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Regulations on medical research involving human subjects (Medical Research (Human Subjects)) Act

26 February 1998

We Beatrix, by the grace of God Queen of the Netherlands, Princess of Orange-Nassau, etc., etc., etc.,

Greetings to all who shall see or hear these presents! Be it known:

Whereas We have considered that it is desirable, partly on the basis of Articles 10 and 11 of the Constitution, to regulate the conduct of medical research involving human subjects;

We, therefore, having heard the Council of State, and in consultation with the States General, have approved and decreed as We hereby approve and decree:

Division 1. General provisions

Section 1

1. For the purposes of this Act and provisions made pursuant to it, the following definitions shall apply:

- a. Our Minister: Our Minister of Health, Welfare and Sports;
- b. research: clinical trials in which persons are subjected to treatment or are required to behave in a certain manner;
- c. subject: a person as referred to under b;
- d. research protocol: the detailed description of proposed trials including their objectives, design, methodology, statistical considerations and organisation;
- e. facilitative institution: institution or company where clinical trials take place;
- f. the sponsor: the party who commissions the organisation or conduct of clinical trials; an individual, company, institution or organisation responsible for the initiation, management and/or financing of the clinical trial;
- g. the investigator: the party responsible for the actual conduct of the clinical trial; a doctor or a person as referred to in section 3 (e) who is responsible for the conduct of the clinical trial at a specific trial site. If the clinical trial is actually conducted by an employee or other assistant, then the party making use of that person's services shall be deemed to be the investigator;
- h. committee: a committee recognised in accordance with section 16;
- i. central committee: the committee referred to in section 14;
- j. Committee for the Safety of Medicines: the Committee for the Safety of Medicines referred to in section 29, subsection 1 of the Medicines Act;
- k. other Member States: Member States of the European Union other than the Netherlands;
- l. the European Agency for the Evaluation of Medicinal Products: the European Agency for the Evaluation of Medicinal Products established by Council Regulation (EEC) No. 2309/93 of 22 July 1993 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, (OJ No L 214);

m. multi-centre clinical trial: clinical trial conducted in accordance with a single protocol but at more than one site and by more than one investigator;

n. clinical trial involving medicinal products: any investigation that involves a medicinal product and is intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of any investigational medicinal product, and/or to identify adverse reactions to any investigational medicinal product and/or to study the absorption, distribution, metabolism and excretion of any investigational medicinal product with the object of ascertaining its safety and/or efficacy;

o. investigational medicinal product: any pharmaceutical form of an active substance or placebo which is being tested or used as a reference in a clinical trial, including any product which already has a marketing authorisation but is used, assembled, formulated or packaged in a way different from the authorised form, or is used in the trial for an unauthorised indication or to gain further information about the authorised form;

p. 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;

q. adverse event: any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product which does not necessarily have a causal relationship with this treatment;

r. adverse reaction: any untoward and unintended response to an investigational medicinal product, irrespective of the dose administered;

s. serious adverse event or serious adverse reaction: any untoward medical occurrence or effect which, at any dose, results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or produces a congenital anomaly or birth defect;

t. unexpected adverse reaction: an adverse reaction, the nature or severity of which is not consistent with the product information included in the investigator's brochure in the case of an unauthorised investigational product or with the summary of product characteristics contained in the patient information leaflet in the case of an authorised product;

u. informed consent: informed, written, dated and signed consent to take part in a clinical trial.

2. Subjecting persons to treatment or requiring persons to behave in a certain manner purely for their own good shall not be deemed to be a clinical trial as defined in subsection 1 (b).

3. This Act shall not be applicable to clinical trials whose conduct requires authorisation under the terms of the Population Screening Act with the exception of sections 7 and 9, and sections 8, 11 and 33, in so far as these relate to section 7, and to clinical trials where the research protocol under the Embryo Act has been approved by the central committee.

Section 2

1. Clinical trials shall be conducted in accordance with a research protocol written for the purpose.

2. The research protocol shall require approval as follows:

a. by a committee which is competent to give such approval if none of the criteria listed in subsection 2 (b) (2°, 3° or 4°) apply;

b. by the central committee referred to in section 14 where:

1°. a ruling on an application for administrative review is required;

2°. the clinical trials are of the kind referred to in the second sentence of section 4,

- subsection 1, if such trials will deliberately alter the condition of the subject without being of direct benefit to him or her;
- 3°. the clinical trials are of a kind which requires review by the central committee in accordance with section 19;
- 4°. the form of research involved has been identified by order in council as a form in which expertise is scarce.

3. Review of the research protocol shall take place in accordance with Divisions 2, 3 and, in so far as clinical trials involving medicinal products are concerned, 5a.

Section 2a

Any clinical trial, including any multi-centre clinical trial, shall be reviewed by a single competent committee designated for this purpose by the sponsor.

Division 2. Regulations on research involving human subjects

Section 3

The committee competent pursuant to section 2, subsection 2 shall only be empowered to approve a research protocol provided that:

- a. it is reasonable to expect that the trial will lead to the advancement of medical science;
- b. it is reasonable to expect that the advancement referred to under a could not be achieved without the participation of human subjects or by less radical means;
- c. it is reasonable to expect that the anticipated benefit to individual subjects and other present or future patients will be proportionate to the risks and inconveniences for subjects;
- d. the methodology of the trial is to be of the requisite standard;
- e. the trial is to be performed at suitable institutions and by or under the supervision of persons possessing research expertise, at least one of whom possesses expertise of direct relevance to the procedures involved in the trial in which the subject is to participate;
- f. it is reasonable to expect that any payment offered to the subject would not be of undue influence upon the decision as to whether consent should be given for the subject's participation in the trial;
- g. any payments to be received by the investigator and the institution at which the trial takes place are reasonably commensurate with the nature, scale and purpose of the clinical trial;
- h. the research protocol clearly indicates the extent of the potential benefits of the clinical trial to the subjects involved in it;
- i. the research protocol includes suitable criteria for the recruitment of subjects;
- j. the trial satisfies all other criteria which may reasonably be set for it.

Section 3a

1. A committee may suspend or withdraw its approval for a research protocol if it has objective grounds for considering that continuation of the trial would lead to unacceptable risks for subjects.
2. Except where there is imminent risk, the committee shall give the sponsor and/or investigator one week in which to express their views before it suspends or withdraws its approval.

3. If a committee decides to suspend or withdraw its approval for a clinical trial involving medicinal products, it shall notify the central committee or Our Minister, if section 13i, subsection 5 applies, and the Committee for the Safety of Medicines of its decision and the reasons for it.

4. The Committee for the Safety of Medicines shall forthwith inform the European Agency for the Evaluation of Medicinal Products and the European Commission of any suspension or withdrawal of approval for a research protocol concerning a clinical trial involving medicinal products and of the reasons for it.

Section 4

1. It is prohibited to conduct trials involving as subjects persons of less than eighteen years of age or persons who cannot be deemed capable of giving informed consent. This prohibition shall not apply to trials which may be of direct benefit to the subjects, nor shall it apply to trials which could not be conducted without the participation of persons of the same category as the subject, provided that the risk associated with participation is negligible and the inconveniences minimal.

2. If a subject involved in trials of either of the kinds referred to in the second sentence of subsection 1 should object to receiving treatment or behaving in the required manner, the person in question shall be excused from participation.

Section 5

It is prohibited to conduct trials involving as subjects persons whose actual or legal relationship with the sponsor or investigator or with the party recruiting the subjects is such that this relationship may reasonably be expected to be prejudicial to the principle of free consent. This prohibition shall not apply to trials which may be of direct benefit to the subjects, nor shall it apply to trials which could not be conducted without the participation of persons of the same category as the subject.

Section 6

1. It is prohibited to conduct trials:

- a. if the subject is of age and if subsection 1 (c) is not applicable: without the subject's written consent;
- b. if the subject is a minor of at least twelve years of age and if subsection 1 (c) is not applicable: without the written consent of the subject and the subject's parents (if they exercise parental responsibility) or legal guardian;
- c. if the subject is at least twelve years of age but cannot be deemed capable of giving informed consent: without the written consent of the subject's parents (if they exercise parental responsibility), or legal guardian, or (if the subject is not a minor) his or her legal representative, or (if no legal representative has been appointed) the person authorised in writing by the subject to act on his or her behalf, or (if no such person is available) the subject's spouse, registered partner or other companion in life;
- d. if the subject is a minor of under twelve years of age: without the written consent of the subject's parents (if they exercise parental responsibility) or legal guardian.

2. If the subject is unable to write, consent may be given orally in the presence of at least one witness.

3. The substitute consent of the persons referred to in subsection 1 at c and d must represent the presumed will of the subject.

4. If the clinical trial can be conducted only in medical emergencies in which the consent required pursuant to subsection 1 cannot be given and if inclusion in the trial may benefit the person in urgent need of medical treatment, procedures to implement the trial may be undertaken without such consent for as long as circumstances continue to prevent the giving of consent.
5. Before consent is sought, the investigator shall ensure that the person whose consent is required has been informed in writing and, if so desired, in a prior interview, of:
 - a. the objectives, nature and duration of the trial;
 - b. the risks which the trial would present to the health of the subject;
 - c. the risks which premature termination of the trial would present to the health of the subject;
 - d. the inconveniences which the trial might cause to the subject.
6. The information shall be given in such a way that it is reasonably certain that the recipient has understood its implications. The recipient shall be given sufficient time for reflection to permit him or her to reach a considered decision on the request for consent on the basis of the information provided.
7. The investigator shall ensure that, where subjects are less than twelve years of age or are incapable of giving informed consent, information about the trial is provided by an appropriately trained person in a manner befitting their ability to understand.
8. The research protocol shall specify how the provisions of this section are to be implemented.
9. The subject or, if that person is, pursuant to this section, incapable of giving informed consent, the person who is competent to give substitute consent, may revoke consent at any time without giving reasons. Any person revoking consent shall have no duty to pay damages on that account.

Division 3. Liability and insurance

Section 7

1. The trial shall not be conducted unless at the time of its commencement a contract of insurance has been entered into covering losses due to death or injury resulting from the trial. Such insurance need not cover injury which is inevitable or almost inevitable, given the nature of the trial.
2. Part 10, Title 1, Book 6 of the Civil Code shall apply *mutatis mutandis* to the insurer's obligation to pay compensation pursuant to subsection 1, insofar as, in view of the nature of the obligation, the purport of the said Part does not oppose such application.
3. Further rules on insurance shall be laid down by or pursuant to order in council. Rules laid down by order in council may include derogations from the provisions of subsections 1 and 2. Rules laid down pursuant to order in council may relate only to changes in sums of money specified in that order which by their nature require regular adjustment. The order in council shall enter into force no less than eight weeks after the date of its publication in the Bulletin of Acts and Decrees. The publication of the order in council shall be notified forthwith to both houses of the States General.
4. The research protocol shall indicate how the requirements of subsections 1 and 6 of this section are to be met.

(Liability for clinical trials)

5. Any liability on the part of the investigator for losses due to the death or injury of the subject shall

be shared by the sponsor. Insofar as procedures relating to clinical trials take place at a facilitative institution, the liability referred to in subsection 1 shall be shared by that institution, even if the institution does not itself conduct or perform the research.

6. Furthermore, the clinical trial may be undertaken only if, at the time of its commencement, provision has been made for insurance to cover the liability of the investigator or the sponsor as referred to in subsection 5, or if there is some other adequate guarantee that their obligations with respect to their liability can be met.

7. Subsections 1 and 6 shall not apply to clinical trials sponsored by central government departments or institutions designated by Our Minister. Injured parties shall have the same rights in relation to a central government department or institution which has made no provision for insurance as referred to in subsection 1 as they would otherwise have in relation to insurers pursuant to this section.

8. The liability of the investigator or, in the case referred to in subsection 5, of the sponsor or facilitative institution, may not be limited or excluded.

Division 4. Obligations resting on the sponsor

Section 8

1. The sponsor shall be responsible for compliance with section 2, subsections 1 and 2, and with section 7.

2. Under the circumstances described in section 7, subsection 5, second sentence, the facilitative institution shall share responsibility for compliance with section 2, subsections 1 and 2.

Section 9

The sponsor shall ensure that the subject is able to consult a doctor named in the research protocol who is not involved in conducting the trial, for information and advice regarding the trial.

Division 5. Further obligations resting on the investigator

Section 10

1. In the event of the trial proving to be significantly less favourable to the subject than the research protocol had suggested, the investigator shall without delay notify both the subject (or, if the subject was incompetent under the provisions of this Act to give consent, the person empowered to consent on the subject's behalf) and the committee which was last to review the protocol in accordance with section 2, and shall apply to the said committee for a further review. Under such circumstances, performance of the trial shall be suspended until such time as continuation is approved by the committee in question, unless suspension or cessation would be prejudicial to the health of the subject.

2. The investigator shall similarly notify the committee referred to in subsection 1 if the trial is prematurely terminated, indicating the reasons for its termination.

Section 11

The investigator shall be responsible for ensuring that the subject is informed in good time of the provisions of section 6, subsections 6, second sentence, and 9, and sections 7, 9, 10 and 12, and is

kept informed about the progress of the research. Additional information shall be provided upon request. The investigator shall be responsible for similarly informing any other person whose consent is required pursuant to Section 6.

Section 12

The investigator shall be responsible for ensuring that the privacy of the subject is respected as far as possible.

Section 13

The investigator shall be responsible for ensuring that before the trial commences those whose professional assistance is required for the conduct of the trial are informed of its nature and aim.

Division 5A. Supplementary rules for clinical trials involving medicinal products

Section 13a

In addition to the provisions of divisions 1 to 5, the provisions of this division shall apply to clinical trials involving medicinal products.

Section 13b

1. All clinical trials involving medicinal products, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of good clinical practice.
2. Rules on good clinical practice shall be laid down by or pursuant to order in council.

Section 13c

It is prohibited to conduct gene therapy trials which are intended to result in modifications to the subject's germ line and genetic identity.

Section 13d

Without prejudice to the provisions of division 2, the committee competent pursuant to section 2, subsection 2 may approve a research protocol relating to clinical trials involving medicinal products only if:

- a. the sponsor or legal representative of the sponsor is established within the territory of the European Community;
- b. the investigational medicinal products or, as the case may be, the devices used for their administration are, except for research with registered medicinal products, to be made available by the sponsor free of charge;
- c. a doctor or dentist registered under the Individual Health Care Professions Act and employed in the provision of health care is to be responsible for the medical care given to the subjects and medical decisions made on their behalf.

Section 13e

Without prejudice to the provisions of division 2, a clinical trial involving medicinal products may be undertaken using subjects who are minors only if:

- a. the trial is essential to validate data obtained in clinical trials involving medicinal products using persons able to give informed consent in accordance with the present Act or by other research methods, and the trial presents some direct benefit for the group of patients involved;
- b. the corresponding scientific guidelines adopted by the European Agency for the Evaluation of Medicinal Products are followed;
- c. the risk referred to in section 4 and the degree of distress are specifically defined and constantly monitored;
- d. the committee competent pursuant to section 2, subsection 2 possesses paediatric expertise or has taken paediatric advice on the clinical, ethical and psychosocial aspects of the trial;
- e. the interests of the patient will always prevail over those of science and society.

Section 13f

Without prejudice to the provisions of division 2, clinical trials involving medicinal products may be undertaken using subjects who have attained the age of majority but are incapable of giving informed consent only if:

- a. the trial is essential to validate data obtained in clinical trials involving medicinal products using persons who are able to give informed consent in accordance with this Act or by other research methods, and the trial relates directly to a life-threatening or debilitating clinical condition from which the subjects suffer;
- b. the risk referred to in section 4 and the degree of distress are specifically defined and constantly monitored;
- c. the committee competent pursuant to section 2, subsection 2 possesses expertise in relation to the relevant disease and the patient population concerned or has taken advice on clinical, ethical and psychosocial issues in the field of the relevant disease and patient population;
- d. the interests of the patient will always prevail over those of science and society;
- e. it is reasonable to expect that administering the medicinal product to be tested to the patient in question will produce a benefit outweighing the risks or produce no risk at all.

Section 13g

1. The committee competent pursuant to section 2, subsection 2 shall consider the investigator's brochure when reaching its approval decision and shall decide on any application for approval of a clinical trial within 60 days of receiving that application.
2. Within the period in which it is considering the application for approval, the committee competent pursuant to section 2, subsection 2 may send a single request for information supplementary to that already supplied by the applicant.
3. In the case of clinical trials involving medicinal products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms, the period of time specified in subsection 1 may be extended by up to thirty days.
4. The periods of time specified in subsections 1 and 3 shall not apply to the consideration of clinical trials involving medicinal products for xenogenic cell therapy.

Section 13h

1. Any application to a committee competent pursuant to section 2, subsection 2 for approval of a clinical trial involving medicinal products must comply with rules laid down by ministerial order. These rules shall concern the application format and the documentation to be submitted with the application, in particular regarding the information that is to be given to subjects and proper safeguards for the protection of personal data.

2. If the application as referred to in subsection 1 relates to clinical trials involving registered medicinal products, only the summary of the product information as laid down with registration has to be submitted with the application. If the dosage, dosage form, indication or study population differs from the registration, additional for the clinical trial relevant information must be added to the summary.

Section 13i

1. Clinical trials involving medicinal products may be carried out only if the central committee has not notified the applicant of any grounds for non-acceptance within the period of time referred to in subsection 3.

2. Before commencing any clinical trial involving medicinal products, the sponsor shall notify the central committee and shall submit the investigator's brochure.

3. Within no more than fourteen days of receiving the notification referred to in subsection 2 the central committee may notify the sponsor of any grounds for non-acceptance. In that case, the sponsor may, on one occasion only, amend the intended research protocol in order to satisfy the objections of the central committee. If the sponsor fails to amend the protocol, the clinical trial may not commence.

4. If the notification referred to in subsection 2 relates to clinical trials involving medicinal products for gene therapy, somatic cell therapy, xenogenic cell therapy or medicinal products containing genetically modified organisms, the clinical trial may commence only if the central committee or, if subsection 5 applies, Our Minister has certified in writing that there is no objection to it. In that case, the period of time referred to in subsection 3 may be extended by up to thirty days, provided that under the present Act there is no maximum period of time for the notification of grounds for non-acceptance of trials involving medicinal products for xenogenic cell therapy.

5. Notwithstanding the provisions of subsections 1 and 2, if the review of the research protocol pursuant to section 2, subsection 2 (b), (2°, 3° or 4°) is conducted by the central committee, the notification referred to in subsection 2 shall be made to Our Minister and Our Minister shall decide on the matter with this section applying *mutatis mutandis*.

6. Rules shall be laid down by ministerial order regarding the format and contents of the notification referred to in subsection 2, the supporting documentation to be submitted, the format and contents of a proposal to make substantial amendments to the protocol and the declaration of the end of the clinical trial.

7. Rules may be laid down by ministerial order regarding the amounts that may be charged to the person who has made the notification referred to in subsection 2 to cover the costs incurred by the central committee or, if section 13i, subsection 5 applies, by Our Minister in relation to the implementation of this section.

Section 13j

1. The central committee or, if section 13i, subsection 5 applies, Our Minister shall notify grounds for non-acceptance of a clinical trial only if the European database already contains information on side-effects of the medicinal product to be tested which pose unacceptable risks to the trial subjects, or if there are other grounds to believe that the trial will be in clearly contravention of the principles of good clinical practice.

2. At the request of the central committee or, if section 13i, subsection 5 applies, at the request of Our Minister, the Health Inspectorate shall verify whether the conduct of a clinical trial involving medicinal products may be expected to be in accordance with the present Act. The provisions of sections 5:12, 5:13 and 5:15 to 5:20 of the General Administrative Law Act shall apply *mutatis mutandis*.

Section 13k

1. The sponsor may amend the research protocol after the commencement of the clinical trial.

2. If an amendment is substantial and may affect the safety of trial subjects or may change the interpretation of the scientific documents used to support the conduct of the trial, or if it is otherwise significant, the sponsor may make it only if:

- a. he has notified the committee competent pursuant to section 2, subsection 2, the body referred to in section 13i, subsection 1 or 5 or, as the case may be, the competent authority of another Member State, whichever was the last to give its approval, of the reasons for and content of the proposed amendment;
- b. the committee competent pursuant to section 2, subsection 2 has approved the proposed amendment to the protocol, and
- c. the body referred to in section 13i, subsection 1 or 5 has raised no grounds for non-acceptance of the proposed amendment to the protocol.

3. If the body referred to in section 13i, subsection 1 or 5 or the competent authorities of other Member States have raised grounds for non-acceptance of the proposed amendment to the protocol, the clinical trial may proceed only if the sponsor modifies the proposed amendment to the protocol to take account of the objections raised.

4. The committee competent pursuant to section 2, subsection 2 shall decide whether to approve the proposed amendment to the protocol within a period of thirty-five days of receiving it.

5. The body referred to in section 13i, subsection 1 or 5 shall raise any grounds for non-acceptance of the proposed amendment to the protocol within a period of thirty-five days of receiving it.

Section 13l

1. Within ninety days of the end of the clinical trial, the sponsor shall notify the committee competent pursuant to section 2, subsection 2, the body referred to in section 13i, subsection 1 or 5 and, where appropriate, the competent authority of another Member State that the clinical trial has ended.

2. Within a period of fifteen days of any necessary premature termination of the trial, the sponsor shall notify the committee competent pursuant to section 2, subsection 2, the body referred to in section 13i, subsection 1 or 5 and, where appropriate, the competent authority of another Member State that the trial has been terminated prematurely and the reasons for this.

Section 13m

1. The body referred to in section 13i, subsection 1 or 5 shall supply the Committee for the Safety of Medicines with such information relating to clinical trials involving medicinal products conducted in the Netherlands as may have been designated by or pursuant to order in council.

2. The Committee for the Safety of Medicines shall ensure that this information is entered in a European database accessible only to the Committee for the Safety of Medicines, the central committee or, if section 13i, subsection 5 applies, Our Minister, the Health Care Inspectorate, the competent authorities of other Member States, the European Agency for the Evaluation of Medicinal Products and the European Commission. Rules may be laid down by or pursuant to order in council in relation to the confidentiality of the information contained in the European database.

3. At the substantiated request of any other Member State, the European Agency for the Evaluation of Medicinal Products or the European Commission, the body referred to in section 13i, subsection 1 and 5 shall supply all further information concerning the clinical trials in question other than the data already in the European database.

4. Further rules may be laid down by ministerial order regarding methods of electronic data exchange.

Section 13n

If there are objective grounds for considering that the sponsor or investigator or any other person involved in the conduct of the trial is failing to meet the obligations laid down, the central committee or, if section 13i, subsection 5 applies, Our Minister shall forthwith inform the person concerned and shall indicate the course of action which that person must take to remedy the situation. The central committee or, if section 13i, subsection 5 applies, Our Minister shall forthwith inform both the committee competent pursuant to section 2, subsection 2 that was the last to give an approval decision on the clinical trial in question and the competent authorities of other Member States and the European Commission of the said course of action.

Section 13o

1. The investigator shall immediately report to the sponsor any serious adverse event with the exception of those specified in the protocol or investigator's brochure as not requiring immediate reporting. The immediate report shall be followed by detailed written reports in which the trial subjects are identified by unique code numbers.

2. Adverse events and/or laboratory abnormalities specified in the protocol as critical to safety evaluations shall be reported to the sponsor within the time period specified in the protocol.

3. In the case of reported deaths, the investigator shall supply any additional information which may be requested by the sponsor and the committee competent pursuant to section 2, subsection 2 that was the last to give an approval decision.

4. The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator. This information shall be supplied on request to the Health Care Inspectorate, the central committee or, if section 13i, subsection 5 applies, Our Minister, and the competent authorities of the Member States in whose territory the clinical trial is being conducted.

Section 13p

The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions to investigational medicinal products that have proved fatal or life-threatening to a trial subject is recorded, and reported as soon as possible, in any event within a maximum of seven days of first knowledge, to the Committee for the Safety of Medicines, the central committee, the competent authorities in all other Member States concerned, and the committee competent pursuant to section 2, subsection 2, and that relevant follow-up information is subsequently communicated to the said bodies within an additional eight days.

2. All suspected serious unexpected adverse reactions to investigational medicinal products other than those referred to in subsection 1 shall be reported as soon as possible, and in any event within a maximum of fifteen days of first knowledge by the sponsor, to the Committee for the Safety of Medicines, the central committee, the competent authorities of all other Member States concerned and the committee competent pursuant to section 2, subsection 2.

3. The sponsor shall inform all other investigators involved in the clinical trial.

Section 13q

1. Once a year throughout the clinical trial, the sponsor shall supply a list of all suspected serious adverse reactions to investigational medicinal products which have occurred in that year and a report on the safety of the trial subjects to:

- a. the Committee for the Safety of Medicines;
- b. the central committee or, if section 13i, subsection 5 applies, Our Minister;
- c. the competent authorities of the other Member States in whose territory the clinical trial is being conducted;
- d. the committee competent pursuant to section 2, subsection 2.

2. The Committee for the Safety of Medicines shall ensure that all suspected serious adverse reactions to an investigational medicinal product which are brought to its attention are entered in the European database referred to in section 13m, subsection 2.

Section 13r

Requirements for the reports referred to in sections 13o, 13p and 13q may be laid down by ministerial order.

Division 6. The committees

Section 14

1. There shall be a central committee for medical research; it shall have at most fifteen members.

2. The members of the central committee shall include at least one doctor, persons with expertise in embryology, pharmacology, pharmacy, nursing, behavioural science, the law, research methodology and ethics, and a person charged with the task of examining protocols specifically from the subject's point of view.

3. An alternate shall be appointed for each member of the central committee.

4. The members of the central committee, including the chair and alternates, shall be nominated by Our Minister and appointed by royal decree for a term not exceeding four years. Our Minister shall

appoint a person to act as an observer at committee meetings.

5. The members of the central committee shall appoint one or more deputy chairs from amongst their number.

6. Members and alternates shall be eligible for reappointment for up to two further terms, each of up to four years. At the request of the person concerned, a member or alternate may be relieved of his or her duties by royal decree prior to expiry of their term of appointment, upon the recommendation of Our Minister.

7. Upon the recommendation of Our Minister, a member or alternate who has not asked to be relieved of his or her duties may be relieved of those duties by royal decree prior to expiry of their term of appointment, under the following circumstances:

- a. if he or she fails to discharge adequately the responsibilities associated with membership of the central committee;
- b. if he or she must be considered no longer physically or mentally fit to discharge his or her duties.

8. Members and alternates of the central committee shall be paid attendance fees and travel and accommodation expenses, in accordance with rules to be laid down by ministerial order.

9. The central committee shall operate in accordance with rules of procedure which shall be subject to the approval of Our Minister. Changes to these rules of procedure shall also be subject to the approval of Our Minister. Approval may not be withheld unless it is reasonable to believe that the work of the committee is not assured or is no longer assured. The rules of procedure shall include a provision that a member or deputy member of the central committee shall not take part in the review of a research protocol if he or she is involved in the proposed trials either as a sponsor or as an investigator.

Section 15

1. The central committee shall have a secretariat; officials shall be appointed to or suspended or dismissed from the secretariat by Our Minister, having heard the central committee. The secretariat shall be under the management of the Secretary of the Health Council of the Netherlands.

2. The secretariat officials shall be answerable to the central committee alone regarding the performance of their duties.

Section 16

1. The central committee shall be empowered to recognise other committees, whose duty it shall be to review research protocols in accordance with provisions made by or pursuant to this Act.

(Criteria for recognition of ethics committees)

2. The central committee shall not recognise a committee unless the following conditions are met:

- a. the members of the committee must include at least one doctor, persons with expertise in the law, research methodology and ethics, a person charged with the task of examining protocols specifically from the subject's point of view and, in the case of the review of clinical trials involving medicinal products, persons with expertise in pharmacy and clinical pharmacology;

- b. the committee's rules of procedure must make adequate provision for cooperation with other experts to enable proper review of the protocols submitted to the committee;
- c. the committee's rules of procedure must state the area in which the committee will be active;
- d. the committee's rules of procedure must make adequate provision for the committee's independence from the organisation that appointed it;
- e. the committee's rules of procedure must make adequate provision for its independence in relation to the organisation that has established the committee;
- f. the committee's rules of procedure must make proper provision for procedural arrangements including a provision that a member or deputy member may not take part in the review of a research protocol if he or she is involved in the proposed research either as a sponsor or as an investigator;
- g. it is reasonable to believe that the committee will receive for review at least the minimum number of research protocols specified by the central committee.

Section 17

1. The central committee shall notify Our Minister without delay of any recognition granted in accordance with section 16, subsection 1.
2. Our Minister shall arrange for recognition granted in accordance with section 16, subsection 1, to be announced in the Government Gazette.

Section 18

Any change in a committee's rules of procedure shall be notified in writing to the central committee.

Section 19

1. Within six weeks of the submission of a protocol for trials of the kind referred to in section 4, subsection 1, second sentence, which trials do not involve any deliberate alteration to the subject's condition, the committee may refer the protocol to the central committee for review. Under such circumstances, the committee shall notify the party submitting the protocol of its referral.
2. The central committee shall be empowered to require that all protocols for trials of a certain category of the kind referred to in subsection 1 of this section are referred to the central committee for review.

Section 20

The committee shall be entitled to charge the party submitting a research protocol a fee to cover the cost of the review procedure.

Section 21

1. A committee recognised pursuant to section 16 may be required by order in council to consider whether certain forms of research (to be specified in the order), which, pursuant to section 2, the committee in question has previously reviewed, have proved to be significantly less favourable for the subjects than the research protocol had suggested. Under such circumstances, the committee in question may give a further decision on the protocol. Section 10, subsection 1, second sentence, shall apply.

2. Further rules may be laid down by order in council regarding the manner in which committees discharge the duties referred to in subsection 1.
3. Subsections 1 and 2 shall apply *mutatis mutandis* to the central committee, insofar as the latter is responsible for the review of research protocols pursuant to section 2, subsection 2 (b), (2°, 3° or 4°).

Section 22

1. The committee shall send the central committee a copy of each decision given in accordance with this Act, together with a copy of the protocol or a synopsis of it. The committee shall also notify the central committee of any notification submitted in accordance with section 10, subsection 2.
2. No later than 31 March each year, the committee shall issue a report of its activities in the previous calendar year. This report shall be submitted to the central committee; copies shall be made available to the general public at cost price.
3. The committee shall cooperate with the central committee in any way which may reasonably be deemed necessary to enable the central committee to perform its duties.

Section 23

Any interested party may lodge an administrative appeal with the central committee against any decision by a committee that does not relate to a clinical trial involving medicinal products.

Section 24

The central committee shall monitor the activities of the other committees and shall be empowered to issue guidelines regarding the conduct of activities they carry out in accordance with this Act. Our Minister shall arrange for publication of such guidelines in the Government Gazette.

Section 25

1. The central committee shall withdraw its recognition of another committee under any of the following circumstances:
 - a. if the committee no longer meets the recognition requirements set out in section 16, subsection 2 (a to f);
 - b. if the committee fails to discharge adequately its responsibilities arising from this Act;
 - c. if the committee's rules of procedure are altered so that they may reasonably be deemed prejudicial to the proper performance of the committee's duties under this Act.
2. The central committee shall be entitled to withdraw its recognition of another committee if the number of research protocols submitted to the committee for review over the preceding three years is lower than the number referred to in section 16, subsection 2 (g).
3. The central committee shall not withdraw its recognition of another committee without first having heard that committee.
4. In the event of the central committee withdrawing its recognition of another committee, the central committee shall notify that committee in writing of its decision. Section 17, subsection 2 shall apply *mutatis mutandis*.

Section 26

Guidelines regarding the performance of the central committee's duties may be issued by order in council.

Section 27

1. No later than 31 March each year, the central committee shall submit to Our Minister a report of its activities in the previous calendar year. Copies of this report shall be made available to the general public at cost price by the central committee.

(Four-yearly report by central committee to Minister)

2. Every four years the central committee shall submit to Our Minister a report reviewing the central committee's performance of its duties and, if appropriate, proposing changes. Our Minister shall forward this report to the States General.

Division 7. Miscellaneous provisions

Section 28

1. Responsibility for verifying compliance with the provisions laid down by or pursuant to this Act shall rest with officials of the Public Health Supervisory Service designated by decision of Our Minister.

2. Any decision as referred to in subsection 1 shall be published in the Government Gazette.

3. Further rules regarding the verification of compliance with provisions laid down by or pursuant to this Act and relating to clinical trials involving medicinal products may be laid down by or pursuant to order in council.

Section 29

(Repealed)

Section 30

This Act shall be applied in accordance with the national and international regulations applicable to the civil service regarding the protection of data which must be kept secret in the interests of the State or its allies.

Section 31

1. Notwithstanding section 7, subsection 1, and section 8, subsection 1 of the Coordination (Exceptional Circumstances) Act, if exceptional circumstances should make it necessary, section 32 may be put into effect by royal decree, upon the recommendation of Our Prime Minister.

2. Should a decree of the kind referred to in subsection 1 be issued, a bill regarding the term of the provision put into effect by that decree shall be presented to the House of Representatives without delay.

3. In the event of the bill being rejected by the States General, the provision put into effect in accordance with subsection 1 shall be suspended without delay by royal decree, upon the

recommendation of Our Prime Minister.

4. The provision put into effect in accordance with subsection 1 shall be suspended by royal decree, upon the recommendation of Our Prime Minister, as soon as We judge that circumstances allow.

5. Any decree of the kind referred to in subsections 1,3 or 4 shall be published in the manner specified in that decree. Any such decree shall come into force upon its publication.

6. Any decree of the kind referred to in subsections 1,3 or 4 shall in any event be published in the Bulletin of Acts and Decrees.

Section 32 (not yet in force)

Our Minister may, with the agreement of Our Minister of Defence, suspend section 16, subsection 2 (a) and section 25, subsection 1 (a), in relation to committees charged with the review of clinical trials relating to protection against the conditions to which military personnel may be exposed on operational duty, insofar as such trials involve military personnel as subjects.

Division 8. Penalty provisions

Section 33

1. Any person who intentionally or unintentionally contravenes a prohibition contained in section 6, subsection 1 shall be liable to a term of imprisonment not exceeding one year or a fourth category fine.

2. Any person who fails to discharge his or her responsibility for compliance with section 2, subsections 1 or 2, or section 7, or who fails to perform a duty referred to in divisions 5 and 5a or fails to follow a course of action as referred to in section 13n shall be liable to a term of imprisonment not exceeding six months or a fourth category fine. Any person who contravenes a prohibition contained in sections 4, 5 and 13c or who conducts a clinical trial without a protocol for which approval has been obtained, or in contravention of such an approved protocol shall be liable to the same penalty.

3. Acts or omissions punishable in accordance with subsection 1 shall be deemed serious offences; acts or omissions punishable in accordance with subsection 2 shall be deemed minor offences.

Division 9. Concluding provisions

Section 34

(Implemented)

Section 35

(Implemented)

Section 36

(Implemented)

Section 37

Within four years of this act coming into force, and thereafter at five-year intervals, Our Minister shall submit to the States General a report on the effectiveness and impact of this act in practice.

Section 38

The articles of this Act shall come into force at a point or points in time specified by royal decree; the various articles or clauses thereof may come into force at different points in time.

Section 39

This Act shall be known as the Medical Research Involving Human Subjects Act.

We order and command that this Act shall be published in the Bulletin of Acts, Orders and Decrees (Staatsblad), and that all ministerial departments, authorities, bodies and officials whom it may concern shall diligently implement it.

Done at The Hague,

The Minister of Health, Welfare and Sports

The Minister of Justice