

Regulation relating to clinical trials on medicinal products for human use

Legal basis: Laid down by the Norwegian Ministry of Health and Care Services on 30 October 2009 pursuant to Sections 3 and 28 of Act no. 132 of 4 December 1992 relating to Medicines etc. (Medicines Act), cf. Delegation Decision, no. 521 of 8 June 1995.

EEA references: Cf. the EEA Agreement Annex II, Chap XIII no. 150 (Directive 2001/20/EC) and no. 15zf (Directive 2005/28/EC).

Amendments: Amended by Regulation no. 1839 of 18 December 2009.

Chapter 1 - General provisions

Section 1-1. Scope

The regulation relates to clinical trials, including multi-centre trials, on medicinal products for human use. The regulation concerns trials on both patients and healthy persons.

The regulation does not cover investigational treatment of individual patients or non-interventional trials.

Clinical trials that entail modification of the trial subject's germ line genetic identity may not be conducted.

Section 1-2. Good clinical practice and the Declaration of Helsinki

All clinical trials, including bioequivalence and bioavailability studies, shall be planned, reported and conducted in accordance with the rules of the regulation and the standard for good clinical practice.

Clinical trials shall take place in accordance with the Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects.

Section 1-3. Fundamental requirements

Considerations relating to the rights, safety and well-being of the persons taking part in the trials prevail over scientific and social interests.

Persons who contribute to the conducting of a clinical trial shall be qualified in terms of training, education and experience to perform their tasks.

Clinical trials shall be scientifically based and governed by ethical principles.

Necessary procedures for ensuring the quality of the trial shall be followed.

The available clinical and preclinical data concerning an investigational medicinal product shall be sufficiently comprehensive to justify a clinical trial.

All information about a clinical trial shall be registered, processed and stored in such a way that it is available for correct reporting, interpretation and verification of the information as well as effective protection of personal data.

Section 1-4. Conditions for initiating clinical trials

Clinical trials shall only be initiated if

- a) the rules in Chapter 2 concerning protection of trial subjects are complied with
- b) there is prior approval from the Ethics Committee pursuant to the rules in Chapter 3
- c) the Norwegian Medicines Agency has no objections pursuant to the rules in Chapter 4.

Section 1-5. Definitions

The following definitions apply in the regulation

- a) *serious adverse event or serious adverse reaction*: harmful and unintended response or effect that in any dose results in death, is life-threatening, necessitates hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect;
- b) *adverse reaction*: an adverse event in a subject who has received a medicinal product in a clinical trial where a causal relationship between the occurrence and the product that is being tested is regarded as probable or possible;
- c) *clinical research organisation (CRO)*: a person or an organisation (commercial, academic or other) engaged by sponsor to perform one or more of sponsor's trial-related duties and functions;
- d) *Ethics Committee*: the regional committee for medical and healthcare research ethics. The Ethics Committee shall ensure that those persons who take part in a clinical trial receive the protection due to them by assessing the protocol, the qualifications of the investigators, the appropriateness of the trial site, and the approach and material used to inform the trial subjects before a statement of informed consent is given;
- e) *trial subject*: a person who takes part in a clinical trial and who either receives an investigational medicinal product or who takes part in a control group;
- f) *good clinical practice (GCP)*: a standard for the design, management, conduct, monitoring, auditing, recording and reporting of clinical trials, which also ensures that data and the reported results are credible and accurate, and that the rights, integrity and confidentiality of the trial subjects are protected;
- g) *principal investigator*: investigator who leads the trial at the individual trial site;
- h) *non-interventional trial*: a study where one or more medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. A therapeutic strategy for each individual patient is not decided in advance by a trial protocol, but falls within current practice, and the prescription of the medicinal products is clearly separated from the decision to include the patient in the study. Additional diagnostic or monitoring procedures for patients shall not be necessary and epidemiological methods shall be used to analyse the collected data;
- i) *informed consent*: a written, dated and signed statement about participation in a clinical trial which is given by a person who is capable of giving consent. The statement must be made voluntarily after the trial subject has received full information about the nature,

significance, scope and risk associated with the trial. If the person is not capable of giving consent, consent is given by the person who can give consent on behalf of the person concerned;

- j) *inspection*: the act by a competent authority of conducting a review of documents, facilities, records (notes), quality assurance arrangements and any aid regarded by the authorities as relating to the clinical trial, and that may be located at the site of the trial, at sponsor's and/or the clinical research organisation's facilities, or at other establishments that the authorities see fit to inspect.
- k) *investigator's brochure*: a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects
- l) *clinical trial*: any systematic study of medicinal products for human use for the purpose of acquiring or verifying knowledge of the effects or influence of the products on physiological function, interactions, adverse reactions, absorption, distribution, metabolism and secretion, or to study their therapeutic value;
- m) *medicinal product*: a substance, drug or formulation etc. as defined in Section 2 of Act no. 132 of 4 December 1992 relating to medicines etc;
- n) *monitor*: the person who shall ensure that the trial is conducted, recorded and reported in accordance with the protocol, standard operational procedures, applicable guidelines for good clinical practice, Norwegian legislation generally, and to ensure that the trial has the agreed progression;
- o) *multi-centre trials*: clinical trial conducted at several centres at the same time and according to the same protocol;
- p) *national coordinating investigator*: investigator in Norway who coordinates the Norwegian sites taking part in a multi-centre trial;
- q) *Protocol*: a document that describes the objective(s), design, methodology, statistical considerations and organisation of the trial. The protocol shall describe which trial subjects can or cannot take part in the clinical trial and the rules for pharmacovigilance and publication;
- r) *protocol amendment*: a written description of one or more changes in, or a formal clarification of the protocol;
- s) *sponsor*: an individual, company, institution or organisation that takes responsibility for the initiation, management and/or financing of a clinical trial, and that signs the request for authorisation;
- t) *investigator*: doctor or dentist who conducts a clinical trial;
- u) *investigational medicinal product*: a pharmaceutical form of an active substance or placebo which is being tested or used as a reference in a clinical trial. Medicinal products with marketing authorisation are also regarded as investigational medicinal products if they are used, formulated or packaged in a manner other than the approved form, or used for a non-approved indication, or to procure further information about the authorised form;
- v) *unexpected adverse reaction*: an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

w) *adverse event*: an untoward medical occurrence in a trial subject to whom a medicinal product has been administered, and which does not necessarily have a causal relationship with this treatment.

Section 1-6. Sponsor or investigator's responsibility pursuant to other legislation

The rules of the regulation do not change the responsibility of sponsor and investigator pursuant to other legislation.

Sponsor may delegate his trial-related duties and functions to an individual, firm, institution or organisation.

Sponsor is responsible for ensuring that the conduct of the clinical trial and the processing of the data that are generated are in compliance with the provisions of this regulation.

Section 1-7. Sponsor's location

Sponsor shall be located in the EEA. However, this does not apply if sponsor has a legal representative who is located in the EEA. The legal representative shall document his authorisation to the Norwegian Medicines Agency.

Section 1-8. Investigator and sponsor

Investigator and sponsor may be one and the same person.

Section 1-9. Financing of the investigational medicinal product

Sponsor shall ensure that the investigational medicinal product and any appurtenant equipment is made available free of charge.

Section 1-10. Permission to process personal data

Sponsor is responsible for ensuring that the necessary advance approval to process health data is obtained from the Ethics Committee pursuant to Section 33, cf. Chapter 3, of Act no. 44 of 20 June 2008 on medical and healthcare research.

Identifiable personal data may only be transmitted between Norway and a country outside the EEA area if the conditions in Section 37 of Act no. 44 of 20 June 2008 on medical and healthcare research are fulfilled.

Section 1-11. Investigator's brochure

The information in the investigator's brochure shall be provided in a concise, simple, objective, balanced non-promotional form, so that a potential investigator can make a neutral assessment of the benefit/risk ratio of the clinical trial.

If there is marketing authorisation for the investigational medicinal product, an approved summary of product characteristics (SPC) may be used instead of an investigator's brochure.

Sponsor shall validate and update investigator's brochure at least once a year.

Section 1-12. *Transfer of right of ownership of documentation*

The right of ownership of the documentation and results of a clinical trial can be transferred. Such transfer shall be documented in writing and a copy sent to the Norwegian Medicines Agency. The new licensee shall keep and archive the material in accordance with the rule in Section 8-2.

Section 1-13. *Further duty to apply for authorisation for special studies*

- a) Clinical trials that involve gene therapy, the use of genetically modified organisms as a medicinal product, predictive or presymptomatic genetic testing or testing to determine whether or not a person is a carrier of hereditary disease that will only be expressed in later generations (carrier testing) shall also be approved pursuant to Act no. 100 of 5 December 2003 relating to the application of biotechnology in human medicine, etc.

Clinical trials of medicinal products that consist of or contain genetically modified organisms may involve the deliberate release of the organism, and shall be approved in advance pursuant to Act no. 38 of 2 April 1993 relating to the production and use of genetically modified organisms (the Gene Technology Act).

Clinical trials that involve the collection, storage, processing, destruction, introduction into Norway and transport out of Norway of human biological material, shall have approval pursuant to Act no. 44 of 20 June 2008 on medical and healthcare research.

Section 1-14. *Manufacture and import of medicinal products for clinical trials*

The manufacture and import of medicinal products for clinical trials requires the approval of the Norwegian Medicines Agency.

Regulation no. 1441 of 2 November 2004 on the manufacture and import of medicinal products applies to the manufacture and import of medicinal products for clinical trials.

Chapter 2 – Protection of trial subjects

Section 2-1. *Assessment of the benefit/risk ratio*

Clinical trials may only be initiated if:

- a) the known benefit/risk ratio is weighed against the assumed benefits to the individual trial subject and to other present and future patients
- b) The Ethics Committee and the Norwegian Medicines Agency find that the expected benefit of the medicinal product can justify the risk of conducting the trial (cf. Chapters 3 and 4).

During the trial, sponsor shall constantly consider whether the requirements in the first paragraph are fulfilled.

Section 2-2. Requirement of informed consent

Before the trial starts, the investigator, or the party leading the information process on behalf of the investigator, shall inform the trial subject about the purpose of the trial, the benefit and risk associated with the trial subject's participation, the conditions for conducting the trial and that the trial subject can withdraw from the trial at any time.

If the trial subject cannot give informed consent, the information as mentioned in the first paragraph shall be given to the person who pursuant to Section 2-8 and 2-9 can consent on behalf of the trial subject.

Before the trial starts, the trial subject shall give his or her consent to participation in the trial. The consent shall be given after the information in the first paragraph has been received. If written consent cannot be given, the consent can be given orally. Oral consent shall be attested to by an independent witness.

If the trial subject cannot give informed consent, the consent as mentioned in the previous paragraph shall be given by the person who pursuant to Section 2-8 and 2-9 can consent on behalf of the trial subject.

Section 2-3. Withdrawal of consent

Consent to take part in a clinical trial pursuant to Section 2-2 can be withdrawn at any time. Patient data and biological material that have been collected up to the time of withdrawal will be included in the trial data, but no further data shall be collected.

Section 2-4. Insurance of trial subjects

Sponsor shall insure the trial subjects who take part in the trial in a satisfactory manner against any harm that may arise during the trial (cf. Act no. 104 of 23 December 1988 relating to product liability).

Section 2-5. Protection of physical and mental integrity and personal data

A clinical trial can only be initiated if the trial subject's right to physical and mental integrity and to a private life are respected and information concerning the trial subject is protected in accordance with the provisions of Act no. 31 of 14 April 2000 relating to processing of personal data, cf. Section 2, third paragraph of Act no. 44 of 20 June 2008 relating to medical and healthcare research.

Section 2-6. Requirements relating to the qualifications of the person providing treatment

The person responsible for treatment and decisions regarding the treatment of trial subjects shall be a qualified doctor or dentist.

Section 2-7. Requirement regarding a point of contact

The trial subject shall be informed about a point of contact where he or she can obtain further information.

Section 2-8. Clinical trials on persons aged under 18

In addition to the requirements in Section 2-1 to 2-7, trials on persons aged under 18 are contingent on the informed consent of parents or some other person with parental responsibility. Trials on persons aged between 16 and 18 also presuppose the consent of the minor. In addition the following conditions must be fulfilled:

- a) the person consenting has received written and oral information about the study in accordance with Section 2-2
- b) the consent is presumed to express the will of the minor
- c) the minor has received information about the trial, risk and benefit, adapted according to the capacity for understanding of the minor concerned
- d) the trial can be expected to be of direct benefit to the patient group
- e) the trial is crucial for verifying data obtained through clinical trial or other investigative methods on persons able to give informed consent
- f) the trial either directly concerns a clinical condition from which the minor suffers, or the trial is of such a nature that it can only be conducted on minors
- g) relevant guidelines from the European Medicines Agency (EMA) are complied with
- h) the trial is designed to minimise pain, discomfort, fear and any other foreseeable risk with respect to the disease
- i) the protocol has been endorsed by the Ethics Committee, which has expertise in paediatrics or has taken advice on clinical, ethical and psychosocial issues in the field of paediatrics
- j) the interests of the subject always prevail over those of science and society.

The view of subjects aged under 18 shall count as an increasingly important deciding factor, in pace with their age and maturity.

All use of inducements for minor trial subjects is prohibited, except compensation in connection with participation in the trial.

Section 2-9. Trials on persons unable to or with limited capacity to give informed consent

In addition to the requirements in Section 2-1 to 2-7, trials conducted on incompetent persons require that the conditions in Section 4-7 of Act no. 63 of 2 July 1999 concerning patient rights are complied with. Trials on adults who are unable to give consent because of inadequate mental powers, an illness or other reasons, are contingent on the consent of the next of kin pursuant to Section 1-3 litra b of Act no. 63 of 2 July 1999 concerning patient rights. In addition the following conditions must be fulfilled:

- a) the person consenting has received written and oral information about the study in accordance with Section 2-2
- b) the consent is assumed to express the trial subject's will, and the subject does not oppose himself or herself to the trial
- c) the trial subject has received information about the trial, risk and benefits, adapted according to the capacity for understanding of the person concerned
- d) there is reason to believe that the results of the trial will directly benefit the health of the subject
- e) the trial is essential for validating data obtained through clinical trials or other research methods on persons able to give informed consent, and relates directly to a life-threatening or debilitating clinical condition from which the subject suffers, or the information cannot be obtained on the basis of consent given pursuant to Section 2-2
- f) the trial only entails minimal risk and distress for the subject
- g) the interests of the subject always prevail over those of science and society
- h) the trial is designed to minimise pain, discomfort, fear and any other foreseeable risk with respect to the disease
- i) the protocol has been endorsed by the Ethics Committee, which has expertise in the disease and patient group in question, or has taken advice on clinical, ethical and psychosocial questions relating to the disease and patient population in question.

Chapter 3 – The Ethics Committee

Section 3-1. *Application to the Ethics Committee to approve a clinical trial*

Applications concerning clinical trials shall be sent to the Ethics Committee. The Ethics Committee must give prior approval before a clinical trial is initiated.

Section 3-2. *The Ethics Committee's evaluation of the application*

In processing the application, the Ethics Committee shall consider the following in particular:

- a) the relevance and design of the clinical trial
- b) whether the presumed risk and inconveniences have been weighed against the benefits to the individual trial subject and to other present and future patients, and whether the conclusion is justified
- c) protocol
- d) the appropriateness of investigator and the other personnel
- e) investigator's brochure
- f) the suitability of the trial site
- g) the relevance and completeness of the informed consent form and the information process in connection with the obtaining of informed consent
- h) grounds for research on persons who are not capable of giving informed consent

- i) provisions concerning indemnity or compensation in the event of the injury or death of a subject as a result of a clinical trial
- j) insurance or compensation to cover the liability of investigator and sponsor
- k) the amounts of, and the detailed rules for payment of any fees or compensation to investigators and trial subjects
- l) relevant clauses in any intended agreement between sponsor and trial site, and
- m) arrangements for the recruitment of subjects.

Section 3-3. *Time periods for considering an application*

The Ethics Committee shall submit its statement to the applicant and to the Medicines Agency 60 days at the latest after a valid application has been received.

The Ethics Committee can ask the applicant to supplement the application once. The deadline is suspended in such cases from the date on which the Ethics Committee sends notification to the applicant and until the information in question is received.

If the application concerns a clinical trial of a medicinal product for gene therapy, somatic cell therapy or genetically modified organisms, the deadline as mentioned in the first paragraph may be extended once for 30 days. If the Ethics Committee is required by current rules and regulations to consult a group of experts, the time limit for such a product can be extended by a further 90 days.

If the application concerns a clinical trial which involves xenogenic cell therapy, there is no maximum processing time for when a statement must be issued.

Section 3-4. *Single declaration in multi-centre trials*

In multi-centre trials that are covered geographically by more than one committee, only one statement shall nevertheless be made, by one Ethics Committee.

In multi-centre trials that cover clinical trials in more than one EEA country, a statement shall be issued by one Ethics Committee in each country.

Section 3-5. *Agenda and storage of documents*

Each individual Ethics Committee adopts an agenda that ensures that the responsibilities in Section 3-1 to 3-5 are taken care of.

Unless other rules require longer storage, the Ethics Committee shall store documents of major significance for the individual clinical trial for a minimum of three years after the trial is finished.

Chapter 4 – The Norwegian Medicines Agency

Section 4-1. *Request to the Norwegian Medicines Agency for authorisation to conduct a clinical trial*

Before a clinical trial is initiated in Norway, a request for authorisation must be sent to the Medicines Agency.

Section 4-2. *Time periods for considering a valid request for authorisation*

A request for authorisation to initiate a clinical trial shall be processed 60 days at the latest after the submission of a valid request for authorisation.

If the request for authorisation concerns a clinical trial that involves gene therapy, somatic cell therapy or genetically modified organisms, the time period as mentioned in the first paragraph may be extended once for 30 days. If the Norwegian Medicines Agency is required by current rules and regulations to consult a group of experts, the time limit for such a product can be extended by a further 90 days.

If the request concerns a clinical trial which involves xenogenic cell therapy, there is no maximum processing time for when processing of the request for authorisation must be completed.

Section 4-3. *The Norwegian Medicines Agency's decision*

If the Norwegian Medicines Agency has no objection to the initiation of the clinical trial, the applicant will be informed of this.

If the Norwegian Medicines Agency has objections to the request for authorisation, the applicant has the right to supplement the request once. If the request for authorisation is not supplemented, or if, despite the amendment, the Norwegian Medicines Agency maintains its objections, the request is regarded as denied and the trial may not be initiated. Grounds shall be given for denying a request for authorisation of a clinical trial.

If the Norwegian Medicines Agency has not delivered its assessment within the time limit as specified in Section 4-2, the trial may commence, provided that the Ethics Committee has approved the trial.

A clinical trial may not commence without a written response from the Norwegian Medicines Agency if the trial concerns:

- a) a medicinal product without marketing authorisation as referred to in Part A of the Annex to Council Regulation (EEA) No. 2309/93
- b) a medicinal product in which the active substance is a biological product of animal or human origin
- c) a medicinal product that contains biological components of animal or human origin, or the manufacturing of which requires such components

- d) a medicinal product for gene therapy, somatic cell therapy, including xenogenic cell therapy, or
- e) a medicinal product that contains genetically modified organisms.

Section 4-4. *Labelling of the investigational medicinal product*

The investigational medicinal product shall be labelled.

Section 4-5. *Dispensing of medicinal products*

Unless the Norwegian Medicines Agency decides otherwise in connection with the request for authorisation of a clinical trial, the investigational medicinal product shall be dispensed from a pharmacy or the individual trial site.

Chapter 5 – Rules during the trial

Section 5-1. *Protocol amendments*

Sponsor may amend the protocol after the clinical trial has been initiated.

If sponsor wishes to make substantial amendments to the protocol

- a) that may have an impact on the safety of the trial subjects, or
- b) that may change the interpretation of the scientific documentation, or
- c) that are significant,

sponsor shall notify the Norwegian Medicines Agency and the Ethics Committee. An account and justification of the changes shall be provided with the notification.

Within 35 days of receiving a valid application, the Ethics Committee shall approve or deny the request according to the criteria in Section 3-3. If the committee rejects the application, sponsor may not make amendments to the protocol.

If the Ethics Committee has approved the application, and the Norwegian Medicines Agency does not oppose amendments within 35 days of receiving a valid application, sponsor may make amendments to the protocol.

If the Ethics Committee has approved the application, but the Norwegian Medicines Agency has opposed the amendments, sponsor can amend the protocol if the objections of the Medicines Agency are taken into account. Otherwise sponsor must withdraw the proposal to amend the protocol.

Section 5-2. *Implementation of safety measures*

Should new circumstances or information concerning the clinical trial or medicinal product emerge which might influence the safety of the trial subject, sponsor and investigator shall

immediately take the safety measures necessary to prevent harm occurring to the trial subjects.

Sponsor shall immediately inform the Ethics Committee and the Norwegian Medicines Agency of the changes and the action that has been taken.

Section 5-3. *Suspension of clinical trials*

The Norwegian Medicines Agency can suspend an initiated clinical trial if

- a) the conditions for initiation are no longer regarded as fulfilled
- b) new information creates doubt about the safety of the trial
- c) new information creates doubt about the scientific value of the trial

Before the Norwegian Medicines Agency makes a decision pursuant to the first paragraph, sponsor or investigator shall be given a time limit of one week to make a statement on the matter, if such postponement of the decision does not entail a risk.

Chapter 6 – Supervision and inspection

Section 6-1. *Supervisory authority*

The Norwegian Medicines Agency exercises supervision to verify compliance with the provisions of this regulation.

The Norwegian Board of Health supervises the health services provided in connection with trials (cf. Act no. 15 of 30 March 1984 relating to the public supervision of health services). The Norwegian Medicines Agency shall at the request of the Board of Health provide information as to which doctors/dentists are engaged in trials, and about conducted and planned inspections.

Section 6-2. *Inspection*

The Norwegian Medicines Agency maintains supervision to ensure that the requirement relating to good clinical practice is fulfilled in connection with clinical trials.

As part of the supervision, the Norwegian Medicines Agency may conduct inspections of the premises of all those who are or have been involved in the conduct of the trial.

Inspection may be carried out

- a) before, during or after a clinical trial
- b) as part of the assessment of a request for marketing authorisation pursuant to Regulation no. 1839 of 18 December 2009 relating to medicinal products
- c) as follow-up of an issued marketing authorisation.

Inspections may be conducted without prejudice to statutory confidentiality (cf. Section 28 second paragraph of Act no. 132 of 4 December 1992 relating to Medicines etc.)

0 Added through Regulation no. 1839 of 18 December 2009 (in force 12 January 2010).

Section 6-3. *Inspection report*

On the basis of the supervision, the Norwegian Medicines Agency prepares an inspection report which is made available to sponsor. This shall be made available on request to the Ethics Committee, the authorities of other EEA countries and the European Medicines Agency (EMA).

Section 6-4. *GCP inspector*

Inspections according to this regulation shall be carried out by one or more GCP (Good Clinical Practice) inspectors. An inspector must

- a) have a university-level education or equivalent experience in medicine, pharmacy, pharmacology, toxicology or other relevant areas
- b) have a knowledge of the principles and procedures associated with the development of medicinal products and of the clinical trials of medicinal products
- c) have a knowledge of national and international rules and regulations concerning the clinical testing of medicinal products and the rules for the issue of marketing authorisations
- d) maintain and develop his or her academic qualifications
- e) be aware of the vow of secrecy concerning confidential information the person concerned might learn through his or her work.
- f) have a knowledge of procedures and systems for registering clinical data
- g) have a knowledge of health service structure and legislation in the EEA and in relevant third countries
- h) be equipped with identification which verifies the status of the person concerned as inspector

If the individual inspector does not meet all the requirements in the first paragraph of the regulation, it is sufficient that the inspectors engaged in a particular inspection meet the requirements as a group.

Each inspector shall receive a document with instructions and detailed information about tasks, areas of responsibility and educational requirements. The document shall be updated regularly.

An inspector shall sign a declaration of impartiality. This declaration shall be assessed when deciding which inspectors should make a particular inspection.

Chapter 7 – Duty to report adverse events and adverse reactions

Section 7-1. Investigator's duty to report adverse events

Investigator shall immediately report to sponsor all serious adverse events that occur in connection with the trial. However, this does not apply if it states in the protocol or in the investigator's brochure that the serious adverse event is not subject to immediate reporting.

The immediate reports shall be followed up with detailed written reports.

The trial subjects shall be identified in the immediate and follow-up reports by means of a personal code number.

In accordance with the rules of the protocol, investigator shall report to sponsor any adverse events or abnormal laboratory readings which are regarded in the protocol as critical to the assessment of the safety of the medicinal product.

In the event of reported deaths, investigator has a duty to send sponsor and the Ethics Committee the information they request.

Section 7-2. Sponsor's duty to store information about adverse events

Sponsor shall keep detailed records of all adverse events that are reported to him by investigator. The records shall be submitted to the Norwegian Medicines Agency on request.

Section 7-3. Sponsor's duty to report unexpected and serious adverse reactions

Sponsor shall immediately, and at the latest seven days after learning of an unexpected and serious adverse reaction that is fatal or life-threatening, send a report to the authorities in all the EEA countries concerned. Thereafter, relevant information about the further course of events shall be given within eight days.

Sponsor shall immediately, and at the latest 15 days after learning of an unexpected and serious adverse reaction that is not fatal or life-threatening, send a report to the authorities in all the EEA countries concerned.

Sponsor shall inform all investigators of the investigational medicinal product in question of suspected unexpected serious adverse reactions (SUSARs).

Section 7-4. Annual report

Sponsor shall annually send the authorities of all countries in which the trial is proceeding,

- a) a list of all assumed serious adverse events that have occurred in the period in question, and
- b) a report on the safety of the trial subjects.

The duty pursuant to the first paragraph applies as long as the clinical trial is in progress.

Chapter 8 – Documentation (Master File) and final report

Section 8-1. *Documentation of the clinical trial*

Sponsor shall prepare and update documentation of the clinical trial.

The documentation shall consist of documents of major significance for the conduct of the clinical trial and which provide a basis for evaluating the quality of the results of the trial.

The documentation shall contain information as to whether investigator and sponsor have adhered to the rules for good clinical practice and the requirements in Annex I to Directive 2001/83/EC.

The documentation shall form a basis for the supervision carried out by sponsor's quality assurance personnel and by the authorities.

The contents of the documents shall be in conformity with the contents of the individual phase of the clinical trial.

Section 8-2. *Sponsor's and investigator's storage of documentation*

Sponsor and investigator shall store documents of major significance to the clinical trial for at least fifteen years after the trial is concluded.

The documents as mentioned in the first paragraph shall be stored for longer than fifteen years if this follows from other rules and regulations or from an agreement between sponsor and investigator.

The archiving of the documents shall take place in such a manner that they can immediately be made available to the authorities on request.

The trial subjects' records shall be stored for the maximum period permitted under Norwegian law.

Section 8-3. *Person responsible and access to archives*

Sponsor shall appoint persons in his own organisation to be responsible for archiving the documents.

Only specified persons with responsibility for the archives shall have access to it.

Section 8-4. *Requirements relating to media for storage of documents*

The media used for archiving documents shall ensure

- a) that the documents remain complete and legible throughout the period they are stored

- b) that it is possible to make the documents available to the authorities on request
- c) that any change in the documents can be traced.

Section 8-5. *Final notification and final report*

Sponsor undertakes to notify the Norwegian Medicines Agency and the Ethics Committee that the clinical trial has ended a maximum of 90 days after the end of the trial.

If the clinical trial has to be halted, sponsor shall report this to the Norwegian Medicines Agency and the Ethics Committee within 15 days. Grounds shall be given for why the trial was stopped.

Sponsor shall submit a final report to the Medicines Agency one year at the latest after the end of the trial. This time limit may be extended by the Medicines Agency on application.

Chapter 9 – Entry into force etc.

Section 9-1. *Entry into force etc.*

This regulation shall enter into force immediately.

At the same time, Regulation no. 1202 of 24 September 2003 relating to clinical trials on medicinal products for human use is repealed.
