VELFERÐARRÁÐUNEYTIÐ

Ministry of Welfare

REGULATION
on clinical trials of medicinal products in humans, No. 443/2004,
as amended by Regulations No. 907/2004 and No. 1099/2010.

CHAPTER I
General provisions.
Article 1
Scope.

This Regulation shall apply to clinical trials in humans.

It shall not apply to medical experiments on individual patients or non-interventional trials.

This Regulation lays down specific provisions concerning the implementation of clinical trials of medicinal products, including multi-centre trials in humans, in particular concerning the implementation of Good Clinical Practice (GCP) in studies on medicinal products.

Concerning processing of personal data in connection with clinical trials, Act No. 77/2000, on the Protection of Privacy as regards the Processing of Personal Data, shall apply insofar as specific provisions of this Regulation do not take precedence.

The arrangements for and implementation and reporting of all clinical trials of medicinal products, including studies of bioavailability and bioequivalence, must comply with the principles of Good Clinical Practice.

[The production and import of medicinal products for clinical trials (investigational medicinal products) shall comply with the provisions of the Regulation on the manufacturing of medicinal products and the Regulation on import and wholesale distribution of medicinal products, as subsequently amended.][1)]

[1)] *Regulation No. 907/2004, Article 1.*

Article 2
Definitions.

For the purposes of this Regulation the following terms shall have these meanings:

a. *Medicinal products:* Medicinal products are substances or compounds covered by the definition of the concept of medicinal products in Article 5 of the Medicinal Products Act, No. 93/1994, as subsequently amended.

[b. *A clinical pharmaceutical study:* A systematic testing of a medicine with the purpose of finding or confirming its effects and/or finding the side effects of the medicine and/or absorption, circulation, metabolism and the excretion of the drug with the purpose of checking its security and functionality.][1)]

c. *Good Clinical Practice (GCP):* A standard for designing, directing, conducting, supervision, recording of data and reporting of results of clinical trials, which ensures that the data and interpretation of results of the trials are credible and accurate and that the rights, safety and welfare of subjects are respected.

d. *Multi-centre clinical trial:* A clinical trial taking place concurrently in more than one location according to the same clinical trial protocol.

e. *Investigator:* a physician or dentist authorised to carry out a clinical trial. If only one investigator is involved in a clinical trial of a medicinal product he/she is also regarded as the principal investigator, *cf.* item f.
f. *Principal investigator:* The investigator responsible for the implementation of a clinical trial of a medicinal product at each research centre. In certain instances the principal investigation may also be a sponsor, *cf.* item i.
g. *Supervisor of the trial:* The principal investigator who co-ordinates implementation of clinical trials on medicinal products in the Icelandic centres involved in a multi-centre trial.
h. *Subject:* an individual participating in a clinical trial of a medicinal product, either as the recipient of the trial product or as part of the control group.
i. *Sponsor:* An individual, company, institution, organisation or enterprise whose role is to initiate, manage and/or finance a clinical trial of a medicinal product. If no sponsor is connected to the study, the principal investigator shall perform this role.
j. *Monitor:* The person who monitors the normal progress of the trial, ensuring that it is carried out in all respects according to the clinical trial protocol, standardised procedures, current guidelines on good clinical practice, and Icelandic laws and regulations.
k. k *Clinical trial protocol:* A document stating the objectives, arrangement, methodology, statistical methods and organisation of a clinical trial of a medicinal product.
l. *Investigator's brochure:* A summary of clinical and pre-clinical data on the trial medicinal product of significance for a clinical trial of the product in humans.
m. *Informed consent:* Written consent give voluntarily after the individual participating in a clinical trial of a medicinal product has been informed, for instance, of its nature, significance, consequences and potential risk. The individual in question must be capable of granting consent or a party who is legally competent to do so must provide this on the person's behalf. If the person is not capable of writing, oral consent given in the presence of witnesses may be provided in exceptional cases.
n. *Inspection:* Action on the part of a public authority consisting of an official review of documents, facilities, records, quality assurance, and all other aspects considered by the public authority to be connected with the clinical trial of a medicinal product and which may be located at a study centre, a sponsor's establishment and/or a laboratory working under contract, or other locations which the public authority deems necessary to inspect.
o. *Adverse event:* Any undesirable medical event experienced by a subject in a clinical trial and not necessarily causally connected with that treatment.
p. *Adverse reaction:* All undesirable, unintentional effects of the dosages of the trial medicinal product used.
q. *Serious adverse event or serious adverse reaction:* A damaging or unexpected reaction or effect where any dosage is fatal, life-threatening, disabling or incapacitating, results in a congenital defect or results in or prolongs hospitalisation.
r. *Unexpected adverse reaction:* An adverse reaction which, in terms of its nature, severity or consequences, is not as mentioned in the investigator's information brochure on the trial medicinal product or the summary of product characteristics (SPC);
s. *Non-interventional trial:* A study where the medicinal product or products are prescribed in a normal manner in accordance with the terms of its marketing authorisation. Treatment of the patient is not pre-determined by a clinical trial protocol, but rather follows current practice. The instructions concerning the medicinal product are clearly separated from the decision that the patient shall take part in the trial. No supplementary analyses or supervision shall be carried out in treating the patient and epidemiological methods used in analysing the data collected.
[*t.* *Investigational medicinal product (test medicinal product):* 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 (specially 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.][2)]

[u. *Investigator´s brochure:* A synopsis of clinical and non-clinical data on the investigational medicinal product or the investigational medicinal products, relevant to the study of the its or their functionality in human beings.][1)]

[1)] Regulation No. 1099/2010, Article 1. [2)] Regulation No. 907/2004, Article 2.

Article 3

Multi-centre trials.

Multi-centre trials in Iceland must have a trial supervisor responsible for co-ordinating the centres involved in the trial in question.

When more than one Icelandic centre is involved in an international multi-centre trial, there must be a trial supervisor for the Icelandic centres.

Article 4

Responsibility.

The principal investigator or, as the case may be, the investigator shall be responsible for the trial in question and for the reports and notifications which are to be submitted as provided for in Articles 29–33, as appropriate, *cf.* however Article 30. The principal investigator or, as the case may be, the investigator shall be responsible for the selection, treatment and supervision of subjects. The principal investigator or, as the case may be, the investigator, and the sponsor signing the application for a clinical trial shall be responsible for ensuring that the trial is carried out in accordance with currently applicable rules. The trial supervisor bears this responsibility in multi-centre trials, with the exception of notification of adverse events, for which the investigators and principal investigator shall be responsible.

When a clinical trial is carried out in co-operation with a sponsor, the sponsor is obliged to take part in preparing the reports and notifications which must be submitted.

[A sponsor is authorised to entrust an individual, enterprise, institution or organisation to carry out his/her activity, in whole or in part, that relate to studies. In such instances, he/she will continue to be responsible for ensuring the implementing arrangements of the study and that the final data, the product of the study, are in accordance with the provisions of this Regulation.

A sponsor is required to assess and upgrade the investigator´s brochure at least once a year.][1)]

[1)] Regulation No. 1099/2010, Article 2.

Article 5

Insurance.

Subjects participating in a clinical trial of a medicinal product must be sufficiently insured against conceivable damage to their health resulting from the trial.

The principal investigator or, as the case may be, the investigator shall be responsible for ensuring satisfactory insurance coverage.

Article 6

Ethical assessment.

All clinical trials of medicinal products must be subject to a scientific and ethical assessment before commencing. This assessment shall be entrusted to the National Bioethics Committee, *cf.* Article 2 of the Act on the Rights of Patients, No. 74/1997, and the Regulation on Scientific Research in the Health Sector, No. 552/1999, or the ethics committee of the institution concerned. [Clinical information and other available investigational medicinal product shall be sufficient to endorse scheduled clinical study.][1)]

A request for assessment by the National Bioethics Committee or, as the case may be, the ethics committee of the institution concerned, must be accompanied by the following documentation:

a. A completed application form.
b. The trial protocol, *cf.* Article 9.
c. Additional information on other aspects connected with the trial, *cf.* Article 10.
d. Information on the trial medicinal product and comparable medicinal products, *cf.* Article 11.
e. A copy of the application to the Icelandic Medicines Agency and a copy of the information to participants and informed consent, *cf.* Article 18.

f. A copy of the confirmation of insurance, *cf.* Article 5.

The application must be signed by the principal investigator. If the application is made at a hospital or other health care institution, a head physician or director of the ward or institution must also sign the application. If the trial is carried out in cooperation with a sponsor, the sponsor's representative must also sign the application.

In preparing its assessment, the National Bioethics Committee or, as the case may be, the ethics committee concerned, shall have regard in particular to the following:

a. The value and arrangement of the clinical trial of a medicinal product.
b. Whether the assessment of the intended benefits and risks involved is satisfactory and whether the conclusions are well-founded.
c. The trial protocol.
d. The qualifications of the investigator/principal investigator and his/her assistants.
e. The investigator's brochure. [The information shall be presented in an incisive, simple, impartial and calm way, without an advertising value, so that it is understandable and possible to assess in an unbiased way an advantage in relation to the rightfulness of a scheduled clinical study. If the investigational medicinal product has a marketing authorisation, it is authorised to apply a synopsis of the properties of the medicine instead of an investigator´s brochure.][1)]
f. The quality of the facilities.
g. Whether the written information provided is satisfactory and exhaustive, and whether the procedures to be followed in obtaining informed consent and the grounds given for study of individuals who are incapable of granting their informed consent are satisfactory, having regard to the special limitations prescribed in Article 19.
h. Whether provisions have been laid down for insurance or compensation if the clinical trial results in injury or death.
i. Insurance or compensation to cover the liability of the investigator and sponsor for compensation.
j. The amount and, as applicable, the means of compensation to the investigators and subjects and what conceivable right to compensation they have.
k. Arrangements for enrolment of subjects.

The ethics committee in question shall have a maximum of 60 days from the date it receives a valid application to deliver a reasoned opinion to the applicant and the Icelandic Medicines Agency.

The ethics committee in question may make one request for additional data after it receives a valid application; the application process shall be suspended until the committee receives the data requested.

The 60-day time limit provided for in paragraph 3 may not be extended except in instances concerning medicinal products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms. In such instances the time limit may be extended by a maximum of 30 days. If the ethics committee concerned considers it necessary to consult with other groups or committees, it may extend the time limit to as long as 180 days from the receipt of a valid application. In the case of xenogenic cell therapy there shall be no set time limit for an assessment of the application.

If the ethics committee in question intends to extend the afore-mentioned time limit, it must notify the applicant of its intention.

The provisions of paragraph 1of Article 15 shall apply to all modifications which may affect the security of subjects or the results of the trial, or which may be significant in other respects.

[The ethics committee in question shall keep essential instruments in relation to clinical studies for at least 3 years after the end a study.][1)]

[1)] Regulation No. 1099/2010, Article 3.

Article 7

Personal data protection.

Notice of all clinical trials of medicinal products must be sent to the Personal Data Protection Authority before they commence, as provided for in the Act on the Protection of Privacy as regards the Processing of Personal Data, No. 77/2000, as subsequently amended, and rules set by the Personal Data Protection Authority based on this Act concerning notification obligations and authorisation requirement for processing personal data.

CHAPTER II

Application for a clinical trial of a medicinal product.

Article 8

Application for a clinical trial of a medicinal product.

An application for a clinical trial of a medicinal product shall be sent to the Icelandic Medicines Agency and the ethics committee concerned, but does not necessarily need to reach both these parties at the same time.

An application to the Icelandic Medicines Agency for authorisation to conduct a clinical trial must be accompanied by the following documentation:

a. A completed application form.
b. The trial protocol, *cf.* Article 9.
c. Additional information on various aspects connected with the trial, *cf.* Article 10.
d. Information on the trial medicinal product and control medicinal products, *cf.* Article 11.
e. A copy of the application to the ethics committee concerned.
f. A copy of the Information to Participants and Informed Consent, *cf.* Article 18.
g. A copy of the confirmation of insurance, *cf.* Article 5.

The application must be signed by the principal investigator. If the clinical trial is carried out at a hospital or other health care institution, a head physician or director of the ward or institution must also sign the application. If the trial is carried out in cooperation with a sponsor, the sponsor's representative must also sign the application.

A multi-centre trial is regarded as a single trial. In the case of multi-centre trials, a single application shall be sent to the Icelandic Medicines Agency, signed by the trial supervisor. The application shall also be accompanied by supplementary application forms for each centre in Iceland, signed by the principal investigator in each case.

The trial protocol must specify whether the trial is part of an international trial.

The Icelandic Medicines Agency can provide further instructions on completing application forms and accompanying documentation.

The application form must indicate the number assigned to the applicants for registration of the trial in a European database for clinical trials. This number should henceforth be used in all communications with the Icelandic Medicines Agency.

Article 9

Trial protocol.

A trial protocol must be prepared for all clinical trials of medicinal products. The trial protocol shall include the following:

a. The background and objective of the trial.
b. Subjects.
c. Design of the trial.
d. Premises for selection of the sample (admission and exclusion criteria).
e. Treatment programme.
f. Control groups and their treatment.
g. Statistical methods and premises concerning the size of the sample.
h. Registration of the effects of the medicinal product and adverse events.
i. Tests to ensure the safety of subjects.
j. Interpretation of results.
k. Quality assurance of data and methods.
l. Ethical assessment.
m. Control of supplies of the medicinal product.

If the trial is carried out in co-operation with a sponsor, an account must be given as to how this trial fits into the overall development of the medicinal product concerned.

Article 10

Additional information on the trial.

In addition to the documentation already mentioned as part of a trial protocol, the Icelandic Medicines Agency must also be sent information on:

a. The qualifications of the principal investigator to carry out the trial (education, positions held and research).
b. A time schedule.
c. Research centres.
d. How previous treatment received by subjects will be suspended if necessary.
e. Follow-up of the subjects after the conclusion of the trial.
f. A training programme for staff involved in the trial.
g. Response to adverse events.
h. Plans as to how the results of the trial will be made public.
i. The handling and record-keeping of medicinal products used in the trial.
j. How the collecting and handling of all information on the subjects will be carried out.
k. Subjects' insurance.
l. Marking of medicinal product packages.

Article 11

Documentation on the medicinal products.

An application for a clinical trial must be accompanied by a summary of information on the chemical, pharmaceutical, pharmacological (in animals and humans), toxicological and clinical characteristics of the medicinal product.

The manufacture and import of trial medicinal products must comply with current rules on the manufacture and import of medicinal products.

The trial medicinal product must be manufactured in compliance with guidelines on Good Manufacturing Practice (GMP).

The Icelandic Medicines Agency may require additional documentation and more detailed reports to be submitted if necessary.

CHAPTER III

Approval and implementation of the trial.

Article 12

Approval of a medicinal product trial.

Assessment by the Icelandic Medicines Agency of an application for a clinical trial of a medicinal product is based on the information submitted with the application, as provided for in Chapter II, and shall include an assessment of the quality, safety and expected effect of the trial medicinal product, the scientific basis of the trial, research method, clinical usefulness and quality standards.

Approval by the ethics committee concerned should also be based in part on the aspects listed in Article 6.

The trial may not commence until the final approval of the ethics committee concerned is available, as provided for in Article 6 and provided the Icelandic Medicines Agency has raised no objections or notified the applicant of its reasons for refusing an application for a clinical trial within the time limits set out in Article 14.

The Icelandic Medicines Agency may refuse an application if:
a. The subjects' safety is at risk.
b. The trial protocol does not comply with current standards.
c. The Icelandic Medicines Agency deems it necessary for other reasons.

No gene therapy trials will be approved if the medicinal products alter the genetic characteristics of gametes.

Once it has received a valid application the Icelandic Medicines Agency will endeavour to send any comments or objections it has to the application within 30 days. Applicants then have about 10 days to submit additional documentation.

Article 13

Approval of the Icelandic Medicines Agency.

If an applicant for a clinical trial has not received any comments or objections from the Icelandic Medicines Agency within the time limit specified in Article 14, the trial may commence. The approval

of the Icelandic Medicines Agency must, however, always be given in writing in the case of clinical trials of medicinal products:

a. For gene therapy.
b. For somatic cell therapy.
c. Containing genetically modified organisms.
d. Developed by biotechnological methods, *cf.* Regulation 2309/93/EC, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products.
e. Where the active ingredient is a biological product of human or animal origin, or contains biological components of human or animal origin, or the manufacturing of which includes such components.

Article 14

Time limits for approval of a clinical trial.

The Icelandic Medicines Agency shall assess an application for a clinical trial within 60 days of receipt of a valid application. The Icelandic Medicines Agency shall assess the documentation upon receipt and inform the applicant as to whether the documentation is considered valid and adequate.

The Icelandic Medicines Agency may extend the time limit for assessing an application for a clinical trial in the case of medicinal products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms. If it is deemed necessary to consult with other groups or committees outside the Icelandic Medicines Agency in assessing a trial of such medicinal products, the time limit may be extended to as long as 180 days from the receipt of a valid application. In the case of xenogenic cell therapy there are no set time limits for an assessment of the application.

If the Icelandic Medicines Agency intends to extend the afore-mentioned time limits, it must notify the applicant of its intention.

Article 15

Modifications to the trial protocol.

All modifications which could affect the safety of subjects or the results of the trial, or which are significant in other respects must be notified to the Icelandic Medicines Agency and the ethics committee concerned, and reasons given for the modifications. The ethics committee in question must deliver its opinion on rejecting or approving the modifications within 35 days. The Icelandic Medicines Agency shall also have 35 days to submit its comments or objections; if none have been received within this time limit, the amendments shall take effect. If the opinion of the ethics committee in question is negative, no modifications may be made to the description of the method. If the opinion of the ethics committee in question is positive and the Icelandic Medicines Agency raises no objections within the above time limit, the sponsor may continue to conduct the trial in accordance with the modified description.

No approval is required in instances where previously unknown circumstances occur which could jeopardise the safety of subjects, in which case the sponsor and investigator should intervene and take the necessary immediate measures to prevent further risk to the subjects. The Icelandic Medicines Agency and the ethics committee in question shall be notified immediately of these circumstances and the response to them.

Article 16

Notification of rejection.

The Icelandic Medicines Agency must notify the principal investigator of a clinical trial of a medicinal product of the rejection of an application for a clinical trial or modifications to a trial within the time limit provided for, *cf.* Articles 14 and 15. In the case of a multi-centre trial, the supervisor of the trial must be notified of the rejection.

Article 17

Notification of the conclusion of a clinical trial.

The Icelandic Medicines Agency and the ethics committee in question must be notified of the conclusion of a clinical trial within 90 days of its conclusion. If a clinical trial has concluded earlier

than anticipated, notification must be given of its conclusion and an explanation for the reasons within 15 days of its conclusion.

CHAPTER IV
Informed consent and personal data protection.

Article 18
The requirement of informed consent.

Subjects' informed consent must be obtained before the clinical trial commences and after the investigator has provided the subjects with oral and written information on the clinical trial. Written confirmation of this must be available from the investigator or whomever the investigator has entrusted with providing information. The information provided must include, *inter alia*:

a. The name, position and address of the sponsor of the clinical trial.
b. The name, position and address of the person responsible for the clinical trial as well as information on the supervisor of the trial, as appropriate.
c. Who is to handle processing of trial data, which other parties are co-operating with the person responsible for the clinical trial and to whom information will be delivered.
d. What the purpose of the clinical trial is, a rough outline of how it will be conducted, what its potential benefit could be, when the clinical trial is to start and when it is expected to conclude.
e. What is the possible risk and conceivable discomfort to subjects in the clinical trial and what their participation involves.
f. Whether the selection is random.
g. Any other possible treatment in the clinical trial.
h. Whether it is necessary to cease previous treatment.
i. Whether a medicinal product which does not have a marketing authorisation in Iceland or a placebo will be part of the clinical trial.
j. Any possible follow-up.
k. Information as to where a subject can obtain further information.
l. Subjects' insurance.
m. Whether access to medical journals by domestic and/or foreign pharmaceutical authorities (supervisory bodies in countries where the medicinal product is to be placed on the market), monitors and representatives from the medicinal product manufacturer's quality control (auditor) may be necessary as part of the clinical trial.
n. That a subject in the clinical trial of a medicinal product may revoke his/her consent and the legal consequences of so doing, including what consequences a revocation would have for the subject of a clinical trial with regard to information concerning the subject which has already been gathered and processed in the clinical trial.

Apart from the above, Rules No. 170/2001, on how informed consent is to be obtained for the processing of personal data in scientific research in the health sector, shall apply.

Article 19
Clinical trials on children and individuals with reduced capacity to give their informed consent.

Before a clinical trial may commence on children under the age of legal majority, the consent of their parents or legal guardians according to the provisions of the Children's Act must be obtained. A child must be consulted whenever possible and always if the child is 12 years of age or older.

Provisions on legal majority shall apply to consent for a clinical trial in adults who, due to mental incapacity, illness or other reason specified by this law, are incapable of granting their own consent. The individual concerned shall be consulted wherever practicable.

Clinical trials on individuals with reduced capacity to give their informed consent may only be carried out if the conditions of this Article are satisfied and if:

a. The results of the trial could be of positive significance for the health of the individual concerned.
b. A comparable clinical trial cannot be carried out on individuals with full capacity to give their informed consent.

c. The individual concerned is not opposed to participating.

Parents or legal guardians according to the provisions of the Children's Act may give consent for a child's participation even if the clinical trial will not give results which could be of direct benefit for the child's health. This is subject to the condition that the clinical trial involves minimum risk and discomfort for the individual concerned, is intended to significantly augment knowledge of his/her condition or illness and this increased knowledge could be of significance for the individual concerned or others of the same age group with the same illness or condition.

Article 20

Written consent or witnessed oral consent.

Consent as provided for in Article 18 must always be in writing, dated and signed by a subject who is capable of giving his/her consent. Oral consent shall be sufficient in exceptional cases where a subject is incapable of writing his/her name, in which case it must be given in the presence of witnesses and this recorded on the declaration of consent.

Consent as provided for in Article 19 must always be in writing.

Article 21

Revoking of consent.

A subject may at any time revoke his/her consent to participate in a clinical trial. Once consent is revoked, the participation of the individual concerned shall conclude immediately and unconditionally. The subject may not in any way suffer retribution for a decision to cease participation.

Article 22

Access to subjects' medical journals.

The provisions of Act on Patients' Rights, No. 74/1997, shall apply concerning access to subjects' medical journals. It must always be explained to subjects in a clinical trial of a medicinal product that the Icelandic Medicines Agency, similar agencies in countries where marketing authorisation will be sought for the product and the monitor and personnel of the medicinal product manufacturer's quality control (auditor) may require information from subjects' medical journals for the purpose of ensuring the quality of the clinical trial and necessary for quality control.

Access to medical journals does not confer the right to remove confidential information from a health care institution. Such information may only be removed in a format which is not personally identifiable.

A foreign medicines control agency must notify the Icelandic Medicines Agency in advance of its proposed surveillance of a clinical trial to be carried out in Iceland.

When access is granted, this shall be noted in a patient's journal.

Article 23

Confidentiality concerning access to medical journals in connection with clinical trials.

A person granted access to a medical journal in connection with a clinical trial shall be bound by obligations of confidentiality concerning information to which the person has access. The Icelandic Medicines Agency may require written confirmation with an application as provided for in Article 8 acknowledging the obligation of confidentiality.

The obligation of confidentiality shall remain even after employment ceases.

Article 24

Information to participants and informed consent.

The investigator must make known to subjects any information which is of major significance and concerns the subjects of a clinical trial and which comes to light during the course of the clinical trial.

In the case of events connected with the carrying out of the clinical trial or development of the trial medicinal product, which are likely to affect the safety of subjects, the sponsor and the investigator shall take all the security measures necessary to protect subjects from immediate risk. The sponsor must immediately notify the authorities of such events and the measures taken and ensure that the ethics committee concerned is also notified thereof.

CHAPTER V

Requirements of an investigator and a clinical trial.

Article 25

Requirements concerning the qualifications of investigators.

An investigator must fulfil suitable qualifications as to education and professional expertise to be allowed to carry out a clinical trial, *cf.* item e of Article 2.

Article 26

International guidelines on clinical trials of medicinal products.

Clinical trials must be carried out in accordance with the provisions of the Helsinki Declaration of the International Medical Association.

Article 27

Protocol and basic information.

A clinical trial must be carried out in accordance with a protocol, *cf.* Article 9. During the course of the clinical trial, all equipment must be accessible through the investigators concerned.

All basic data of the clinical trial must be preserved in an accessible form at the research centre for at least 15 years after the final report on the study becomes available.

All procedures and information recorded by all parties participating in carrying out a clinical trial must be preserved in an accessible form for at least 15 years after the final report on the study becomes available.

Article 28

Marking and delivery of medicinal products.

All packaging of medicinal products used in a clinical trial must be marked clearly with the words "For clinical trial" (Icelandic „*Til klínískrar rannsóknar*"). This shall also apply to packages of medicinal products with marketing authorisations.

In addition, the following information shall be printed on the packaging:

a. The name of the medicinal product or its code.
b. The batch number or identification number.
c. The name, address and telephone number of the principal investigator or sponsor.
d. Directions for use of the medicinal product.
e. Dosage of the medicinal product.
f. Storage instructions.
g. Shelf life.
h. Technical instructions on use (if appropriate).

The information shall be in Icelandic.

Medicinal products for clinical trials shall be preserved in the custody and under the supervision of a pharmacy or hospital pharmacy, which shall be responsible for their preservation and handling.

The Icelandic Medicines Agency may, in exceptional instances, grant exceptions to the requirements of this Article after receiving a written request to this effect, [for instance due to the compounding of investigational medicinal products for usage or packing at hospitals, health care centres or clinics if the process is implemented by pharmacists or parties who have authorisation to do so, in accordance with good manufacturing practice for pharmaceutical production (GMP), and the investigational medicinal products are solely to be used at the institution in question.][1)]

[1)] *Regulation No. 1099/2010, Article 4.*

Article 29

Obligation to give notification of adverse events.

The investigator must notify the sponsor without delay of all serious adverse events which are not described in the trial protocol, investigator's brochure and/or summary of product characteristics (SPC). Detailed written information may be sent to the sponsor later. The sponsor shall assign a special number to each notification.

The investigator shall notify the sponsor of all adverse events and/or research results outside the safety limits of the trial.

If an adverse event is fatal, the investigator must notify the sponsor, the Icelandic Medicines Agency and the ethics committee concerned; any of these parties may demand more detailed data.

Article 30

Obligation to give notification of adverse reactions.

[A sponsor shall ensure that the Icelandic Medicines Agency and the ethics committee in question are notified of all suspected unexpected serious adverse reactions (SUSARs), resulting in death or life-threatening condition, caused by investigational medicinal product. Notifications shall be forwarded as soon as possible and no later than seven days since the occurrence was brought to a sponsor's knowledge. If no sponsor is related to the study, *cf.* item i of Article 2, this obligation rests on the shoulders of the principal researcher or researcher where applicable.

All other suspected unexpected serious adverse reactions shall be notified to the Icelandic Medicines Agency and the ethics committee in question within 15 days since the occurrence was brought to a sponsor's knowledge.

A sponsor shall forward information to all researchers on the above mentioned side effects, related to the investigational medicinal product.

A register shall be kept on all suspected unexpected reactions caused by a medicinal product and this register shall be a part of an annual report of a study.

A register shall be kept on all adverse events caused by a investigational medicinal product and the register shall be publicised in its entirety in the final report of the study.

An explanatory report shall be annexed to the notification pursuant to paragraphs 1 and 2 on whether the study was terminated or whether blinding was relieved (decoding) and risk assessment of the researcher of the repercussion of the continuation of a study.

The Icelandic Medicines Agency and the ethics committee in question may demand a special synopsis of adverse events.

The Icelandic Medicines Agency shall ensure that all suspected unexpected reactions caused by an investigational medicinal product, that are reported, shall immediately be registered into a European database that only the medicines agencies of Member States of European Agency for the Evaluation of Medicinal Products, The European Medicines Evaluation Agency and the European Commission shall have access to.][1)]

[1)] *Regulation No. 1099/2010, Article 5.*

Article 31

Obligation to give notification of modifications to a clinical trial

The principal investigator or, as the case may be, the investigator, the supervisor of the trial in the case of a multi-centre clinical trial, the sponsor or the sponsor's representative must send a written, reasoned notification to the Icelandic Medicines Agency and the ethics committee concerned when modifications are made to a clinical trial protocol:

a. If there is a possibility of changes to the patients' safety.
b. If a modification will result in a change in the interpretation of the results.
c. In the case of substantial modifications to a previously approved trial protocol.

The sponsor shall inform the Icelandic Medicines Agency:

a. If there will be any delay in the commencement of the clinical trial.
b. When a clinical trial is terminated prior to its expected conclusion.

The Icelandic Medicines Agency and the ethics committee concerned shall assess and must approve any substantial modifications to a previously approved trial protocol before they take effect, *cf.* Articles 12–17.

Article 32

Obligation to give notification of modifications to a trial medicinal product, etc.

The principal investigator or, as the case may be, the investigator, must notify to the Icelandic Medicines Agency all substantial modifications made to the registration documentation of medicinal products used in clinical trials, *inter alia*:

a. All modifications to chemical or pharmacological registration documentation.

b. All modifications to the pharmacology, toxicology and clinical references which may be of significance for the continuation of the clinical trial.

Notifications provided for in this Article must be made in accordance with Articles 12–17.

Article 33

[Annual report, final report and the preservation of data.][1)]

[1)] *Regulation No. 1099/2010, Article 7.*

If a clinical trial lasts for more than one year, an annual report must be sent to the Icelandic Medicines Agency and the ethics committee concerned, giving an account of the status of the clinical trial and a summary of all serious adverse events, *cf.* Articles 29 and 30.

No later than one year following the conclusion of the clinical trial, the final report must be sent to the Icelandic Medicines Agency and the ethics committee concerned. If the volume of information which must be processed is sizeable, a request may be submitted for an extension of the deadline for submitting the final report. The same shall apply if, due to other special conditions, it is impossible to complete the preparation of the final report within one year of the conclusion of the clinical trial.

The final report should be a concise summary of the principal results and an assessment of them, together with a summary of all adverse events.

The principal investigator, sponsor or the sponsor's agent must submit the final report, except in the case of a multi-centre clinical trial, in which case the supervisor of the clinical trial shall submit the final report. If a clinical trial is carried out in cooperation with a sponsor or the sponsor's agent, the latter shall also be responsible for submitting the annual report and final report to the Icelandic Medicines Agency and the ethics committee concerned.

[Sponsor and researcher shall keep the essential instruments that relate to clinical study for at least five years after the end of the study or longer if such a demand is made or the sponsor and the researcher have made an agreement about it.

Documents pursuant to paragraph 5 shall be saved to ensure their availability for inspection for competent authorities upon request.

Clinical records of participants in the studies shall be kept in accordance with applicable law on clinical records.][1)]

[1)] *Regulation No. 1099/2010, Article 6.*

CHAPTER VI

Supervision, suspension and penalties.

Article 34

[The surveillance of the Icelandic Medicines Agency.][1)]

[1)] *Regulation No. 1099/2010, Article 9.*

[The Icelandic Medicines Agency supervises that the provisions of this regulation are followed in the implementation of clinical studies, *cf.* Article 47 of the Medicinal Products Act, No. 93/1994, as subsequently amended.

The supervision of the Icelandic Medicines Agency with the implementation of good clinical practical procedures may be carried out in all the following cases:

- Before a clinical study, during it or following it.
- As part of a verification of applications for marketing authorisation.
- As follow up re licensing.

The items in Annex 1 apply to the education and obligations of inspectors.][1)]

[1)] *Regulation No. 1099/2010, Article 8.*

Article 35

[The registration of rules of procedure due to surveillance.][1)]

[1)] *Regulation No. 1099/2010, Article 11.*

[An appropriate procedure shall be determined for verification of fulfilling the provisions of good clinical practice. The procedure shall cover methods for operational instructions checks of the management of studies and conditions of organisation, implementation, surveillance of and registration of clinical studies, and measures due to follow up.

Appropriate rules of procedure shall be set in order to:

- Designate experts to follow inspectors when necessary.
- Request surveillance or assistance from a EU Member State, if necessary, and because of cooperation of surveillance in another Member State.
- Have a surveillance carried out in a third country.][1)]

[1)] *Regulation No. 1099/2010, Article 10.*

[Article 35 a

[Registration of surveillance.][1)]

[1)] *Regulation No. 1099/2010, Article 13.*

Records on domestic territory surveillance shall be kept and, if applicable, on international surveillance, including information on the situation with regard to whether provisions on good clinical practical procedures are fulfilled and their follow up.][1)]

[1)] *Regulation No. 1099/2010, Article 12.*

Article 36

Suspension of clinical trials.

The Icelandic Medicines Agency may temporarily suspend or prohibit the carrying out of a clinical trial out of concern for the patients' safety, if the carrying out of the clinical trial is in any respect flawed, or if there are other valid reasons for so doing. The Icelandic Medicines Agency must notify the sponsor of a clinical trial of its decision.

Article 6 of the Regulation on Scientific Research in the Health Sector shall apply concerning the revocation of approval by the National Bioethics Committee or, as the case may be, the ethics committee of the institution concerned.

Article 37

Penalties.

Violations against the provisions of this Regulation shall be liable to penalty as provided for in Chapter XV of the Medicinal Products Act, No. 93/1994, as subsequently amended. Any cases arising concerning infringements against this Regulation shall be dealt with in accordance with the Code of Criminal Proceedure.

CHAPTER VII

Legal authority. Entry into Force. Repeal.

Article 38

This Regulation is set by authority of Articles 9 and 47 of the Medicinal Products Act, No. 93/1994, as subsequently amended, and shall enter into force immediately.

As of the same date Regulation No. 284/1986, on clinical trials of medicinal products, shall be repealed [and the Directive of the European Commission No. 2005/28/EC from April 8 2005 on principles and detailed policy on good clinical practical procedures with regard to investigational medicinal product for human use and also on requirements regarding license for manufacturing or importing such drugs.][1)]

The provisions of this Regulation are based on Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use and Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

[1)] *Regulation No. 1099/2010, Article 14.*

[Annex 1

Education and obligations of inspectors.

Inspectors are bound by a duty of confidentiality on anything they may notice during their surveillance duties.

Inspectors shall have graduated from a university, or have an equivalent experience, in the area of medicine, pharmacy, pharmacodynamics, toxicology or in another comparable area.

Inspectors shall get an appropriate vocational training, their need for vocational training shall be regularly assessed and applicable measures taken in order to maintain and enhance their skill.

Inspectors shall have knowledge of those principles and processes that apply to the development of medicines and clinical studies. Inspectors shall also have knowledge of applicable legislation of the European Union on the implementation of clinical studies and the granting of marketing authorisations.

Inspectors shall have knowledge of operational instructions and systems in order to register clinical data and of the organisation and rules of the health system and it shall apply to third countries.

Records on education qualification, vocational training and experience of each inspector shall be maintained and upgraded.

Each inspector shall receive a document, specifying standard operational instructions and information on the duties, responsibility and requirements for continuing vocational training. Those operational instructions shall always include the latest information.

Inspectors shall have appropriate identity documents.

Each inspector shall sign a statement, including financial ties or other ties to those parties that are subject to checks. This statement shall be take into account when the inspectors are allocated regulatory tasks.][1)]

[1)] *Regulation No. 1099/2010, Article 15.*

Ministry of Health and Social Security, 12 May 2004.

Árni Magnússon.

Davíð Á. Gunnarsson

[*This translation is published for information only.*
The original Icelandic text is published in the Law Gazette.
In case of a possible discrepancy, the original Icelandic text applies.]