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Act of 26 February 1998, containing rules on medical research involving human subjects (Medical Research (Human Subjects) Act)

Division 1. General provisions

Section 1

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

- a. Our Minister: Our Minister of Health, Welfare and Sport;
- b. clinical trial: medical research in which persons are subjected to treatment or are required to follow a certain behavioural strategy;
- c. subject: a person as referred to under b;
- d. research protocol: the detailed description of a proposed trial including its objectives, design, methodology, statistical design and organisation;
- e. facilitative institution: institution or company where clinical trials take place;
- f. the sponsor: an individual, company, institution or organisation responsible for the initiation, management and/or financing of the clinical trial;
- g. the investigator: a physician 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 is 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. Medicines Evaluation Board: the Medicines Evaluation Board referred to in section 2, subsection 1 of the Medicines Act;
- k. other member states: member states of the European Union other than the Netherlands;

- l. the European Medicines Agency: 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. multicentre 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: an investigation 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. written informed consent: informed, written, dated and signed consent to take part in a clinical trial.

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

3. This Act does not apply to clinical trials whose conduct requires authorisation under the terms of the Population Screening Act and, with the exception of sections 7 and 9, and sections 8, 11 and 33, in so far as these relate to section 7, to clinical trials where the research protocol, pursuant to the Embryo Act, has been approved by the central committee referred to in section 14.

Section 2

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

2. The research protocol must have been approved:

- 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 trial is of the kind referred to in the second sentence of section 4, subsection 1, if such research will deliberately alter the condition of the subject without being of direct benefit to him or her;

3°. the clinical trial is 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 having social, ethical or legal considerations which make assessment by the central committee desirable.

3. The research protocol is reviewed in accordance with divisions 2 and 3 and with sections 9, 11 and 12, and, in so far as clinical trials involving medicinal products are concerned, division 5a.

Section 2a

Any clinical trial, including any multicentre clinical trial, will be reviewed by a single competent committee designated for this purpose by the sponsor.

Division 2. Rules on research involving human subjects

Section 3

The committee competent pursuant to section 2, subsection 2 is only empowered to approve a research protocol if:

- 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 burden 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 well-founded reasons to conclude that continuation of the trial would lead to unacceptable risks for the subjects.

2. If there are well-founded reasons to conclude that continuation of the trial would lead to unacceptable risks for the subjects, the central committee or, if section 13i, subsection 5 applies, Our Minister may decide to suspend the performance of the trial until a committee has once again approved the clinical trial's research protocol. The central committee or, if section 13i, subsection 5 applies, Our Minister will report the suspension to the committee that was the last to approve the research protocol, and to the sponsor and investigator.

3. Except where there is imminent risk, the committee, the central committee or, if section 13i, subsection 5 applies, Our Minister will give the sponsor and/or investigator one week in which to express their views before it suspends or withdraws its approval, or suspends the performance of the clinical trial.

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

5. The Medicines Evaluation Board will immediately inform the European Medicines Agency 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. Clinical trials may not be performed using as subjects persons of less than eighteen years of age or persons who cannot be deemed capable of giving informed consent. This prohibition does not apply to trials which may be of direct benefit to the subjects, nor does 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 burden 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 the treatment administered or behavioural strategy imposed, the person in question will be excluded from participation.

Section 5

Clinical trials may not be performed using 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 does not apply to trials which may be of direct benefit to the subjects, nor does 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 life companion, or (if no such person is available) the subject's parents, or (if no such persons are available) the subject's children provided they are of age and can be contacted reasonably easily, or (if no such persons are available) the subject's siblings provided they are of age and can be contacted reasonably easily;
- d. if the subject is 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 (c) and (d) must represent the presumed will of the subject.

4. If the clinical trial can be conducted only in emergency situations 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 must 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 subject's health;
- c. the risks which premature termination of the trial would present to the subject's health;
- d. the possible burden of the trial for the subject.

6. The information must be given in such a way that it is reasonably certain that the recipient has understood its implications. The recipient will 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. Specific conditions with regard to the information provided to persons whose consent is sought may be laid down by ministerial order.

7. The investigator must 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 must 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. A person who revokes his consent is not liable to pay compensation on that account.

Division 3. Liability and insurance

Section 7

1. The trial may not be conducted unless at the time of its commencement a contract of insurance has been entered into covering losses, as designated by order in council, due to the death or injury of a subject resulting from the trial. Such insurance need not cover losses which are inevitable or almost inevitable, given the nature of the trial.

2. Articles 95 and 96, paragraph 1, articles 97, 100 to 102, 105 to 107a, paragraph 1, and article 108 of Part 10, Title 1, Book 6 of the Civil Code apply *mutatis mutandis* to the insurer's obligation to pay compensation pursuant to subsection 1.

3. Further rules on insurance and the cover provided will be laid down by order in council. 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 will 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 will be notified immediately to both houses of the States General.

4. The insurance covers losses suffered by natural persons only.

5. If the committee responsible for assessing the trial protocol in question believes the clinical trial represents no risk to the subjects, at the sponsor's request it may, upon its approval of the protocol, exempt the sponsor from the obligation to take out insurance.

6. If the purpose of a clinical trial is to compare procedures that are commonly used in the medical profession, at the sponsor's request the committee responsible for assessing the protocol in question may, upon its approval of the protocol, exempt the sponsor from the obligation to take out insurance if it believes the risks of the clinical trial to the subjects are at most negligible on account of its comparative nature.

7. The research protocol must indicate how the requirements of subsections 1 and 9 of this

section are to be met.

8. Any liability on the part of the investigator for losses due to the death or injury of the subject is shared by the sponsor. Where procedures relating to clinical trials take place at a facilitative institution, the liability is shared by that institution, even if the institution does not itself conduct or perform the research.

9. Furthermore, the clinical trial may be conducted only if, at the time of its commencement, a contract of insurance has been entered into to cover the liability of the investigator or the sponsor as referred to in subsection 8, or if there is some other adequate guarantee that their obligations with respect to their liability can be met.

10. Subsections 1 and 9 do not apply to clinical trials sponsored by central government services or agencies, or companies working under the authority of central government, designated by Our Minister. Injured parties 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.

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

Division 4. Obligations resting on the sponsor

Section 8

1. The sponsor is 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 (sic), the

facilitative institution shares responsibility for compliance with section 2, subsections 1 and 2.

Section 9

The sponsor must ensure that the subject is able to obtain information and advice regarding the trial from a physician named in the research protocol, or from another person who possesses relevant expertise, and who is not involved in conducting the trial.

Division 5. Further obligations resting on the investigator

Section 10

1. In the event of the trial proving to be significantly more unfavourable to the subject than the research protocol had suggested, the investigator is required to notify both the subject (or, if the subject was incapable under the provisions of this Act of giving 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 without delay, and apply to the said committee for a further review. Under such circumstances, performance of the trial will 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 must similarly notify the committee referred to in subsection 1 of the premature termination of the trial, giving reasons, within fifteen days of that termination.

Section 11

The investigator is 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 trial. Additional information will be

provided upon request. The investigator is responsible for similarly informing any other person whose consent is required pursuant to Section 6.

Section 12

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

Section 13

The investigator is 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 apply to clinical trials involving medicinal products.

Section 13b

1. All clinical trials involving medicinal products, including bioavailability and bioequivalence studies, must be designed, conducted and reported in accordance with the principles of good clinical practice.

2. Rules on good clinical practice are laid down by or pursuant to order in council.

Section 13c

It is prohibited to conduct gene therapy clinical trials which are intended to result in modifications to the subject's germ line and individual 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 to be made available by the sponsor free of charge, except where the trial involves the use of authorised medicinal products;
- c. a physician or dentist registered under the Healthcare 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 using persons capable of giving informed consent in accordance with the present Act, or in trials involving other research methods, and the trial presents some direct benefit for the group of patients involved;
- b. the relevant scientific guidelines adopted by the European Medicines Agency are followed;
- c. the risk referred to in section 4 and the degree of burden 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 are of age but are incapable of giving informed consent only if:

- a. the trial is essential to validate data obtained in clinical trials using persons capable of giving informed consent in accordance with this Act, or in trials involving 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 burden 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 investigational medicinal product 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 forms its opinion partly on the basis of the investigator's brochure and decides on an application for approval of a clinical trial within 60 days of receiving that application.

2. In 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 a gene therapy medicinal product, a somatic cell therapy medicinal product or medicinal products containing genetically modified organisms, the time limit specified in subsection 1 may be extended by up to thirty days.

4. The time limits specified in subsections 1 and 3 do not apply to the consideration of clinical trials involving xenogeneic cell-based medicinal products.

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 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 referred to in subsection 1 concerns a clinical trial involving one or more previously authorised medicinal products, only the Summary of Product Characteristics, supplied during the authorisation procedure need be submitted with the application. If the trial involves an authorised product which is administered in another form, at another dosage or for another indication or patient population than for which the product was authorised, additional data relevant to the trial must be provided with the Summary of Product Characteristics.

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 time limit referred to in subsection 3.

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

3. Within 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 gene therapy medicinal products, somatic cell therapy medicinal products, xenogeneic cell-based medicinal products 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 time limit referred to in subsection 3 may be extended by up to thirty days, provided that under the present Act there is no maximum time limit for the submission of substantiated grounds for non-acceptance of trials involving xenogeneic cell-based medicinal products.

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 must be made to Our Minister and Our Minister will decide on the matter with this section applying *mutatis mutandis*.

6. Rules will 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 will submit substantiated grounds for non-acceptance of a clinical trial if the European database already contains information on adverse reactions to the medicinal product to be tested which pose unacceptable risks to the trial subjects, or if there are other reasons to believe that the trial will lead to unacceptable risks to the trial subjects.

2. At the request of the central committee or, if section 13i, subsection 5 applies, at the request of Our Minister, the Health Inspectorate will verify whether the conduct of a clinical trial involving medicinal products is 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 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 submitted substantiated 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 must decide whether to approve the proposed amendment to the protocol within a time limit of thirty-five days of receiving it.

5. The body referred to in section 13i, subsection 1 or 5 must submit any substantiated grounds it may have for non-acceptance of the proposed amendment to the protocol within thirty-five days of receiving it.

Section 13l

1. Within ninety days of the end of the clinical trial involving medicinal products, the sponsor must 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 fifteen days of any necessary premature termination of the clinical trial, the sponsor must 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 must supply the Medicines Evaluation Board 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 Medicines Evaluation Board must ensure that this information is entered in a European database accessible only to the Medicines Evaluation Board, 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 Medicines Agency 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 Medicines Agency or the European Commission, the body referred to in section 13i, subsection 1 and 5 will 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 will inform the person concerned immediately and 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 will immediately 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 must 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 must 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 must be reported to the sponsor within the time period specified in the protocol.
3. In the case of reported deaths, the investigator must 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 must keep detailed records of all adverse events which are reported to him by the investigator. This information will 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 must 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 Medicines Evaluation Board, 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 must be reported as soon as possible, and in any event within a maximum of fifteen days of first knowledge by the sponsor, to the Medicines Evaluation Board, 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 must inform all other investigators involved in the clinical trial.

4. The Medicines Evaluation Board must ensure that all suspected serious unexpected adverse reactions to an investigational medicinal product which are brought to its attention are entered into the European database referred to in section 13m, subsection 2.

Section 13q

Once a year throughout the clinical trial, the sponsor must 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 central committee or, if section 13i, subsection 5 applies, Our Minister;
- b. the competent authorities of the other member states in whose territory the clinical trial is being conducted;
- c. the committee competent pursuant to section 2, subsection 2.

Section 13r [repealed as of 1-7-2012]

Division 6. The committees

Section 14

1. There is a central committee for medical research; it has at most fifteen members. The Autonomous Administrative Authorities Framework Act applies to the central committee, except for section 22 of that Act, where the central committee's decisions relate to the implementation of this Act and to sections 10, 16 and 19 of the Embryo Act.
2. The members of the central committee include at least one physician, 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 subjects' point of view.
3. An alternate is appointed for each member of the central committee.
4. Our Minister appoints a person to act as an observer at committee meetings.
5. The members of the central committee appoint one or more deputy chairs from amongst their number.
6. Members and alternates are eligible for reappointment for up to two further terms, each of up to four years.
7. The central committee operates in accordance with rules of procedure. The rules of procedure include a provision that a member or deputy member of the central committee may 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

The central committee has a secretariat; officials are appointed to or suspended or dismissed from the secretariat by Our Minister, having heard the central committee.

Section 16

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

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

- a. the committee members must include at least one physician, 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 members must satisfy further requirements to be established by the central committee with regard to education and experience;
- c. the committee members are appointed for a term of up to four years. They may be reappointed for up to two further terms, each of up to four years;
- d. the committee's rules of procedure must make adequate provision for cooperation with other experts to enable proper review of the research protocols submitted to the committee;
- e. the committee's rules of procedure must state the area in which the committee will be active;
- f. the committee's rules of procedure must make adequate provision for the committee's independence from the organisation that appointed it;
- g. the committee's rules of procedure must properly regulate its working methods and include 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;
- h. 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 notifies Our Minister without delay of any recognition granted in accordance with section 16, subsection 1.
2. Our Minister will 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, or its discontinuation, will 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 notifies the party submitting the protocol of its referral.
2. The central committee is empowered to require that all protocols for trials of the kind referred to in subsection 1 of this section are referred to the central committee for review.

Section 20

The committee and the central committee are entitled to charge the party submitting a research protocol a fee to cover the cost of the review procedure.

Section 21

1. It may be provided by order in council that the committees recognised pursuant to section 16 ascertain whether certain kinds of clinical trial (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, applies.

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 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 sends 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 within seven days of reaching its decision. The committee also informs the central committee within seven days of any notification submitted in accordance with section 10, subsection 2.

2. No later than 31 March each year, the committee issues a report of its activities in the previous calendar year. This report is submitted to the central committee; copies are made available to the general public at cost price.

3. The committee cooperates 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 application for administrative review with the central committee against any decision by a committee.

Section 24

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

Section 25

1. The central committee will 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 g);

- 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 is entitled to withdraw its recognition of another committee if the number of research protocols reviewed by the committee over the preceding two years is lower than the number referred to in section 16, subsection 2 (h).

3. The central committee may 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 will notify that committee in writing of its decision. Section 17, subsection 2 applies *mutatis mutandis*.

Section 26 [repealed as of 1-7-2011]

Section 27

Every five years the central committee submits to Our Minister a report reviewing the central committee's performance of its duties and, if appropriate, proposing changes. Our Minister must give his opinion of the review in his report to both houses of the States General as referred to in section 39, subsection 1 of the Autonomous Administrative Authorities Framework Act, and attaches the review as an annexe to this report.

Division 7. Miscellaneous provisions

Section 27a

Rules may be laid down by ministerial order on supplying by electronic means the information to be submitted pursuant to this Act to the central committee, to Our Minister if section 13i, subsection 5 applies, and furthermore to the committee, the Medicines Evaluation Board or the Healthcare Inspectorate.

Section 28

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

2. Any decision as referred to in subsection 1 is 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 as of 1-12-1999]

Section 30

The committees are required to apply this Act 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 will 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 will 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 will 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 will be published in the manner specified in that decree and will enter into force upon its publication.

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

Section 32 [not yet in force]

[Ed.: This section is not yet in force. If exceptional circumstances should make it necessary, this section may be put into effect by royal decree, upon the recommendation of Our Prime Minister.] 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, where 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 is liable to a term of imprisonment not exceeding one year or a fourth-category fine.

2. Any person who fails to discharge his responsibility for compliance with section 2, subsections 1 or 2, or section 7, or who fails to perform a duty referred to in division 5 or 5a or fails to follow a course of action as referred to in section 13n is liable to a term of imprisonment not exceeding six months or a fourth-category fine. Any person who contravenes a prohibition contained in section 4, 5 or 13c or who conducts a clinical trial without a protocol for which approval has been obtained, or in contravention of such an approved protocol, or who conducts a trial when the committee has suspended or withdrawn its approval of the protocol, or when the central committee or Our Minister, if section 13i, subsection 5 applies, has ordered that the conduct of the clinical trial be suspended is liable to the same penalty.

3. Acts or omissions punishable in accordance with subsection 1 are indictable offences; acts or omissions punishable in accordance with subsection 2 are minor offences.

Division 9. Concluding provisions

Section 34

[Amends the Coordination (Exceptional Circumstances) Act.]

Section 35

[Amends this Act.]

Section 36

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*Auteursrecht vertalingen voorbehouden.
Ministerie van Buitenlandse Zaken, Directie Vertalingen (AVT)*

[Amends this Act.]

Section 37

1. Four years after this Act enters into force, and every five years thereafter, Our Minister will send the States General a report on the effectiveness of the Act and its effects on the practice of clinical trials.

2. The report referred to in section 39, subsection 1 of the Autonomous Administrative Authorities Framework Act is encompassed in the report referred to in subsection 1.

Section 38

The sections of this Act enter into force on a date to be determined by Royal Decree, which may vary for the different sections or points thereof.

Section 39

This Act may be cited as the Medical Research (Human Subjects) Act.