations for Clinical Trials CPMP/ICH/291/95" must be noted.

3. Manufacture, import and distribution

Manufacture and import

The manufacture and release of medicinal products used in a clinical trial on medicinal products (investigational medicinal products) in the EU/EEA is subject to a manufacturing authorisation granted by a competent supervisory authority for medicines. A corresponding authorisation is also required of the importer of investigational medicinal products manufactured outside the EU/EEA.

The manufacturing practices to be observed in the production of investigational medicinal products and the role of the Qualified Person (QP) are set out in the Fimea administrative regulation on Good Manufacturing Practice (GMP).

Moreover, it must be noted that pharmacies, hospital pharmacies and pharmaceutical wholesalers may only import into Finland investigational medicinal products that have already been released on the market in the EEA/EU. Private individuals may not import investigational medicinal products into Finland. All aspects of the importation, storage and delivery of medicinal products used in clinical trials shall comply with relevant legislation.

Manufacturer in Finland

In Finland, investigational medicinal products must be manufactured by a pharmaceutical company or a unit manufacturing medicinal products for clinical trials. The operating licence of the pharmaceutical company or unit manufacturing medicinal products for clinical trials must cover the pharmaceutical form used in the trial. A corresponding licence is also required when investigational medicinal products are imported directly into Finland from outside the EEA/EU.

A pharmacy or auxiliary pharmacy, a hospital pharmacy or a medical centre may only manufacture investigational medicinal products for its own use. Under section 15a of the Medicines Act, such manufacturers must submit a notification to Fimea on the manufacture of a medicinal product for a clinical trial before commencing such manufacture. The notification shall provide data on the medicinal product, its pharmaceutical form, the trial code, an estimate of production volumes and a brief account of the quality control and release procedures.

No licence or GMP certificate needs to be submitted to Fimea in the case of above-mentioned manufacturers that conform to the provisions of the Finnish Medicines Act.

If human cells or tissues collected in Finland are used in the manufacture of an investigational medicinal product, they must be obtained at a tissue establishment licensed in accordance with Section 20b of the Act on the Medical Use of Human Organs, Tissues and Cells (101/2001).

Manufacturer abroad

The manufacturer of and/or importer and party releasing the investigational medicinal products in the EEA/EU must be a pharmaceutical company located in the EEA/EU, for which a copy of the current pharmaceutical factory operating licence or GMP certificate issued by the EU authority supervising the activity must be submitted. The licence or certificate must cover the manufacture/importation/release in the EEA/EU of the pharmaceutical form to be used in the trial. In addition, a notification must be provided concerning the qualified person, as referred to in Directive 2001/83/EC, responsible for the release and certification of the medicinal products for the trial. The said qualified person shall sign an affirmation that the said investigational medicinal products have been manufactured in accordance with GMP as required in the EU.

In respect of those manufacturers of the investigational medicinal product located outside the EEA/EU, the qualified person shall issue an affirmation containing the information necessary to Fimea to assess the manufacturer's GMP compliance and the need for a GMP inspection by the authorities. GMP compliance and the need for inspection is assessed by Fimea on a case by case basis on the basis of the information provided on the manufacturer and a risk assessment based on the content of the trial. Factors taken into consideration in the risk assessment include:

- pharmaceutical form and type of investigational medicinal product,
- number of trial subjects and duration of treatment,
- the number of trials conducted using the same manufacturer's medicinal products,
- GMP inspections and/or supervision of licensed operations performed by the competent supervisory authority for medicines of the relevant country
- the system of licensing of quality control tests performed outside the EEA/EU, if any

4. Vaccines and blood- and plasma-derived medicinal products in clinical trials

Fimea oversees the release of the batches of vaccines and plasma-derived medicinal products for use in clinical trials on medicinal products in Finland. Immunoprophylaxis vaccines only are subject to batch control. Immunotherapy products are excluded from this requirement. Blood- and plasma-derived blood products comprise all medicinal products, containing an active substance or other component (e.g. carrier) derived from human blood or plasma as well as certain immune serum products derived from animal sources.

Fimea shall be provided with the manufacturer's own analysis certificates, the relevant batch release certificates signed by the QP, details of the dose quantities of the batches to be imported into Finland, the person responsible for the trial, the EudraCT number and the clinical trial authorisation granted by Fimea. The documents can be sent by e-mail in PDF format to batch.control@fimea.fi. Batches for use in clinical trials may only be taken into use following authorisation by Fimea. If the clinical investigational product originates from outside the EEA/EU area, it shall be released in the EU/ETA area and a certificate of the release shall be submitted to Fimea.

If a product subject to a marketing authorisation is used as a control or to supplement a vaccination programme, an EU Official Control Authority Batch Release Certificate and details of the dose quantities of the batch to be imported to Finland must be provided.

APPENDIX 3. LINKS

Legislation

National Code of Statutes	http://www.finlex.fi
Medicines Act	
Act on the Status and Rights of Patients	
Medical Research Act and Decree	
Data Protection Act	
Gene Technology Act and Decree	
Patient Injuries Act	
Act on the Medical Use of Human Organs, Tissues and Cells	
Ethical guidelines	
Finnish Medical Association	http://www.laakariliitto.fi/etiikka/
World Medical Association (WMA) Declaration of Helsinki	
Other WMA declarations	
Other ethical guidelines	
Council of Europe	http://www.coe.int/
Convention on Human Rights and Biomedicine	
National Committee on Medical Research Ethics (TUKIJA)	https://tukija.fi/etusivu
Ethical evaluation	
Investigations involving children	
Requests for Ethics Committee opinions	
DNA investigations	
Withdrawal periods prior to pregnancy	
CIOMS	http://www.cioms.ch/
Ethical guidelines	
Adverse reaction report form CIOMS-I content/uploads/2017/05/cioms-form1.pdf	https://cioms.ch/wp-
Guidance for clinical trials on medicinal products	
EMA and ICH guidelines	http://www.ema.europa.eu/ema
Good Clinical Practice (GCP)	
Quality of medicinal products (quality)	
Clinical trials (efficacy)	
Preclinical trials (safety)	
Adverse reactions (pharmacovigilance)	
Biologicals	
Advanced therapies	
European Clinical Trials Database EudraCT	http://eudract.emea.europa.eu/
Acquisition of EudraCT number	
Notification form for clinical trials on medicinal products	
EudraVigilance	http://eudravigilance.ema.europa.eu/human/index.asp
Detailed instructions on clinical trials	
Eudralex Volume 10	http://ec.europa.eu/health/documents/eudralex/vol-10
Substantial Amendment Notification Form and Declaration of the End of Trial Form	
European Commission guidelines and Directives use/clinical-trials/index_en.htm	http://ec.europa.eu/health/human-
Good Manufacturing Practice (GMP)	
https://ec.europa.eu/health/documents/eudralex/vol-4_en	
Good Clinical Practice (GCP)	
Detailed instructions for clinical trials on medicinal products	
Guidance material relating to the Personal Data Act	
MedDRA	http://www.meddrasso.com/
Fimea's instructions for academic researchers	

Instructions for completing the EudraCT form

https://www.fimea.fi/documents/160140/744738/26692_ohje_akateemiselle_versio_23.7.2014

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Trial protocol template

https://www.fimea.fi/valvonta/kliiniset_laaketutkimukset/ohjeita_akateemisille_tutkijoille