Ministerie van Volksgezondheid, Welzijn en Sport – NL

The Medical Research Involving Human Subjects Act (WMO)

International Publication Series Health, Welfare and Sport nr. 2

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This series provides an introduction to legislation of the Netherlands which specifically relates to the health, welfare and sports sectors. In addition, the series reproduces relevant laws in full text. The target groups are counterparts of the Ministry of Health, Welfare and Sport in other countries, Embassies of the Kingdom of the Netherlands abroad, foreign Embassies in the Netherlands, researchers and other experts.

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Introduction

The Medical Research Involving Human Subjects Act was adopted by the Lower House in 1997 and by the Upper House 1998. One of the principal aims of this Act is to provide protection to subjects who take part in medical research. Over the past 20 years in the Netherlands, a thorough practice has been established of medical research involving human subjects and reviewing such research in terms of medical ethics. The Act lays down the general requirements for this practice. New is the establishment of a central committee for medical research involving human subjects. The central committee's tasks include recognizing medical ethics review committees and collecting and keeping the protocols on medical research involving human subjects. The central committee itself reviews the protocols on medical research in a number of cases.
The Medical Research Involving Human Subjects Act came into force on December 1, 1999.

In 1998, new rules also came into force in the Netherlands in line with the European directive for 'good clinical practice'. This directive is intended to establish a common standard to protect the rights, safety and well-being of human subjects in medical research carried out for the development of drugs. The directive is also intended to guarantee the quality and reliability of the drug research. The provisions of the Medical Research Involving Human Subjects Act are in line with the European requirements, as far as possible.

Chapter 1 of this brochure explains what the Act regulates and the parties for which the Act is intended.
Chapter 2 describes how the Act operates in practice. Amongst other things, there is a description of the new method of review and its consequences, especially for medical ethics review committees and researchers.
The central committee and its role vis-à-vis the medical ethics review committees are discussed separately in chapter 3.
Chapter 4 states how two decrees based on the Act are dealt with. This includes, amongst other things, the compulsory insurance.
Chapter 5 describes the interim procedure for approving scientific research that involves the use of gametocytes and embryos.

The text of the Act is included as an appendix.

1 What does the Act regulate?

REVIEW

In the Netherlands, medical research involving human subjects may only be carried out if a recognized review committee has approved it. The Medical Research Involving Human Subjects Act regulates this review. Research in the sense of the Act is medical research that is intended to lead to generally valid statements based on systematic observations and reasoning. Amongst other things, this may relate to the effects of new methods of treatment but also to obtaining information about the normal physiological situation or pathological processes.
Medical ethics committees generally conduct the review, taking the criteria included in the Act as their starting point.
Research protocols are only approved if it is reasonable to assume that:

- the research will lead to the advancement of medical science;
- the aforementioned advancement could not be achieved without the participation of human subjects or with a less radical intervention;
- the risks and burden borne by the subject will be in proportion to the potential value of the research.

A central committee for medical research involving human subjects regulates the recognition of the medical ethics review committees, keeps up-to-date records of the research protocols, and acts as a regulatory body for the parties that wish to conduct the research. The central committee itself reviews the protocols on medical research in a number of cases. The tasks of the central committee are described in greater detail in chapter 3 of this brochure.

LEGAL PROTECTION OF HUMAN SUBJECTS

The Medical Research Involving Human Subjects Act was established because the legal position of patients in health care requires additional protection in certain situations. In the Netherlands, general regulations on the legal position of patients already exist in the form of the Medical Treatment Contracts Act, which is mainly concerned with ensuring that the medical practitioner's patient receives sufficient information to take a well-considered decision about the treatment. The patient's consent is required for treatment to start.

The Medical Research Involving Human Subjects Act is specifically concerned with people – healthy human subjects and patients – who participate in medical

research. Thanks to the Act, these subjects now have greater legal protection than they had in the past. This was considered necessary because medical research raises issues not only in connection with the interests of the patients themselves but also with those of third parties. Such issues may concern the advancement of medical science, the interests of future patients, the risk of infection to the population as a whole or the marketing of new drugs by the pharmaceuticals industry.

The Act pays particular attention to research involving people who are unable to give informed consent. The 'not unless' principle applies to granting permission for research involving human subjects who are unable to give informed consent or are otherwise dependent, as in the case of minors. The legislator considered that research of this kind involves making a choice between, on the one hand, a particular encroachment on the physical and mental integrity of subjects who are unable to give informed consent and, on the other hand, seeking possibilities for improving the care of this category of patients. A total prohibition of research involving people who are unable to give informed consent is not advisable, as improvements are often only achievable through conducting medical research with the co-operation of the patients concerned. Seen from that point of view, it is conceivable that researchers could require basic knowledge about, for example, the functioning of newborn infants, young children, mentally handicapped people, people suffering from senile dementia or people who are temporarily unable to give informed consent owing to an accident or the consequences of an operation.

The central committee itself reviews the protocols for certain types of research involving people who are unable to give informed consent. This is intended to provide additional legal protection for patients who are unable to give informed consent. In cases involving people participating in non-therapeutic medical research, who are unable to give informed consent, the Act also stipulates that the risks must be negligible and any burden minimal.

The Medical Research Involving Human Subjects Act: additional legal protection for patients

- the patient must be informed in writing about the research;
- a doctor not involved in the research is available to provide the patient with information;
- the patient must give written consent for participation in the research;
- insurance must be taken out to cover any harm to the subject caused by the research;

- the Act sets requirements for the compulsory review of the research;
- the written consent of parents or guardians is required for research involving people who are unable to give informed consent; the subject is informed as fully as possible; the person's participation is terminated in the case of objection; certain types of research involving people who are unable to give informed consent are reviewed by the central committee;
- the annual reports of the local committees and the central committee are available to the public.

2 The Act in practice

TYPES OF RESEARCH

The Act concerns all medical research in which people are subjected to treatments or rules of behaviour. Medical research is a broad term that covers various types of research. These include observational research in which the researcher does not want to change the existing situation but only to ascertain it as accurately as possible. An example of this is the documentation of the course of pathological processes or the collection of data describing the normal situation (research to ascertain standard values). Observations may entail making all kinds of measurements in connection with examining blood and urine samples, as well blood-pressure measurements, tissue-biopsy analyses and so forth. Invasive treatments are therefore sometimes necessary. The term medical research also covers intervention research. Intervention research also involves observations and measurements but only after the researcher's intervention to intentionally alter a particular condition. Comparisons are often made between people who have undergone the intervention and members of a control group. This type of research is also known as experimental research. Intervention research may be divided into two categories, depending on the objective: research into the working mechanisms of the human body and research into the therapeutic effect of an intervention. Research into working mechanisms attempts to clarify the working of given organic or psychological processes. This includes research into the body's response to exposure to external influences or toxicity, for example. This also covers the initial phases of drug research, which are only concerned with how the substance behaves in the body.

The second category of intervention research examines the effectiveness or value of therapeutic, diagnostic, preventive and nursing interventions.

The Act distinguishes between medical research that may benefit the participants and research in which that is not the case. Research that may directly benefit the participants is also known as therapeutic research. Research into the effectiveness or value of therapeutic, diagnostic, preventive or nursing interventions is often therapeutic, whereas observational research is hardly ever of any direct benefit to the human subjects involved. Likewise, research into working mechanisms seldom benefits the participants.

As mentioned, medical research only comes within the scope of the Act if it concerns research in which people are subjected to treatments or rules of behaviour. In practice, this means that the Act covers research involving some form of encroachment on a person's integrity. Therefore, the Act would not, in the majority of cases, cover medical research for which a single urine sample was provided, whereas it would cover research that involved providing urine samples for a three-week period. The once-only completion of a questionnaire would not be covered by the Act, but a questionnaire containing questions that constituted a serious encroachment on the psychological integrity of the person completing it would.
The Act does, of course, cover drug research conducted within the scope of drug registration, but it also covers research into the use of registered drugs for another medical indication.

The above means that epidemiological research may also be covered by the bill, namely research in which human subjects undergo treatments or have to follow particular rules of behaviour. On the other hand, the Act does not cover retrospective research using data from patients' medical records. This type of research is only covered by the Medical Treatment Contracts Act.

REVIEW

Medical research involving healthy volunteers or patients must be submitted to recognized medical ethics review committees for approval before being allowed to commence. In certain cases, the research proposal must be submitted to the central committee for medical research. Medical research involving human subjects that has not been approved by a review committee is prohibited under the Act.

The research protocol (a description of the research) contains, amongst other things, an accurate description of the objective, method of working and procedure. Moreover, a standard application form is often used for this.
The documentation that has to be enclosed includes the written information for

the subjects and a form for their written consent. The local or central committee may request additional information from the party that will be conducting the research.

The committees on medical ethics review the research protocols in accordance with the rules set out in the Medical Research Involving Human Subjects Act. The review committees may work for general hospitals, teaching hospitals, research institutions (such as the TNO organization for applied scientific research, the Netherlands Organization for Scientific Research, or the National Institute of Public Health and Environmental Protection) or, in the case of drug research, for pharmaceuticals companies. Some committees only operate at the local level, others have a regional or national task and there are review committees that operate categorically. Sofar approximately 75 committees have been recognized. The central review committee operates at the national level (see chapter 3).

HUMAN SUBJECTS

The Medical Research Involving Human Subjects Act requires subjects who take part in medical research to give their written consent.
In the first place, the Act distinguishes between human subjects according to age. Written consent from the parents or legal guardians is required for subjects under the age of 12. For subjects aged between 12 and 18, written consent is required from the subject and from the parents or legal guardians. Adults must give written consent themselves.

In the second place, an essential question in the provision of consent is whether or not the subject is capable or giving informed consent. Those who are not include children, and people suffering senile dementia or a mental handicap, for example.
The written consent has to be provided by the parents, legal guardians or attorneys of human subjects aged 12 and over who are incapable of assessing what is in their own interest and consequently unable to give informed consent in the sense intended by the Act. People who are unable to give informed consent must be told what will happen in a way they are capable of understanding, and, if they object, the research is not permitted to proceed.

The overwhelming majority of human subjects are patients and this is why they are asked to participate in research. Any payment received by healthy volunteers must be in reasonable proportion to the burden borne by the subjects and not have any undue influence on their decision to participate in the research.

Human subjects are entitled to stop participating in the research at any time without explanation and without incurring any liability.

INFORMATION

Subjects have to be fully informed in writing before they can take a well-considered decision about participating in medical research. Their decision to do so is therefore taken ‘willingly and wittingly’. The researcher must have ascertained that the subject is aware of the intention of the research and how it will be performed. Moreover, the researcher must allow subjects a reasonable time to take a well-considered decision about whether to consent on the basis of the information provided.

Subjects are entitled to information and to ask questions at any time, which means prior to, during and after the research. The party (i.e., the sponsor) conducting the research is obliged to appoint a doctor who can provide the subject with information about the research and who is not involved in its performance. The researcher must ensure the private life of the subject is respected as far as possible.

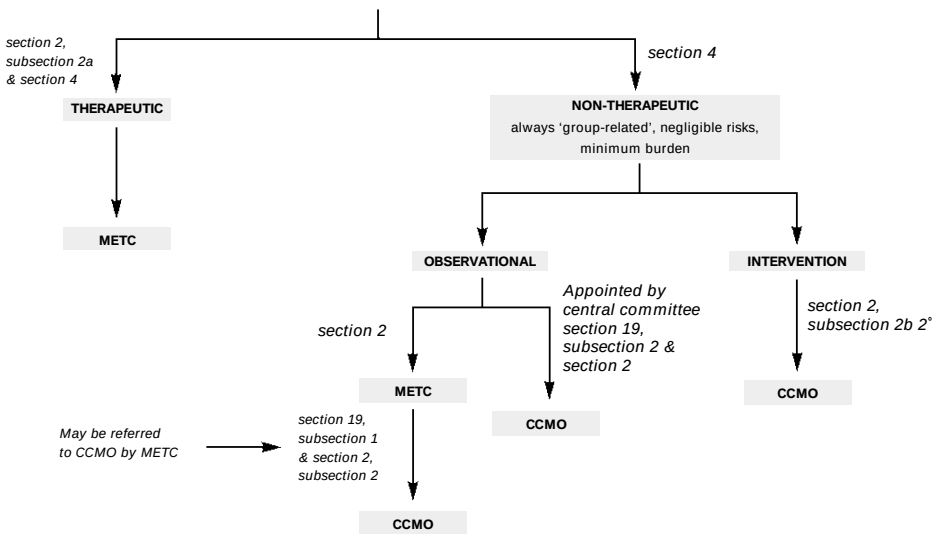
3 The central committee for medical research involving human subjects

The central committee, established pursuant to section involving human subjects 14 of the Medical Research Involving Human Subjects Act, has the task of recognizing the medical ethics review committees and monitoring their work. A medical ethics review committee may only be recognized if it consists of one or more doctors, plus experts in law, research methodology and ethics. The committee must also include someone with the task of examining the research protocols specifically from the subject's point of view. The Act sets requirements for the statutes of the committees, and stipulates the periods within which any referral of protocols must occur, and the fees for conducting the review and compiling the report. The central committee may also establish supplementary directives on the operation of the local committees. Interested parties may appeal to the central committee against any negative decision taken by a local committee.

The central committee keeps a record of medical research being conducted in the Netherlands. The Act requires the medical ethics review committees and the central committee to compile annual reports. These annual reports are available to the general public.
The central committee itself reviews any type of medical research into developments that are so new that there is a lack of expertise in the field concerned. Research of this kind is designated as such by order in council. All forms of research involving gene therapy and xenografts are reviewed by the central committee.
The central committee is also responsible for reviewing protocols for non-therapeutic intervention research involving subjects who are unable to give informed consent. This refers to research which alters the condition of subjects, for example through the use of drugs, without any direct benefit to them.
The central committee also comes into operation when it is requested to approve certain types of observational research involving subjects who are unable to give informed consent. This may concern research protocols that a medical ethics review committee has referred to the central committee, or protocols in a category of research that has been designated as the central committee's responsibility.

The central committee consists of no more than thirteen members, of which one or more must be a doctor. The Act also stipulates that the committee must appoint experts in pharmacology, nursing, behavioural science, law, research methodology and ethics. It must also appoint someone with the task of reviewing research applications specifically from the subject's point of view. The members of the central committee are nominated by the minister of Health, Welfare and Sport, and appointed for a maximum of four years. Each member has a deputy.

REVIEW OF MEDICAL RESEARCH INVOLVING PEOPLE WHO ARE UNABLE TO GIVE INFORMED CONSENT



METC = COMMITTEE ON MEDICAL ETHICS

CCMO = CENTRAL COMMITTEE FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

4 Decrees based on the Act

A number of decrees have been passed on the basis of the Act. These decrees deal with the arrangements for centralised medical ethics review and the compulsory insurance of research projects. The texts are reproduced in full at the back of this leaflet.

A Decree on the Centralised Medical Ethics Review of Protocols for Medical Research Involving Human Subjects. There are relatively few people in the Netherlands with the expertise necessary to review protocols for research in the fields of gene therapy or xenotransplantation. A decree has therefore been passed, requiring all such protocols to be reviewed by the central committee. Most forms of clinical xenotransplantation research will in any case remain prohibited for some years to come.

B Temporary Decree on the Compulsory Insurance of Medical Research Involving Human Subjects. This decree makes a number of additional provisions regarding the insurance of medical research involving human subjects, which is compulsory under section 7 of the Act. The decree specifies the minimum sums that must be insured and lays down rules on the type of insurer with whom a policy may be closed. Other provisions relate to the minimum period over which cover must extend, the types of exclusion that are permitted and the subject's personal rights over the insurer. Account is taken of the fact that compulsory insurance serves no useful purpose in relation to types of research which entail no risk for the subjects. Medical ethics review committees accordingly have the power to waive the insurance obligation in cases where there is demonstrably no risk to the subject (see Article 4, clause 1, of the decree). Provision is also made for research projects which involve insignificant or negligible risk for the subject. Under such circumstances, the medical ethics review committee can give a special dispensation allowing the closure of a lower-value insurance policy (see Article 4, clause 2, of the decree). Article 8 of the decree limits the validity of its provisions to a period of three years. Before the end of this period, the subject of compulsory insurance will be reviewed in the light of wider developments in liability law.

5 Scientific research involving gametocytes and embryos

The intention is that responsibility for the review of protocols for medical research projects involving gametocytes and/or embryos should in due course also be given to the central committee for medical research involving human subjects. The Bill on Procedures Involving Gametocytes and Embryos (known by its Dutch initials, WGE), which is expected to come before the lower house of the Dutch parliament in the course of 2000, makes provision for this centralisation of responsibility. Until the WGE comes into effect, the central committee will look at the ethical and scientifical acceptability of protocols for medical research projects involving gametocytes and embryos in an advisory capacity.

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Appendix I

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

26 February 1998

(The translation below is not certified and it has not been authorized by the Dutch government)

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 Sections 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:

1 General provisions

SECTION 1

1 Within the context of this Act and the associated provisions, the meanings of terms listed in this paragraph under a to g shall be as indicated.
a Our Minister: Our Minister of Health, Welfare and Sports;
b research: medical research 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 research;
e facilitative institution: institution or company at which research activities take place;
f the party conducting the research: the party who commissions the organization or performance of research;

g the party performing the research: the party responsible for the actual performance of the research. If the research is actually performed by an employee or other assistant, then the party making use of that person's services shall be deemed to be the party performing the research.

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 research as defined in this Section, first subsection, under b.

3 This Act shall not be applicable to research whose conduct requires authorization under the terms of the Population Screening Act (Bulletin of Acts, Orders and Decrees ...)

SECTION 2

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

2 The research protocol shall require approval as follows:

a Approval by a suitably authorized committee recognized under the terms of Section 16 shall be required where clause b, under 2°, 3° or 4°, is not applicable.

b Approval by the central committee referred to in Section 14 shall be required where:

1° a ruling on an administrative appeal is required;

2° the research is of the kind referred to in the second sentence of Section 4, first subsection, if such research is to alter the condition of the subject without being of direct benefit to him or her;

3° the research 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 a form in which expertise is scarce.

3 Review of the research protocol shall take place in accordance with Sections 2 and 3.

2 Regulations on research involving human subjects

SECTION 3

A committee shall only be empowered to approve a research protocol provided that the following conditions are met:

a it is reasonable to expect that the research 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 with a less radical intervention;
c it is reasonable to expect that the risk to and burden for the subject will be in proportion to the potential value of the research;
d the methodology of the research is to be of the requisite standard;
e the research is to be performed by or under the supervision of persons possessing research expertise, at least one of whom possesses expertise of direct relevance to the research activities 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 research;
g the research protocol clearly states the extent to which the research may be beneficial to the subject;
h the research satisfies any other reasonable requirements.

SECTION 4

1 It shall be forbidden to conduct research involving as subjects persons of less than eighteen years of age or persons who cannot be deemed capable of reasonably assessing their interests in the matter. This prohibition shall not apply to research which may be of direct benefit to the subjects, nor shall it apply to research 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 research of either of the kinds referred to in the second sentence of this Section, first subsection, should object to receiving treatment or behaving in the required manner, the person in question shall be excused from participation.

SECTION 5

It shall be forbidden to conduct research involving as subjects persons whose actual or legal relationship with the party conducting or performing the research 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 research which may be of direct benefit to

the subjects, nor shall it apply to research which could not be conducted without the participation of persons of the same category as the subject.

SECTION 6

1 It shall be forbidden to conduct research under the following conditions:

a if the subject is of age and if clause 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 clause c is not applicable: without the written consent of the subject and the subject's parents (if they are the legal guardians) or legal guardian;

c. if the subject is at least twelve years of age but cannot be deemed capable of reasonably assessing his or her interests in the matter: without the written consent of the subject's parents (if they are the legal guardians), or legal guardian, or (if the subject is not a minor) his or her legal representative, or (if no legal representative is available) the person authorized in writing by the subject to act on his or her behalf, or (if no such person is available) the subject's spouse 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 are the legal guardians) or legal guardian.

2 If the nature of the research is such that it can only be performed in emergency situations, thereby making it impossible for consent to be obtained in accordance with the first subsection, and if the research may be of direct benefit to the subject, research activities may be performed without consent, so long as the circumstances which make it impossible for consent to be obtained continue to prevail.

3 Before consent for a person's participation as a subject is requested, the party performing the research shall ensure that the person from whom consent is requested is informed in writing of the following:

a the aim, nature and duration of the research;

b the risks to the subject's health which could be associated with participation;

c the risks to the subject's health which could be associated with premature cessation of the research;

d the burden for the subject which could be associated with participation.

4 The information referred to in this Section, third subsection, shall be provided in such a way that there may be no reasonable doubt that it has been understood by the recipient. The recipient shall be given sufficient time to properly consider the information and to reach a reasoned decision regarding consent.

5 A party performing research in which minors under the age of twelve or persons who cannot be deemed capable of reasonably assessing their

interests in the matter are involved as subjects shall ensure that such subjects are told what is to happen in a way they are able to understand.

6 The research protocol shall indicate how the requirements set out in this Section are to be met.

7 A person who has consented to participation as a subject or who has consented to the participation of another who, in accordance with this Section, is not deemed competent to consent personally, shall be entitled to withdraw such consent at any time, without explanation and without incurring any liability.

3 Liability and insurance

SECTION 7

1 The research shall not be conducted unless at the time of its commencement a contract of insurance has been closed covering liability for death or injury resulting from the research. Such insurance need not cover injury which is inevitable or almost inevitable, given the nature of the research.

2 Chapter 10 of Title 1 of Book 6 of the Civil Code shall apply equally to the insurer's obligation to pay compensation pursuant to this Section, first subsection, insofar as the provisions of the said Title are not in conflict with the nature of the obligation.

3 Further rules regarding the requisite insurance shall be laid down by order in council. Such rules may depart from the provisions of the first and second subsections of this Section in certain respects. The relevant order shall not take effect for at least eight weeks from the publication date of the Bulletin of Acts, Orders and Decrees in which it is included. Both Houses of Parliament shall be notified of the order's publication at the earliest opportunity.

4 The research protocol shall indicate how the requirements of this Section, first subsection, are to be met.

5 Any liability of the party performing the research for the death or injury of the subject shall be shared by the party conducting the research. Insofar as research activities take place at a facilitative institution, the liability referred to in this Section, first subsection, shall be shared by that institution, even if the institution does not itself conduct or perform the research.

6 The requirements of this Section, first subsection, are not applicable to national government services, institutions or companies specified by Our Minister. An aggrieved party shall have the same rights in relation to a national government service, institution or company without insurance of

the kind referred to in this Section, first subsection, as the said party would otherwise have had, in accordance with this Section, in relation to an insurer.

7 Neither the party performing the research nor, if this Section, fifth subsection should apply, the party conducting the research nor the facilitative institution, shall be entitled to limit or disclaim liability for injury or death resulting from the research.

4 Duties of the party conducting the research

SECTION 8

1 The party conducting the research shall be responsible for compliance with Section 2, first and second subsections, and with Section 7.

2 Under the circumstances described in Section 7, fifth subsection, second sentence, the facilitative institution shall share responsibility for compliance with Section 2, first and second subsections.

SECTION 9

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

5 Other duties of the party performing the research

SECTION 10

1 In the event of the research proving to be significantly less favourable to the subject than the research protocol had suggested, the party performing the research shall without delay notify both the subject (or, if the subject was unable under the provisions of this Act to give informed 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 research 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 party performing the research shall similarly notify the committee referred to in this Section, first subsection, in the event of the research being prematurely terminated, indicating the reasons for its termination.

SECTION 11

The party performing the research shall be responsible for ensuring that the subject is provided in good time with information as specified in Section 6, fourth subsection, second sentence, and seventh subsection, Section 7, Section 9, Section 10 and Section 12, and is kept informed about the progress of the research. Additional information shall be provided upon request. The party performing the research shall be responsible for similarly informing any other person from whom permission is required pursuant to Section 6.

SECTION 12

The party performing the research shall be responsible for ensuring that the private life of the subject is respected as far as possible.

SECTION 13

The party performing the research shall be responsible for ensuring that before research commences those whose professional assistance is required for the performance of the research are informed of its nature and aim.

6 The committees

SECTION 14

1 There shall be a central committee for medical research; it shall have at most thirteen members.
2 The members of the central committee shall include at least one doctor, persons with expertise in pharmacology, 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 A deputy shall be appointed for each member of the central committee.
4 The members of the central committee, including the chairperson and the deputies, 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 chairpersons from amongst their number.

6 Members and deputy members 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 deputy member may be relieved of his or her duties by royal decree prior to expiry of the six-year term of appointment, upon the recommendation of Our Minister.

7 Upon the recommendation of Our Minister, a member or deputy member 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 the six-year 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 deputy members of the central committee shall be paid attendance fees and travel and accommodation expenses, in accordance with rules made by order in council.

9 The central committee shall operate in accordance with standing orders which shall be subject to the approval of Our Minister. Changes to these standing orders shall also be subject to the approval of Our Minister. Our Minister shall withhold approval only if the standing orders may reasonably be deemed prejudicial to the proper performance of the central committee's duties.

SECTION 15

1 The central committee shall have a secretariat; the appointment of civil servants to, and their suspension and dismissal from the secretariat shall be undertaken 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 Regarding the performance of their duties, the civil servants of the secretariat shall be answerable to the central committee alone.

SECTION 16

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

2 The central committee shall not recognize 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, and a person charged with the task of examining protocols specifically from the subject's point of view;

b the committee's standing orders must make adequate provision for cooperation with other experts to enable proper review of the protocols submitted to the committee;

c the committee's standing orders must state the area in which the committee will be active;

d the committee's standing orders must properly regulate the committee's operations;

e there must be a reasonable expectation that the number of research protocols submitted to the committee for review will be at least the minimum specified by the central committee.

SECTION 17

1 Upon recognition being granted in accordance with Section 16, first subsection, the central committee shall notify Our Minister without delay.

2 Our Minister shall arrange for notice of recognition granted in accordance with Section 16, first subsection, to be given in the Government Gazette.

SECTION 18

A committee recognized pursuant to Section 16 shall notify the central committee in writing in the event of a change being made to the committee's standing orders.

SECTION 19

1 Within six weeks of the submission of a protocol for research of the kind referred to in Section 4, first subsection, second sentence, which research does 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 research of a certain category of the kind referred to in the first subsection 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 recognized 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 less favourable for the subjects than the research protocol had suggested. If, under such circumstances, the committee in question should find that the research is indeed less favourable than suggested, the committee may revise its earlier decision. Section 10, first subsection, 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 this Section, first subsection.
3 The provisions of this Section, first and second subsections, shall apply equally to the central committee, insofar as the latter is responsible for the review of research protocols pursuant to Section 2, second subsection, clause b, under 2°, 3° or 4°.

SECTION 22

1 The committee shall send the central committee a copy of each decision made 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 notice submitted in accordance with Section 10, second subsection.
2 Not 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 a decision made by the committee.

SECTION 24

The central committee shall monitor the activities of the other committees and shall be empowered to issue directives regarding the conduct of such activities as they carry out in accordance with this Act. Our Minister shall arrange for publication of such directives 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 a to d set out in Section 16, second subsection;
b if the committee fails to discharge adequately its responsibilities arising out of this Act;
c if the committee's standing orders 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, second subsection, under e.
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, second subsection, is similarly applicable.

SECTION 26

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

SECTION 27

1 Not 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.
2 Not less than once 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.

7 Miscellaneous provisions

SECTION 28

Compliance with the provisions of this Act or provisions made pursuant to this Act shall be monitored by public health inspectors appointed for the purpose by Our Minister, and by the civil servants working under these inspectors at the Public Health Supervisory Service.

SECTION 29

1 Insofar as may reasonably be deemed necessary for the fulfilment of their duties, the persons referred to in Section 28 shall be empowered to require the provision of information and the production of documents, and to make copies of such documents.
2 All parties shall have a duty to cooperate with the persons referred to in Section 28 in any way which may reasonably be deemed necessary to enable those persons to perform their duties.

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 interest of the State or its allies.

SECTION 31

1 Notwithstanding Section 7, first subsection, and Section 8, first subsection, of the Exceptional Situations Coordination Act, if exceptional circumstances should make it necessary, Section 32 may be brought into effect by royal decree, upon the recommendation of Our Prime Minister.
2 Should a decree of the kind referred to in the first subsection of this Section be issued, a bill regarding the term of the provision brought into effect by that decree shall be presented to the Lower House without delay.
3 In the event of the bill being rejected by the States General, the provision brought into effect in accordance with the first subsection of this Section

shall be suspended by royal decree, upon the recommendation of Our Prime Minister, without delay.

4 The provision brought into effect in accordance with the first subsection of this Section 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 the first, third or fourth subsection of this Section shall be published in a manner specified in that decree. Any such decree shall come into force upon its publication.

6 Any decree of the kind referred to in the first, third or fourth subsection of this Section shall in any event be entered in the Bulletin of Acts, Orders and Decrees.

SECTION 32

Our Minister may, with the agreement of Our Minister of Defence, suspend Section 16, second subsection, under a, and Section 25, first subsection, under a, in relation to committees charged with the review of research relating to protection against the conditions to which military personnel may be exposed on operational duty, insofar as such research involves military personnel as subjects.

8 Penalty provisions

SECTION 33

1 Any person who intentionally or unintentionally contravenes a prohibition contained in Section 6, first subsection, shall be punished by imprisonment for a period not exceeding one year or by imposition of a fine of the fourth category.

2 Any person who fails to discharge his or her responsibility for compliance with Section 2, first or second subsection, or Section 7, or who fails to perform a duty referred to in Section 5 or the duty referred to in Section 29, shall be punished by imprisonment for a period not exceeding six months or by imposition of a fine of the fourth category. Any person who contravenes a prohibition contained in Section 4 or Section 5, or who performs research for which no protocol has been approved, or who performs research in a manner contrary to the protocol approved for it, shall receive a similar punishment.

3 Acts or omissions punishable in accordance with the first subsection of this Section shall be deemed indicatable offences; acts or omissions punishable in accordance with the second subsection of this Section shall be deemed summary offences.

9 Concluding provisions

SECTION 34

The full stop following the words “Section 41b” in lists A and B accompanying the Exceptional Situations Coordination Act shall be replaced by a semicolon, after which the words “of the Medical Research Involving Human Subjects Act: Section 32.” shall be added.

SECTION 35

When the act of 20 June 1996 supplementing the General Administrative Law Act (General Administrative Law Act: Third Tranche) comes into force, Sections 28 and 29 shall be replaced by a single section, the text of which shall be as follows:

“Section 28

1 Responsibility for supervising compliance with the provisions of this Act or provisions made pursuant to this Act shall rest with the officials of the Public Health Supervisory Service appointed by Our Minister.
2 Any appointment of the kind referred to in the first subsection of this Section shall be published in the Government Gazette.”

SECTION 36

When the act of 20 June 1996 supplementing the General Administrative Law Act (General Administrative Law Act: Third Tranche) comes into force, the passage“, or with the obligation contained in Section 29” in Section 33, second subsection, first sentence, shall be deleted.

SECTION 37

Within four years of this act coming into force, and thereafter at five-year inter-

vals, 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 Sport

The Minister of Justice

Appendix II

Regulations on the Central Review of Medical Research Involving Human Subjects Decree
(Central Review of Medical Research Involving Human Subjects Decree)

(The translation below is not certified and it has not been authorized by the Dutch government)

On the recommendation of 7 December 1998, of Our Minister of Health, Welfare and Sport, DWJZ-U-981341, made on behalf of Our Minister of Justice;
Having taken into account section 2, subsection 2, under b 4°, of the Medical Research Involving Human Subjects Act;
Having heard the Council of State (advisory report of 21 January 1999, no.W13.98.0574);
Having seen the subsequent report of February 1999, DWJZ-U-99188, of Our Minister of Health, Welfare and Sport, also published on behalf of Our Minister of Justice;
We have approved and decreed:

SECTION 1

The research protocol for the following types of medical research shall require the approval of the central committee referred to in section 14 of the Medical Research Involving Human Subjects Act:

a medical research in which intentional alterations to genetic material in human-body cells are made;
b medical research in which animal parts are introduced or applied into or onto the body of a human being.

SECTION 2

This decree shall come into force on a date determined by royal decree.

SECTION 3

This decree shall be known as the: Central Review of Medical Research Involving Human Subjects Decree.

We order and command that this decree shall be published in the Bulletin of Acts, Orders and Decrees (Staatsblad).

The Minister of Health, Welfare and Sport,

The Minister of Justice,

Appendix III

Decree of 5 July 1999, regulating obligatory insurance for medical research involving human subjects. (Temporary decree regulating obligatory insurance for medical research involving human subjects.)

(The translation below is not certified and it has not been authorized by the Dutch government)

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

On the advice of Our Minister of Justice, as presented on 2 November 1998, under reference number 725342/98/6, on his own behalf and that of Our Minister of Health, Welfare and Sport,
In view of the provisions of Section 7, clause 3, of the Medical Research Involving Human Subjects Act;
We, having heard the Council of State (report of 4 January 1999),
And having taken account of the further report of Our Minister of Justice, dated 28 June 1999, under reference number 773851/99/6, produced in his own name and in the name of Our Minister of Health, Welfare and Sport,
Have approved and decreed as We hereby approve and decree:

SECTION 1

In the context of this decree, the meanings of the following terms shall be as specified below.
a Act: the Medical Research Involving Human Subjects Act;
b insurance: insurance of the kind referred to in Section 7 of the Act.

SECTION 2

The insurance shall be closed and maintained by an insurer who is in possession of a licence, or who meets the requirements of Section 37 or 38 of the 1993 Insurance Industry Supervisory Board Act regarding the maintenance of a branch office in the Netherlands, or who, if he provides services in the Netherlands of the kind referred to in the said act, complies with the provisions of Section 111, subsection 1, clauses a to c, or clause 2, or Section 113, subsection 1 or subsection 4, or Section 116, subsection 1, clauses a to c, or subsection 3, or Section 118, subsection 2 or subsection 5, of the said act.

SECTION 3

1 The minimum sum insured shall be NLG 1,000,000 per subject and NLG 15,000,000 per research project. However, if the party conducting the research is conducting or has conducted one or more other medical research projects, the minimum total sum insured for injuries arising out of these activities shall be NLG 20,000,000 per insurance year. In the event of the contract of insurance being terminated, a further sum of at least NLG 20,000,000 shall be insured for injuries coming to light in the five-year period referred to in Section 5, subsection 1, of the Act.

2 If there should be more than one injured party and if the total amount of the injuries due to the injured parties should exceed an insured sum, the insurer's liability towards each injured party shall be reduced proportionately, to the point where the insured sum is sufficient to meet that liability. Nevertheless, if the insurer, being unaware of the existence of other injured parties, should in good faith pay one injured party a greater sum than that to which the said party is properly entitled, the insurer's total liability towards the other injured parties shall be limited to that part of the total sum insured which remains after payment of the first party.

SECTION 4

1 If, in the opinion of the committee responsible for reviewing the research protocol in question, the nature of the research is such that participation entails no inherent risk for the subject, and if the research protocol is approved, the said committee may, at the request of the party conducting the research, discharge the latter from his obligation to close a contract of insurance.

2 If, in the opinion of the said committee, the nature of the research is such that for the subject the risk inherently associated with participation is negligible or minimal, and if the research protocol is approved, the said committee may, at the request of the party conducting the research, grant the latter dispensation with regard to the minimum sums insured, subject to the understanding that the absolute minima corresponding to those cited in Section 3 are NLG 150,000 per subject, NLG 3,000,000 per research project and NLG 5,000,000 per insurance year. Under such circumstances, Section 3, subsection 2, shall remain applicable.

SECTION 5

1 The insurance shall cover death and injury to the subject occurring or coming

to light while the subject is participating in the research, as well as death and injury occurring or coming to light during the five-year period immediately following the subject's participation in the research. Injuries shall be deemed to have come to light at the time that the insurer is notified.

2 The insurance need not cover injury suffered by the subject's progeny as a result of the adverse effects of the research on the subject's genetic material.

3 The insurance need not cover injury to the subject's health which would also have come to light if the subject had not participated in the research.

SECTION 6

1 An insurer shall not be entitled to deny a claim by an injured party on the grounds of invalidity, counterclaim or dissolution arising out of the legal provisions governing the insurance contract or out of the insurance policy itself. The provisions of the preceding sentence apply only up to the minimum sum or sums which must be insured. However, an insurer shall be entitled to deny a claim by an injured party on the grounds of counterclaim or dissolution arising out of the injured party's own failure to meet his obligations, provided that this failure is significantly detrimental to the insurer's interests.

2 An insurer who, pursuant to the provisions of subsection 1, settles in full or in part a claim made by an injured party, even though the injury suffered by the injured party is not covered by a contract of insurance closed with the insurer, shall be entitled to recover from the party who conducted the research the compensation paid.

SECTION 7

1 Before consent of the kind referred to in Section 6 of the Act is requested, the party performing the research shall ensure that the party whose consent is required is informed in writing of the sums insured, the exclusions of the insurance, and of the name and address of the insurer. If the party conducting the research has been discharged from his obligation to close a contract of insurance, the person whose consent is required shall be informed of this fact in writing by the party performing the research.

2 The party performing the research shall ensure before consent is requested that the subject or, where relevant, the person from whom consent is required pursuant to Section 6 of the Act, is informed in writing in the Dutch language of the obligations imposed on him by the contract of insurance.

SECTION 8

This decree shall take effect on a date to be fixed by royal decree and shall expire three years after the date of entry into force.

SECTION 9

This decree shall be known as the Temporary Decree on Obligatory Insurance for Medical Research Involving Human Subjects.

We order and command that this decree and the associated explanatory notes be entered in the Bulletin of Acts, Orders and Decrees.

The Minister of Justice,

The Minister of Health, Welfare and Sport,

Explanatory notes

GENERAL

This decree regulates obligatory insurance for medical research involving human subjects, which is required under Section 7 of the Medical Research Involving Human Subjects Act. First, it sets out the minimum sums which must be insured and specifies certain criteria which the insurer must meet. The decree also states the minimum periods of time which must be covered by the insurance policy. It includes a special provision defining the risks which may be excluded from cover and creates certain rights for the subject in relation to the insurer.
The insurance referred to in Section 7 of the Act shall provide compensation in the event of the subject suffering death or injury, irrespective of whether the researchers are guilty of negligence. However, if the death or injury is attributable to negligence, the party performing the research is also liable towards the subject. This can be important to the subject if, in the event of serious injuries, the sum insured is insufficient to meet all claims, or if the death or injury does not occur or become apparent until after the period covered by the insurance. If the party performing the research is found to be liable, the Act states (Section 7, subsection 5) that the party conducting the research is also liable. The party conducting the research is defined in the Act (Section 1, subsection 1, clause f) as the party who ordered the research to be organized or performed. Hence, there is another party to whom any injured subject can turn for redress.
Account is taken of the fact that some research, by its very nature, entails no inherent risk for the subject. In such cases, it would be pointless to require the researchers to take out insurance. The committee responsible for reviewing a given research protocol is therefore allowed to release the party conducting the research from the general obligation to take out insurance (see Section 4, subsection 1, of the decree). Provision is also made for research whereby the risk for the subject is inherently minimal or negligible; in these cases, the committee can give the party conducting the research permission to obtain a lower level of cover (see Section 4, subsection 2, of the decree). Scope for these provisions is created by the Act (Section 7, subsection 3), which states that departures from the provisions of subsection 1 (including, therefore, those regarding obligatory insurance) may be introduced by Order in Council.
This decree was drawn up after consultation with the Association of Dutch Insurers and other interested organizations, including the Dutch Patients' and Consumers' Federation (NP/CF), the Dutch Association of the Research-based Pharmaceutical Industry (Nefarma) and the Netherlands Association of Medical

Ethics Committees (NVMETC). The Association of Dutch Insurers indicated that only foreign insurances could presently offer insurance for the sums specified in Sections 3 and 4, and that, given the provisions of Section 6, subsection 1, almost none would be likely to. However, the Association of Dutch Insurers has indicated that in the case of a limited term of validity of this decree, it is expected that insurers affiliated with the Association will be able to arrange cover for this limited term. Section 8 of this decree establishes a term of validity for this decree of three years. The decree will be evaluated during this period in the light of developments in liability jurisdiction in general. Taking account of the results of the evaluation and of developments in medical liability jurisdiction in particular, a new decree will be prepared.

In this context, it is worth noting that a survey of Nefarma members revealed that Dutch pharmaceutical companies are nearly all covered by foreign insurers. In general, the survey indicated that the insurances carried by such companies already meets the requirements of this decree in most respects, and that the financial and other consequences of this decree's implementation for the industry would therefore be limited. It may be assumed that most pharmaceutical companies will simply need to make a one-off modification to their insurance contracts. Hence, the decree is not expected within the industry to interfere with the pharmaceutical companies' research activities in the Netherlands.

Nor is it anticipated that the decree will compromise the ability of other institutions, such as hospitals, to conduct research involving human subjects. The regulations set out in this decree should not prevent such institutions obtaining insurance at a cost which is acceptable, given the nature of the research.

Notes regarding individual sections of the decree

SECTION 2

This section of the decree states that the contract of insurance must be closed with and maintained by an insurer who meets the requirements for access to the insurance market in the Netherlands, pursuant to the 1993 Insurance Industry Supervisory Board Act. In this way, the decree seeks to provide the best possible guarantee that the insurer will honour his obligations towards any subject who might suffer injury as a result of participation in the research.
As indicated in the general notes, nearly all Dutch pharmaceutical companies are covered by foreign insurers, most of whom already meet the requirements of this section. Some of these insurers have branch offices in the Netherlands, while others conduct their business from abroad. Where pharmaceutical companies are covered through foreign parent companies by foreign insurers who do not meet the requirements of this section, the insurer should be able to achieve compliance without undue difficulty.
It should also be noted that, where multi-centre trials (research projects performed at several hospitals are concerned, a single insurance policy is sufficient to comply with the decree, in much the same way as the approval of a single review committee is required.

SECTION 3

This section specifies the minimum sums which must be insured. Under Section 8 of the Act, the duty to obtain insurance lies with the party that conducts the research. In most cases, this party is a pharmaceutical company, although the research – which typically involves a new medicinal product – will often be performed by a hospital. Sometimes, however, the research will focus on a method or technique which is thought to have potential medical benefits; in such cases, the party conducting the research is normally a hospital or other care institution, such as a nursing home.
The sums specified in subsection 1 are sums for which cover is available: NLG 1,000,000 per subject, NLG 15,000,000 per research project and NLG 20,000,000 per insurance year. The decree does not prevent the responsible party obtaining higher levels of insurance cover.
A total per insurance year is specified because pharmaceutical companies and hospitals generally have tacitly renewable or “rolling” insurance policies, which provide cover for all medical research (as defined in the Act) undertaken in the course of a year. In any given year, it is possible that subjects will suffer death or

injury during the course of or following completion of more than one research project. The cover provided for all claims arising under such circumstances has to be at least NLG 20,000,000 per year.
A subject can also die or develop the first signs of injury after the termination of a tacitly renewable insurance policy which was in force at the time of the research in which the subject was involved. Section 5 of the decree accordingly requires that the insurance taken out must at least provide cover for death or injury suffered by subjects within five years of participation. During this period, which may, of course, extend beyond termination of the policy, a sum of at least NLG 20,000,000 must remain insured in accordance with the third sentence of subsection 1.
Consideration has been given to the affordability of insurance for the sums specified, given that some of the parties conducting research (e.g. hospitals) lack the resources of pharmaceutical companies. However, it would be difficult to justify a situation whereby the degree of protection offered to subjects differed, depending on the nature of the party conducting the research. In this context, readers are referred to the content of Section 4, which makes it possible for a party conducting a research project to obtain a special dispensation: if the research involves no risk, the obligation to take out insurance can be waived altogether, while lower levels of cover can be obtained for research which involves minimal or negligible risks.
Subsection 2, which is based upon Section 6, subsection 2, of the Motor Insurance Liability Act (Wam), and Section 12, subsection 2, of the Hunting Act, regulates situations in which there is more than one injured party and the sum insured per research project or per insurance year is not sufficient to meet all the claims in full. The provisions of the decree ensure that, in principle, all injured parties are entitled to proportional compensation. This subsection applies whether the party conducting the research is insured for the minimum sum(s) only, or for (a) higher amount(s). It is possible, however, that an insurer, being unaware of the existence of other injured parties, settles one or more claims by paying to the claimant(s) more than would strictly have been due on a proportional basis if the existence of all injured parties had been taken into account. The second sentence of this subsection provides for such an eventuality, by stating that, if an insurer in good faith overcompensates a claimant, the insurer's total liability towards other injured parties is limited to the remaining portion of the sum insured.

SECTION 4

Some research of the kind covered by the Act entails no inherent risk for the subject. The Act regulates not only research aimed at the development or

improvement of diagnostic or curative treatments, but also observational research, in which subjects can often participate without placing themselves at risk. Such research may involve discomfort for the subject, but under circumstances which, given the nature of the research, involve no inherent risk.
All non-invasive observational research – such as studies which simply involve urine analyses, breath analyses or electroencephalography (obtaining EEGs) – generally comes under this category. If the possibility of the subject suffering injury as a result of participation in the research can be excluded, there is no reason for insurance. Parties applying to conduct research which involves no inherent risk for the subject may therefore ask the committee responsible for reviewing the research protocol to exempt them from the normal insurance obligation. The committee may only grant such exemption if the research unquestionably entails no inherent risk for the subject.
The nature of a research project may also be such that, while the possibility of the subject suffering injury as a result of participation cannot be entirely excluded, the inherent risk may be regarded as minimal or negligible. Thus, much observational-invasive research entails a known risk, since it involves procedures which are commonplace and standard within the health care sector. Such research will frequently involve nothing more than taking a blood sample from the subject, for example. This procedure, performed once on a healthy adult, might be deemed to involve no risk at all. However, if the subject is an infant or an unhealthy adult, it is more reasonable to conclude that a minimal or negligible inherent risk exists. Trials of slightly modified versions of established low-risk nursing procedures might similarly be considered to involve minimal or negligible risk for the subjects. A party wishing to conduct such research could find insurance of the sums specified in Section 3 prohibitively expensive. For the risk associated to be deemed minimal or negligible, not only must the likelihood of injury be very small, but the nature of any potential injury must be very minor. Concerning the magnitude of the risks, it may also be of importance whether the injury would also come to light without the subject's participation in the research. A reason for this is, amongst others, that the inherent risk of this injury can be excluded from the insurance cover on the basis of Section 5, subsection 3.
It should be noted that Section 4 of the Act prohibits the participation of incapacitated persons as subjects in non-therapeutic medical research projects unless the risk to them is at worst negligible. Consequently, since a research project involving incapacitated persons as subjects must by definition entail no more than a negligible risk, it is sufficient for the party conducting the research to obtain insurance for the lower sums specified in the relevant section (if, indeed, there is any risk at all).
If, when the research is planned and assessed, it is anticipated that the risk for subjects will at worst be minimal or negligible and the potential injuries will not

exceed the sums specified in this section, the party conducting the research may ask the committee responsible for reviewing the research protocol to grant a dispensation, whereby lower levels of insurance may be obtained. Again, the committee may only grant this request if the nature of the research is such that the inherent risk for the subject may unquestionably be regarded as minimal or negligible. Under such circumstances, the sums insured must be consistent with the nature of the risk and must be at least NLG 150,000 per subject, NLG 3,000,000 per research project and NLG 5,000,000 per insurance year. The latter figure (the sum insured per insurance year) is only relevant in cases where the party conducting the research is also conducting one or more other projects for which a similar dispensation has been granted.

It should be noted that the risks which are relevant in the context of this section are only those which stem from the nature of the research itself, i.e. the inherent risks associated with participation. Such risks do not include those which derive from the possibility of negligence on the part of the party performing the research. Hence, when assessing the level of risk associated with a research protocol in accordance with this section of the decree, a review committee should not make allowance for the possibility of negligence. If a subject suffers death or injury as a result of negligence, the party performing the research is liable on the grounds of unlawful behaviour or default, which can be significant if the insured sum is insufficient to meet the claims of all injured parties.

Consideration has been given to the possibility of research being conducted by a government body, institution or company, of the kind referred to in the Act (Section 7, subsection 6). Such entities are exempt from the obligation to take out insurance. Section 4 of the decree makes provision for situations in which, given the level of risk associated with participation, it would be unreasonable to expect the party conducting the research to take out insurance, or to obtain the level of cover specified in Section 3. This presents no problems in relation to government bodies, institutions and companies which are exempt from the obligation to take out insurance. However, the level of risk can be relevant in relation to such entities' payment obligations, since an injured party would be entitled to redress from such an entity, consistent with that to which he would have been entitled if insurance had been taken out. In the event of a subject suffering injury or death, such an entity might therefore claim that the injured party had no right to compensation, or was entitled only to a level of compensation consistent with the sums specified in Section 4, on the basis that the research entailed no risk or only a minimal or negligible risk. However, if a subject were to suffer injury or death as a result of participation in research which such an entity claimed to entail no inherent risk, the explanation would have to be either that the entity's claim was false, or that the research was negligently carried out. In either case, the party conducting the research would

be liable to compensate the injured party on the grounds of unlawful behaviour or default. A similar situation would exist if a subject were to suffer injuries valued at more than NLG 150,000 as a result of participation in research which such an entity claimed to entail only minimal or negligible risk: again, either the entity's claim was false, or the research was negligently carried out. So the party conducting the research would be liable to compensate the injured party for injuries up to and in excess of NLG 150,000. Consequently, parties conducting medical research are liable for up to the sums specified in Section 3 of the decree, and possibly more, if subjects suffer injury or death as a result of negligence.

SECTION 5

Section 7 of the Act states that the insurance must cover the subject's injury or death as a result of the research. In its first subsection, Section 5 of the decree additionally specifies the minimum period for which this cover must be valid. Its provisions are formulated both with tacitly renewable insurance and with policies covering individual research projects in mind. It establishes a minimum period of cover beyond the date of participation, which applies in the event of policy termination, while providing limitation in the event of the policy continuing in force. The insurance has to cover death or injury occurring during participation and death or injury occurring or coming to light in the five years following participation. It should be noted that an injury may be deemed to have been suffered even though the subject has yet to suffer its adverse effects. Provided that sufficient certainty exists regarding their manifestation, future injuries of the kind referred to in Article 6:105 of the Civil Code (loss of income, medical expenses, etc) may, for example, be claimed. The point at which a subject's participation in a medical research project ends will normally be clear. In most cases, it will be the last day that, in the context of the research project, substances are administered to the subject and/or that the subject receives medical treatment such as a final check-up.

To prevent injured parties making claims against insurance companies long after the period covered by a policy, injury is deemed to have come to light at the time it is reported to the insurer. It does not matter who reports the injury, since the object is simply to ensure that injuries are reported promptly. If a subject should suffer injury which does not come to light within the period covered by the insurance, it is quite possible that the injured party will be able to make a claim against the party who performed the research, assuming that the latter was demonstrably negligent. In this context, readers are also referred to the points made in the general notes, regarding Section 7, subsection 5, of the Act.

The second and third subsections of Section 5 of the decree specify classes of

injury for which insurance cover is not compulsory. In the second sub-section this concerns injuries suffered by the subject's offspring as a result of injuries done to the subject's genetic material in the course of the research. The medical research liability insurance policies currently available generally exclude injuries of this kind. The provisions of the decree do not, however, prevent the inclusion of such injuries within the scope of the policy.
The third subsection offers the possibility of excluding from the insurance cover injury which would also have come to light if the subject had not participated in the research. This is also a standard exclusion in the policies currently available. An example would be injury resulting from the subject's illness, which would also have come to light without participation in the research. If, however, the insurer wants to invoke this exclusion because he is of the opinion that a certain injury would also have come to light without the research, then the burden of proof is on him.
Furthermore, the policies currently available usually contain various other standard exclusions which are also linked to Section 7 of the Act. The first of these is injury which, in view of the nature of the research, was certain or almost certain to occur, as referred to in the second sentence of Section 7, subsection 1. Second, there is injury which results from the subject's failure to follow instructions or directions which he was capable of following. This exclusion is based upon Article 6:101 of the Civil Code, which applies equally in cases of the kind regulated by the Act. Further exclusions are considered undesirable. Consequently, no special provisions limiting the scope of cover other than those made in Section 5 of the decree are necessary or, indeed, permissible.

SECTION 6

The aim of making insurance compulsory is to ensure that subjects who volunteer to act as medical research subjects, and who thus generally serve the public interest, do not go without compensation for any injuries they might suffer as a result. The decree therefore states that such individuals cannot be denied compensation by the insurer, despite the existence of an insurance policy, on the grounds of invalidity, counterclaim or dissolution. Thus, a subject cannot become the innocent victim of, for example, policy suspension resulting from the non-payment of a premium instalment. The protection afforded to the injured party by the provisions of this section of the decree is limited to the minimum sums for which insurance is required. However, an insurer can deny an injured party compensation on the grounds of counterclaim or dissolution arising out of the latter's own failure to meet his obligations, provided that the failure in question was significantly detrimental to the insurer's interests. So, for example, a claim may be denied if the injured party has failed to report the injury to the

insurer within a specified reasonable period, or to provide the insurer with the necessary information or documentation. On the basis of Section 7 of this decree the subject must be informed in writing of the obligations imposed upon him by the contract of insurance before he gives his consent.
Similar provisions are made in Section 11, subsection 1, of the Wam and Section 12b, subsection 3, of the Hunting Act. The inclusion of such provisions in this decree is actually even more important than it is in the latter pieces of legislation, since, where compulsory liability insurance is concerned, if no insurance is in place, an injured party can always turn to the liable party for redress. However, with direct liability insurance of the kind provided for in the Act, it is not always the case that someone is liable for any injuries which may be suffered. It should be noted that the Wam and the Hunting Act also allow for claims to be made directly against the insurer. Such a provision is not required in the decree, because with direct liability insurance, the subject is the insured party, so the insurer automatically bears directly liability to the subject in the event of injury.
Section 6 of the decree could have the effect of obliging the insurer to offer any injured party wider cover than that which the policy holder has actually paid for. The hypothetical situation described earlier – in which a policy is suspended because the party conducting the research has failed to pay a premium instalment – again serves as an example of the circumstances under which this might be the case. Section 6, subsection 2, of the decree (which is based on Section 12b, subsection 3 of the Hunting Act) accordingly allows the insurer to reclaim from the party conducting the research any compensation the former is obliged to pay to injured parties above and beyond that due under the terms of the insurance policy.

SECTION 7

Every subject (or the person empowered to act on the subject's behalf, in accordance with Section 6 of the Act) must give his informed consent to participation in the research project. In this context, it is essential that the prospective subject (or his representatives) is told whether insurance cover is provided for him. If such insurance cover is provided, for purposes of his consent it is of importance that he knows the sums and the exclusions of the insurance. It is also essential that the subject is given the name and address of the insurer in good time, since it is to the insurer that the subject must go if he wishes to claim compensation for any injury suffered. This information must be given to the subject in writing as part of the provision of information necessary for his consideration of whether to consent to take part in the research.
The person in question is then able to take everything into account before arriving at a decision regarding participation. Section 7, subsection 1, accordingly

states that the party performing the research must provide each prospective subject with written details of the insurance arrangements before asking whether he wishes to participate.
The party performing the research is also responsible for providing the subject with written information on the obligations imposed upon him by the policy, before the subject gives his consent. This information is particularly important to the subject in the case of sanctions, such as invalidity of the claim, resulting from his failure to comply with these obligations. Because it is expected that many contracts of insurance will be entered into outside of the Netherlands, it has been stipulated that the subject is to be informed in writing in the Dutch language. Section 7, subsection 2, states that this information is also to be provided to the subject even though, according to Section 6 of the Act, consent is required from another person, because the obligations will nevertheless still be imposed upon the subject.

The Minister of Justice,

The Minister of Health, Welfare and Sport

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The Medical Research Involving Human Subjects Act aims to provide protection to subjects who take part in medical research. This brochure explains what the Act regulates, the parties for which the Act is intended and how it will operate in practice. Amongst other things, there is a discussion of the new method of review and its consequences, especially for local review committees and researchers.
The establishment of the central committee and its role vis-à-vis the local review committees are discussed separately

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