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Decree of 23 June 2003 containing rules for compulsory insurance in medical research involving human subjects (Medical Research (Human Subjects) Compulsory Insurance Decree)

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

On the recommendation of Our Minister of Justice of 3 April 2003, no. 5219262/03/6, made in agreement with the State Secretary for Health, Welfare and Sport,

Having regard to section 7, subsection 3 of the Medical Research (Human Subjects) Act,

Having heard the Council of State (report no. W03.03.0138/I of 28 May 2003),

Having seen the further report of Our Minister of Justice of 18 June 2003, no. 5230446/03/6, issued in agreement with the State Secretary for Health, Welfare and Sport;

Have approved and decreed:

Article 1

For the purposes of this Decree, the following definitions shall apply:

- a. Act: the Medical Research (Human Subjects) Act;
- b. insurance: the insurance referred to in section 7 of the Act;
- c. ending of participation in the clinical trial: the time at which the human subject within the meaning of section 1, subsection 1 (b) of the Act is no longer subject to treatment or is no longer required to conduct himself in a certain manner.

Article 2

- 1. Insurance shall be taken out and maintained with an insurer that is licensed within the meaning of section 24, subsection 1, of the Insurance Supervision Act 1993 or that satisfies the procedure required pursuant to section 37 or 38 of that Act with regard to an office in the Netherlands or, if the service referred to in that Act is provided to the Netherlands, satisfies

the provisions of section 111, subsection 1 (a to c) or subsection 2, section 113, subsection 1 or 4, section 116, subsection 1 (a to c) or subsection 3, or section 118, subsection 2 or 5, of the Act.

2. If the insurance is taken out with an insurer that has its registered office outside the Netherlands, the policy shall name a loss adjuster with a registered office in the Netherlands that shall deal with and settle insurance claims.

Article 3

1. The sums insured shall be €450,000 per subject and €3,500,000 per clinical trial. However, if the sponsor is sponsoring or has sponsored more than one clinical trial, the sum insured, subject to the amount for which the insurer may be held liable per clinical trial, shall be €5,000,000 in respect of losses caused by a clinical trial that manifest themselves during the insurance year. For the purposes of the previous sentence, a loss shall be deemed to have manifested itself when it is reported to the insurer.
2. If a clinical trial is conducted by more than one institution and the loss suffered by the subjects is insured by the institution at which they participate in the clinical trial, the total sum insured jointly for that clinical trial shall be €3,500,000.
3. Upon the insurer's cancellation of an insurance agreement, the losses referred to in the first sentence of article 5, paragraph 1 suffered by subjects who had started to participate in the clinical trial before the agreement was cancelled shall in any event be covered. Upon the policyholder's cancellation of an insurance agreement, the losses referred to in the first sentence of article 5, paragraph 1 suffered by subjects whose participation in the clinical trial had ended before the agreement was cancelled shall in any event be covered. With due regard to the insurer's liability per clinical trial if more than one clinical trial is insured, the cover provided by a cancelled insurance agreement for losses that manifest themselves after the cancellation shall be €5,000,000.
4. Notwithstanding the first and second sentences of paragraph 3, upon cancellation of an insurance agreement taken out by an institution, the losses referred to in the first sentence of article 5, paragraph 1 suffered by subjects who are or are about to start participating in a clinical trial that commenced before the cancellation of the agreement shall be covered. For the purposes of the previous sentence, the clinical trial shall commence on the day that the committee responsible for assessing the trial protocol in question approves that protocol. The third sentence of paragraph 3 shall apply.

5. If more than one subject has suffered a loss and the total amount of the compensation payable exceeds the sum insured, the subjects' rights vis-à-vis the insurer shall be reduced in proportion to the sum insured. An insurer that is unaware of the existence of claims made by other subjects and that has, in good faith, paid a greater amount to a subject than the part to which he was entitled shall nevertheless be obliged to pay the others only up to the amount of the remaining part of the sum insured.

Article 4

1. 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.
2. 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.

Article 5

1. Having regard to article 6, the insurance shall cover losses due to the death or injury of a subject as a result of the occurrence of risks attaching to the clinical trial that had not been explained to the subject in writing in accordance with section 6, subsection 3 (b) of the Act and also of risks attaching to the clinical trial that had been explained to the subject in writing but which proved more serious than foreseen and of risks that had been explained to the subject in writing but which had been thought during the preparation and assessment of the protocol in question to be so improbable in an individual case that their potential occurrence had not prevented the committee from approving the protocol. The losses referred to in the previous sentence shall be covered if they manifest themselves during the subject's participation in the clinical trial or within four years of the end of his participation in the clinical trial. For the purposes of the previous sentence, a loss shall be deemed to have manifested itself when it is reported to the insurer.
2. The insurance need not cover losses:
 - a. that are due to the subject's health problems not being alleviated or the subject's health problems deteriorating further if the subject participated in the clinical trial as part of the treatment of those health problems;

- b. that are due to the subject's health being impaired if it is plausible that the subject's health would also have been impaired if he had not taken part in the clinical trial;
 - c. that are due to the subject's health being impaired owing to his participation in a comparative clinical trial as referred to in article 4, paragraph 2 if it is plausible that the losses were the result of the treatment referred to in that paragraph being administered to the subject;
 - d. that manifest themselves in a descendant of the subject as a result of the clinical trial having an adverse effect on the subject or the descendant.
3. The insurance shall cover losses suffered by natural persons only.

Article 6

1. The insurance shall cover only:
- a. losses due to the subject's inability to work up to a maximum of €60,000 per annum;
 - b. loss of livelihood suffered by the persons referred to in article 108, paragraph 1, Book 6 of the Dutch Civil Code up to a maximum of €60,000 per annum;
 - c. the cost of domestic help up to an amount of €7.50 per hour if hiring such help is reasonable;
 - d. the right to compensation for non-financial loss, provided the compensation is not less than €1,500 and in so far as the total of such compensation is not more than €45,000;
 - e. losses referred to in article 108, paragraph 2, Book 6 of the Dutch Civil Code up to a maximum of €10,000;
 - f. reasonable costs in respect of medical assistance, medical facilities, devices and adaptations up to a maximum of €50,000;
 - g. reasonable costs in respect of transport by taxi or public transport and reasonable costs in respect of private transport to an amount of €0.40 per kilometre up to a maximum of €10,000.
2. If a right to compensation can be claimed under another insurance policy or under any law or other provision but full compensation cannot be received therefrom, the insurance shall cover the losses and costs referred to in paragraph 1 in so far as is necessary to compensate the subject for such losses and costs in full. Notwithstanding the first sentence, if someone is liable for losses due to the subject's death or injury, the insurance shall cover the losses and costs referred to in paragraph 1 as though that liability did not exist.

Article 7

Articles 98, 99, 103, 104, 107a, paragraph 2, and 109 of Book 6, Title 1, Part 10 of the Civil Code shall not apply to the insurer's obligation to provide compensation for losses in accordance with the Act and this Decree.

Article 8

1. An insurer may not invoke invalidity, counterclaim or dissolution against the subject if such arises from statutory provisions concerning the insurance agreement or from the agreement itself. Counterclaim or dissolution arising from the subject's non-fulfilment of an obligation resting upon him may be invoked against the subject, except in so far as such non-fulfilment does not harm a reasonable interest of the insurer. The provisions of the first sentence shall apply only to the amount or amounts for which the insurance must be taken out. The first sentence shall not apply in respect of subjects who begin to participate in the clinical trial after the end of the insurance agreement or the cover unless their losses are covered regardless of the agreement having ended.
2. An insurer who compensates a subject pursuant to the provisions of paragraph 1 in whole or in part for losses suffered, even though the losses were not covered by an agreement concluded by it, may recover the amount of the compensation from the person with whom it concluded the agreement.

Article 9

1. Before requesting the consent referred to in section 6 of the Act, the investigator shall ensure that the person whose consent is required is informed in writing of the sums insured, exclusions from the insurance in so far as they may be invoked against the subject, and the name and the address of the insurer and, in the event referred to in article 2, paragraph 2, of the loss adjuster. If the sponsor is exempt from the obligation to take out insurance, the person whose consent is required shall be informed thereof in writing by the investigator.
2. Before consent is requested, the investigator shall also ensure that the subjects are informed in writing in Dutch about their obligations under the insurance agreement. There shall be a similar requirement with regard to the other persons whose consent is required pursuant to section 6 of the Act.

Article 10

Derogations from this Decree may not be to the detriment of the subject.

Article 11

This Decree shall not apply to clinical trials whose protocol had been approved by the committee responsible for its assessment before this Decree enters into force. The Interim Medical Research (Human Subjects) Compulsory Insurance Decree, as applicable up to the date on which this Decree enters into force, shall remain applicable to such clinical trials.

Article 12

This Decree shall enter into force on 1 September 2003.

Article 13

This Decree may be cited as the Medical Research (Human Subjects) Compulsory Insurance Decree.

We order and command that this Decree and the Explanatory Memorandum pertaining to it shall be published in the Bulletin of Acts and Decrees.

Done at The Hague on 23 June 2003

Beatrix

The Minister of Justice,
J.P.H. Donner

The State Secretary for Health, Welfare and Sport,
C.I.J.M. Ross-van Dorp

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The Minister of Justice,
J.P.H. Donner

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Sdu Uitgevers
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The Council of State's recommendation has been made public by its display for inspection at the Ministry of Justice. The recommendation, together with the relevant documents, will also be published in the supplement to the Government Gazette of 8 July 2003, no. 128.

Explanatory Memorandum

General

1. Introduction

This Decree contains certain further rules for the compulsory insurance in medical research involving human subjects, as provided for in section 7 of the Medical Research (Human Subjects) Act ("the Act"). The rules mainly relate to the sums that must be insured, the losses covered and the insurer with whom the insurance must be taken out. The Decree also lays down the minimum duration of the cover, includes a special provision on what losses may be excluded from the cover and contains a "personal right" of the subject vis-à-vis the insurer.

This Decree replaces the Interim Medical Research (Human Subjects) Compulsory Insurance Decree ("the Interim Decree"), which will cease to have effect as of 1 September 2003 when this present Decree enters into force. In view of the circumstances in which the Interim Decree was drafted – insurance cover could be provided by virtually only foreign insurers, although members of the Dutch Association of Insurers could provide cover if the duration was limited – the Interim Decree was introduced for a period of three years (which period was extended by Decree of 26 August 2002 (Bulletin of Acts and Decrees 460) by nine months). It was also decided at the time that the regulation would be evaluated. The Interim Decree was evaluated on behalf of the Netherlands Organisation for Health Research and Development (ZonMw) by the Health Law Section of Maastricht University in cooperation with the Maastricht-based European Institute for Transnational Legal Research and the European Centre for Tort and Insurance Law in Vienna. The evaluation report was published on 15 April 2002. Some of the differences between this Decree and the Interim Decree are based on the recommendations made in the evaluation

report. In addition, this Explanatory Memorandum clarifies some uncertainties referred to in the evaluation report.

2. Further contraction of the insurance market and insurance-related problems

The insurance market for medical risks has deteriorated further since the introduction of the Interim Decree. This applies to the insurance of clinical trials initiated by the pharmaceutical industry and particularly to the insurance of clinical trials conducted by hospitals. Nearly all commercial insurers have withdrawn from the latter market and most of the insurance available for hospital clinical trials is now provided by two mutual insurers – Medirisk and Centramed.

Furthermore, several specific problems relating to clinical trials by both the pharmaceutical industry and hospitals make it difficult to insure the risks. Firstly, the limited number of trials means the premium income is relatively small. It is therefore very difficult to accumulate sufficient reserves to cover the relatively high sums insured. Secondly, the cumulative risk of a clinical trial might be very high since a problem will quickly cause losses for several subjects. To cover such cumulative risks, moreover, insurers must rely largely on reinsurers and since the 11 September 2001 attacks it has become increasingly difficult for insurers to obtain sufficient cover for this risk. Thirdly, a specific problem regarding the insurance of clinical trials using patients is that it may be unclear in certain cases whether a loss is due to the trial or to the subject's illness. Since the provisions of the Interim Decree might conceivably reverse the burden of proof, the insurer might be held liable if there is any doubt about the causal relationship between the clinical trial and the loss. This might lead to the insurer having to pay compensation for a loss that was due to the illness. This, too, makes it more difficult to insure the risk.

In view of the limited availability and the aforementioned insurance problems, it was considered whether the obligation to take out insurance should be maintained. It was decided to continue on the current course. Alternative ways to provide subjects with appropriate protection, such as the establishment of a compensation fund, would be accompanied by considerable administrative and practical difficulties and would face the same problems as insurance. In view of the limited number of clinical trials and the relatively high compensation, it would again be difficult to build up sufficient reserves. Since the government moreover considers the protection available to subjects pursuant to this Decree to be fair, it has decided not to pursue other alternatives.

In view of the above, this Decree differs from the Interim Decree on a number of points, all of which are necessary to ensure that compulsory insurance cover is available. The Dutch Association of Insurers has indicated that this Decree will enable its members to continue offering cover in the longer term so that the Decree need no longer have a limited period of validity. As noted above, the government believes that thanks to the Decree a sound decision can be made to become a subject, partly because the protection enjoyed by subjects is in addition to that available to all patients (including the subjects themselves) under liability law (see section 4 below).

3. Main differences from the Interim Decree

The main differences in the scope of the cover and the main legal improvements between this Decree and the Interim Decree are as follows:

- a. if the insurance is taken out with a foreign insurer, the policy must now name a loss adjuster that is registered in the Netherlands and that is responsible for dealing with and settling claims made by the subject (art. 2 (2));
- b. the sum insured per subject is unchanged but the sums per clinical trial and per insurance year are lower (art. 3 (1));
- c. there is a specific rule on the sum insured in a multi-centre trial (art. 3 (2));
- d. the rule on the cover provided when insurance is cancelled is more detailed and clearer than in the Interim Decree (art. 3 (3));
- e. pursuant to the Interim Decree, the sponsor could be exempted from the obligation to take out insurance only if there were no risks attaching to the clinical trial. This Decree also provides for an exemption if the additional risks of a comparative trial of two customary treatment methods are at most negligible (art. 4);
- f. in connection with the above, this Decree does not include the category of clinical trial with limited or negligible risks to the subjects that could be insured for lower sums under the Interim Decree;
- g. the clinical trial risks that should be covered by the insurance are described more precisely (art. 5 (1));
- h. the period in which the insurance should cover losses that manifest themselves after the subject ends his participation in the clinical trial has been reduced from five to four years (art. 5 (1));

- i. in contrast to the Interim Decree, losses can be excluded from the cover if – in brief – they are the result of a deterioration in the subject’s health problems and the subject participated in the clinical trial with a view to those problems (art. 5 (2));
- j. to remove any doubt on this point, a provision has been included to prevent private and social insurers having recourse against the insurer (art. 5 (3));
- k. an exclusive provision states which losses and costs are covered and to what amount (art. 6 (1));
- l. an “if not insured elsewhere” clause has been included (art. 6 (2));
- m. to provide greater clarity, it is now stated which provisions of Book 6, Title 1, Part 10, of the Civil Code are not applicable (art. 7).

4. Relationship to liability

The insurance referred to in section 7 of the Act will provide compensation in the event of the subject’s death or injury regardless of whether or not the clinical trial was conducted in a culpably negligent manner. It should be borne in mind though that the insurance might not always cover a loss suffered by the subject in full, for instance if the loss is so great that it exceeds the sum insured or if a specific loss is not covered in full or in part or if a loss manifests itself when it is no longer covered by the insurance. However, if the clinical trial was conducted in a culpably negligent manner the investigator is liable for all or part of the loss suffered by the subject. This may be important to the subject if the insurance does not cover his loss in full. He can then claim the uninsured loss from the investigator. If the investigator is liable, pursuant to section 7, subsection 5 of the Act the sponsor is also liable. Pursuant to section 1, subsection 1 (f) of the Act, the sponsor is the party that ordered the clinical trial to be organised or carried out. This opens up another avenue for the subject to claim compensation.

It should also be noted that Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Official Journal, L 121) entered into force on 4 April 2001. Article 3, paragraph 2 (f) of this Directive lays down that a clinical trial on a medicinal product may be undertaken only if provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor. This insurance relates to the investigator’s or sponsor’s liability as described above, not to the insurance required pursuant to section 7 of the Act, which offers the subject extra protection in addition to that available under liability law. In the case of a

clinical trial on a medicinal product, therefore, insurance must be taken out pursuant to this Decree and, pursuant to the Directive, the clinical trial may be undertaken only if adequate insurance or indemnity is provided to cover the liability of the investigator and sponsor. The Bill currently before the House of Representatives to implement the Directive (Parliamentary Papers, House of Representatives, 2002/2003, 28 804, nos. 1–3) will be amended by memorandum of amendment so that this requirement is satisfied.

5. Consultation

This Decree was drafted following consultation with the Dutch Association of Insurers. It was also submitted to the Dutch Association of Teaching Hospitals, the Dutch Association of Hospitals and other interested organisations, including the Federation of Patient and Consumer Organisations in the Netherlands (NP/CF), Nefarma and the Central Committee on Research Involving Human Subjects (CCMO). Their comments have been taken into account.

Articles

Article 2

Paragraph 1 lays down that insurance must be taken out and maintained with an insurer that satisfies the requirements regarding access to the Dutch insurance market pursuant to the Insurance Supervision Act 1993. This should ensure that the insurer fulfils its contractual obligations to the subject as far as possible. If the insurance is concluded with a foreign insurer, paragraph 2 prevents a subject who has suffered a loss from having to have his claim dealt with and settled outside the Netherlands. In such cases, paragraph 2 requires the policy to name a loss adjuster registered in the Netherlands. It should be borne in mind that the sponsor takes out the insurance, not the subject.

Article 3

This article lays down the amounts for which the insurance must be concluded. Section 8 of the Act requires the sponsor of a clinical trial to ensure that insurance is concluded. The sponsor is usually a pharmaceutical manufacturer even though the trials themselves are often conducted in a hospital. Clinical trials are usually concerned with new medicines but they might also relate to therapeutic methods or techniques, in which event a hospital or other institution, such as a nursing home, is usually the sponsor.

The amounts stated in paragraph 1 of this article are amounts for which cover can be obtained in the current insurance market: €450,000 per subject, €3,500,000 per clinical trial and €5,000,000 per insurance year. This last amount is relevant if the insurance provides cover for several clinical trials. This does not mean, of course, that the cover offered per clinical trial must be more than €3,500,000. The statutory provisions do not prevent those obliged to conclude insurance from insuring themselves for a higher sum or sums. The amount per subject is virtually the same as in the Interim Decree but has been rounded for practical purposes. The amounts per clinical trial and per insurance year, however, are lower. As noted in the general section of this Explanatory Memorandum this is because the premium income earned on the limited number of clinical trials has proved inadequate to build up sufficient reserves to cover the amounts that have been set so far per clinical trial and per insurance year. It should be noted that the amounts stated in this paragraph are virtually the same as the current maximum amounts available for medical liability insurance. With regard to the limit per insurance year, it is noted that the pharmaceutical industry and hospitals usually conclude continuous insurance to cover all clinical trials within the meaning of the Act. In any particular year, therefore, losses might arise in respect of several clinical trials, some of which will still be ongoing, while others will already have ended. To avoid discussion arising about the insurance year in which a loss manifests itself, the second sentence of paragraph 1 states that a loss is deemed to manifest itself when it is reported to the insurer.

Paragraph 2 contains a specific rule on the sum insured in a multi-centre trial. A multi-centre trial is one that is conducted by several institutions. Paragraph 2 attempts to resolve a number of problems that have arisen in practice. Firstly, such clinical trials are often conducted by several institutions working together as equals. Since it is often impossible to designate a single sponsor who must ensure that insurance is taken out, it is often agreed in such cases that each institution insures its own subjects. Secondly, in certain cases an institution can be identified as the clinical trial's sponsor but for various reasons it is often desirable for each participating institution to insure its own subjects.

In both situations, there was the practical problem that insurers were not always willing to insure an individual institution's subjects, which made it increasingly problematic to conduct multi-centre clinical trials. Insurers were less willing to provide cover because the Interim Decree did not clearly state what amount of cover should be provided for such clinical trials. The insurers were therefore concerned that a multi-centre clinical trial would have to be classified as a

separate clinical trial at every participating institution, with a corresponding sum insured per clinical trial. Paragraph 2 makes it clear that the sum insured per multi-centre trial is the normal sum insured per clinical trial even if a subject's loss is covered by the insurance taken out by the institution at which he is participating in the trial. This means that if several subjects suffer losses and they can claim compensation under the policies taken out by the institutions at which they participated in the clinical trial, the total loss insured is €3,500,000. It is up to the institutions and their insurers to make agreements amongst themselves on whether and to what extent they may have recourse against each other for the total compensation paid out so that the loss is divided among the policies on a pro rata basis. It should be noted that such agreements may not be invoked against the subjects. Finally, if the total loss exceeds the sum insured of €3,500,000, paragraph 5 of this article is applicable in full (see below). To determine the pro rata reduction in the injured party's rights vis-à-vis the insurer if the sum insured is exceeded, the insurers must agree amongst themselves who insures the multi-centre trial. This is also necessary for the application of the second sentence of paragraph 5; if such an agreement has not been made, an insurer cannot claim it acted in good faith if it paid an injured party more than the amount to which he was entitled pursuant to the first sentence of that paragraph because it was unaware that another insurer had already paid compensation to other injured parties. Since this means that later subjects will also be entitled to a pro rata reduction in compensation, the insurers will have a greater total liability than the applicable sum insured. This obliges insurers to make agreements on how claims are settled. How they make such agreements can be left to the insurers.

Paragraphs 3 and 4 provide for the run-off after a policy has been cancelled. This rule is clearer and more detailed than in the Interim Decree because it was not always certain how it should have been interpreted. The rule on the run-off relates to a continuous policy taken out for one or more clinical trials that is cancelled before the clinical trials are completed.

The first and second sentences of paragraph 3 are necessary to prevent losses suffered by subjects who participated in a clinical trial before the insurance was cancelled or who were participating in a clinical trial when the insurance was cancelled from no longer being covered owing to the cancellation. It should be noted that paragraph 4 contains a more specific, stricter rule for cases in which a hospital took out the insurance. Paragraph 3 is concerned principally with insurance taken out by the pharmaceutical industry.

The first sentence of paragraph 3 states that on the insurer's cancellation of the insurance, cover should be provided for at least the losses referred to in the first sentence of article 5 (1) that are suffered by subjects who had started participating in the clinical trial before the insurance was cancelled. Losses suffered by subjects who started participating in the clinical trial during the term of the insurance should in any event therefore be covered. Premiums will have been received in respect of these subjects and, moreover, a new insurer might not be willing to insure them because the insured risk may already have materialised without the loss having manifested itself. This prevents subjects who started participating in a clinical trial before the insurance was cancelled from no longer being insured if the insurer cancels the insurance agreement.

If the sponsor in particular cancels or transfers the insurance, pursuant to the second sentence of paragraph 3, cover should in any event be provided for losses suffered by subjects whose participation in the clinical trial had ended before the insurance was cancelled. Insurance is usually transferred for financial reasons. In such cases, the rule is less strict because the sponsor can and pursuant to section 8 of the Act must ensure that the new insurance covers losses suffered by subjects who were still participating in a clinical trial when the insurance was cancelled. The transfer of risks when new insurance is taken out is standard practice in the pharmaceutical industry.

Notwithstanding the provisions of paragraph 3, paragraph 4 regulates the run-off if a hospital cancels an insurance policy it has taken out. This rule is in agreement with current practice. Under paragraph 4, if insurance taken out by an institution is cancelled it must continue to provide cover for clinical trials that had already commenced before the cancellation. This goes without saying because the full premium will usually have been paid before the conduct of the clinical trials begins. Despite the cancellation, cover will be provided for losses suffered by subjects who participate in the clinical trial after the cancellation. For practical reasons it has been decided that a clinical trial commences on the day it is approved by the committee responsible for assessing its protocol since the assessment also considers the insurance required for the clinical trial to be undertaken. It should be noted that a change of insurer might create significant practical problems particularly for long-term clinical trials involving several institutions and a large number of subjects.

With regard to the difference in run-off on account of paragraphs 3 and 4, it has emerged from various talks that both the pharmaceutical industry insurers and the hospital insurers are very

much in favour of the regimes that are currently in place for them. Talks with hospital insurers also found that they had no objection to the regime provided for in paragraph 4.

If an insurance agreement that covers a single clinical trial is cancelled, pursuant to paragraph 1 the insurance should still provide cover to an amount of €3,500,000. It is not important whether the loss manifests itself before or after the cancellation. If a cancelled insurance agreement provided cover for several clinical trials, pursuant to the third sentence of paragraph 3 and the third sentence of paragraph 4 it should still provide cover to an amount of €5,000,000 for losses that manifest themselves after the cancellation. The wording of this sentence takes account of the fact that if there are several clinical trials compensation may already have been paid before the cancellation, for example €2,000,000 in respect of one clinical trial and €1,000,000 in respect of another. Upon cancellation, therefore, the insurer's maximum liability in respect of the first clinical trial is €1,500,000 and in respect of the second €2,500,000. In respect of these clinical trials, the insurer's total liability for losses that manifest themselves after the cancellation therefore cannot exceed €4,000,000

Paragraph 5, which is derived from section 6, subsection 2 of the Motor Insurance Liability Act (WAM), provides for situations in which more than one subject suffers a loss and the limit per clinical trial or per insurance year is exceeded. In principle, the subjects have a pro rata right to compensation. This rule applies even if the sponsor has taken out insurance to a higher amount than the obligatory amount required under paragraph 1. Since the insurer might not know about the existence of other injured parties, it might have paid more compensation to a subject than it was obliged to pursuant to the rule on pro rata reduction. The second sentence of this paragraph anticipates such situations and lays down that an insurer who has, in good faith, paid more compensation to a subject than he was entitled to pursuant to the first sentence is obliged to pay only the remaining part of the sum insured to the other subjects.

Article 4

Clinical trials that do not put the subjects at risk also fall within the meaning of the Act. The Act relates not only to clinical trials for the development or improvement of diagnostic and curative treatments but also to observational trials that do not always entail risks to the subjects. Such clinical trials may be inconvenient to the subject but in certain circumstances, owing to their nature, might not represent any risk whatsoever to the subject. This is the case, for example, in a non-invasive observational trial, e.g. a clinical trial comprising only urine analyses, breath

analyses or the use of an electroencephalogram (EEG). In such cases, insurance serves no purpose. Pursuant to paragraph 1, if the clinical trial entails no risks, the sponsor may request the committee responsible for assessing the protocol to exempt it from the obligation to take out insurance. There is also little point in taking out insurance if the clinical trial consists of a comparison of the procedures customary in the medical profession and the risks to the subjects are negligible at worst. Comparison of customary procedures should also be understood to include a comparison of recorded medicinal indications. It should be noted that the procedures required to obtain the observations necessary to make the comparisons will usually be quite common health care procedures. In many cases, for example, only a blood sample will be taken and the risks to the subject will be negligible (although the subject should be informed of them). Insuring against such additional but negligible risks would be too onerous and would serve little purpose. In such cases, pursuant to paragraph 2, the sponsor may also request the committee responsible for assessing the protocol to exempt it from the obligation to take out insurance. If the additional risks of a comparative trial are not negligible and insurance must be taken out, however, the insurance should cover those risks only. Pursuant to article 5, paragraph 2 (c), losses suffered by a subject undergoing a customary treatment method need not be covered. Finally it should be noted that article 4, paragraph 2 does not relate to clinical trials that consist of a comparison of a customary and a non-customary procedure.

These provisions are concerned with risks relating to the nature of the clinical trial, i.e. risks that are inherent in the trial. This is separate from the fact that a subject may suffer a loss because the clinical trial is conducted carelessly. The assessment required by this article is not intended to take such risks into account. If the clinical trial is conducted in a culpably negligent manner, the investigator is liable on the grounds of tort or breach of contract for any losses suffered.

This Decree does not include the category of clinical trial that involves limited or negligible risks to subjects that could be insured under the Interim Decree for lower amounts. Under the Interim Decree, certain comparative clinical trials fall into this category, but in many cases it is now possible to be released from the obligation to take out insurance. There is no demand in practice for a separate regime for the other clinical trials with limited or negligible risks.

Article 5

Section 7 of the Act lays down that the insurance should cover the death or injury of a subject due to a clinical trial. Paragraph 1 of this article describes which losses that subjects might suffer

are covered and specifies the minimum period of the cover. Losses due to death or injury should be covered in accordance with article 6. Such losses are therefore covered subject to the limits of article 6, which precisely defines what specific related losses should be covered.

The first sentence of paragraph 1 first lays down that losses arising from the realisation of a risk inherent in a clinical trial are covered. This means that losses suffered by a subject because, for example, he stumbled on his way to the treatment room or fainted when a blood sample was taken are not covered. In other words, the insurance must cover the losses considered below that are due to the realisation of a risk inherent in a clinical trial.

In the first place, the insurance must cover losses caused by the realisation of a risk inherent in the clinical trial that was not explained to the subject when his informed consent was sought. It should be borne in mind that a clinical trial might involve totally unexpected risks that could not have been explained to the subject. Resultant losses are covered by the insurance. Similarly, if the risks were known and explained to the subject but proved to be more serious than foreseen, the adverse consequences of this unforeseen factor are also covered by the insurance. In many cases, this will involve situations in which the conduct of a clinical trial should be suspended in accordance with section 10, subsection 1 of the Act.

In the second place, the insurance must also cover losses caused by the realisation of the following types of risk. Certain risks are sometimes known and explained to the subject but the sponsor and subsequently the medical ethics committee consider their realisation in an individual case to be so unlikely that the clinical trial is approved. In a clinical trial on a medicine to treat cancer, for example, it might be known that the medicine causes a low incidence of liver damage. Since such damage is unlikely in an individual case it need not prevent the clinical trial from being approved in view of the trial's importance. Where such damage does occur, the subject concerned will be covered by the insurance. Pursuant to the second sentence of paragraph 1, the insurance should cover losses that manifest themselves during the subject's participation in the clinical trial and losses that manifest themselves within four years of the end of his participation in the clinical trial. The Interim Decree had set the time limit at five years but insurers had commented that a shorter period would better safeguard the insurability of the risks in the longer term. Losses may manifest themselves before the subject has actually suffered them, for example future losses that can be claimed pursuant to article 105, Book 6 of the Civil Code provided they are sufficiently certain (loss of income, medical expenses, etc.). It will

usually be clear when participation in a clinical trial ends. It is the last day upon which the subject is administered substances as part of the clinical trial and/or undergoes medical treatment or, for example, the day on which the subject undergoes a final examination by the person who conducted the clinical trial. Pursuant to article 1 (c) this is when a subject within the meaning of section 1, subsection 1 (b) of the Act ceases to undergo treatment or need no longer conduct himself in a certain manner.

To prevent losses that manifest themselves during this period from being reported to the insurer some considerable time thereafter, a loss is deemed to have manifested itself when it is reported to the insurer. It is not important who reports the loss but the insurer must be informed on a timely basis.

Paragraph 2 lays down which losses may be excluded from the cover. Pursuant to point (a), which is new in comparison with the Interim Decree, losses caused by the subject's health problems not improving or even deteriorating may be excluded from the cover if the subject participated in the clinical trial with a view to those problems. This exclusion has been included chiefly because it is often impossible to determine whether a deterioration in the subject's health is due to his participation in the clinical trial or to the natural course of his illness. Insurers feared they might be held liable for every deterioration in the subject's health, which would have made it extremely difficult to insure this risk. This exclusion is therefore only relevant to subjects who are ill. Application of article 5, paragraph 2 (a) will be monitored and evaluated in the coming period in so far as this provision means the insurance need not cover losses caused by a deterioration in an ill subject's health.

In many cases, these losses were not covered under the Interim Decree either, since losses due to a subject's illness that would have manifested themselves even without participation in the clinical trial could also be excluded from the cover. A consequence of point (a), however, is that no cover need be provided for losses due to a deterioration in the subject's health that probably would not have occurred, or at least not to the same degree, if the subject had opted for a normal course of treatment. An example of this is a subject who dies six months after participating in a clinical trial when his life expectancy if he had undergone normal treatment would have been a year at the most. It should be borne in mind, though, that a subject who opts to participate in a clinical trial instead of undergoing normal treatment does so after weighing up the pros and cons. If the results of the clinical trial are disappointing he has no right to

compensation. The same is true of a patient who opts for normal treatment that has a disappointing result. In both instances, however, the investigator or doctor is liable for losses if the disappointing result is due to carelessness on the part of the investigator or doctor or if the subject or patient is not informed about the risk to his health.

Losses due to possible complications resulting from a clinical trial, however, must be covered in accordance with paragraph 1. This means, for example, that a loss suffered by a cancer patient because his condition deteriorated after undergoing an experimental radiation treatment need not be covered but a loss due to an impairment of his liver caused by the radiation must be covered. It also means that a loss caused by an adverse reaction to medicines that a patient is administered as part of a clinical trial must be covered, in so far as it is covered pursuant to paragraph 1 and in so far as the impairment and adverse reaction would not have occurred if the patient had undergone normal treatment. The latter rule is in agreement with point (b), which enables the cover to exclude losses that would have occurred if the subject had not participated in the clinical trial. This exclusion, which was also permitted under the Interim Decree, has little independent meaning in addition to point (a) because losses that are due to the subject's illness and that would have manifested themselves even without participation in the clinical trial can already be excluded under point (a). As noted above, point (b) is relevant chiefly to complications that are a result of the clinical trial and that would probably have occurred even if the subject had undergone normal treatment. An example of this is an adverse reaction to a registered medicine that it had been hoped would not have occurred on the administration of the medicine used in the clinical trial. If an insurer wishes to make use of this exclusion because it believes a particular loss would have occurred even without the clinical trial, it need only show that the loss would probably have occurred anyway.

If the additional risks in a comparative clinical trial are not negligible and therefore must be insured pursuant to article 4 (2), point (c) allows the insurance to cover only those additional risks. Pursuant to point (c) the loss a subject suffers because he undergoes normal treatment as part of the clinical trial need not be covered. This loss would have occurred even if the subject had undergone this treatment outside the clinical trial.

Point (d) allows the cover to exclude losses that occur in descendants owing to the clinical trial's adverse effect on the subject or his descendants. The adverse effect will usually relate to the subject's or his descendant's genetic material but there may be other adverse effects, as was

the case with thalidomide. Unlike the corresponding provision in the Interim Decree, this point takes account of the fact that the clinical trial may have a direct adverse effect on a descendant or his genetic material. This could be the case, for example, in a clinical trial involving pregnant women. This provision, too, has little independent meaning in addition to the first sentence of paragraph 1 of this article. Other relevant insurance agreements also exclude damage to genetic material since insurers have for many years been unable and unwilling to offer significant cover for such damage. This provision, however, does not prevent an insurance agreement from providing cover for this loss.

If, pursuant to this article, the insurance agreement does not cover the loss suffered by a subject, the subject can recover the loss from the investigator if that person was culpably negligent. Reference is made here to the general part of this Explanatory Memorandum, which considers the relationship with section 7, subsection 5 of the Act.

Paragraph 3 prevents private and social insurers from taking recourse against the insurance concluded for the subjects. Where it excludes the application of article 107a, Book 6 of the Civil Code, article 7 of this Decree also prevents an employer from taking recourse against the salary paid to a subject, which, in conjunction with paragraph 3, may be important if the employer is a natural person. It also follows from article 284 of the Commercial Code that a private insurer cannot take recourse against the insurance. Article 284 of the Commercial Code limits the subrogation to claims for compensation other than from insurance.

Insurance agreements concluded pursuant to the Interim Decree almost automatically include a number of exclusions arising from section 7 of the Act. Firstly, they exclude losses that were inevitable or almost inevitable given the nature of the clinical trial, as expressed in the second sentence of section 7, subsection 1. Secondly, losses that were the result of the subject not following instructions in full or in part if he was at least capable of doing so were generally already excluded. This also follows from article 101, Book 6 of the Civil Code, which is applicable *mutatis mutandis*.

Article 6

This provision is new in comparison with the Interim Decree. Paragraph 1 explains precisely what losses and costs are covered and to what amount. This makes it easier for insurers to calculate the size of the risk they must cover, which also improves the insurability of such risks in

the longer term, in part because standardising and limiting the loss items reduce implementation costs.

Point (d) is formulated so as to take account of a possible statutory regulation to provide compensation for emotional loss, which loss might also be subject to the limits of this point in the future. In this connection, see the Bill to amend the Civil Code, the Code of Criminal Procedure and the Criminal Injuries Compensation Fund Act with regard to the ability to compensate the next of kin for losses due to death or permanent injury (Parliamentary Papers, House of Representatives, 2002/03, 28 781, nos. 1–3). This point also introduces a threshold of €1,500. Preventing the compensation of minor losses in this way reduces implementation costs. Some of the costs named in paragraph 1 might be incurred not by the subject but by a third party on the subject's behalf, for example travelling expenses, the cost of domestic help or the cost of making adaptations. Pursuant to article 107, Book 6 of the Civil Code, such third-party costs are covered by the insurance subject to the limits of article 6, paragraph 1. Paragraph 1 does not name reasonable costs incurred to obtain satisfaction out of court because it would be wrong to expect such extrajudicial costs to be covered by the insurance. This does not mean, however, that a subject should not be reimbursed for such costs. If a subject wins a dispute with the insurer, the insurer is in breach of contract and must pay compensation pursuant to article 74, Book 6 of the Civil Code. The subject can claim extrajudicial costs pursuant to article 96, paragraph 2 (c), Book 6 of the Civil Code.

It follows from the first sentence of paragraph 2 that the insurance covers the losses and costs referred to in paragraph 1 up to the amounts stated in that paragraph in addition to the compensation that can be claimed under another insurance agreement or any law or other provision. This is a concession to both the insurer and the subject. For the insurer it has the advantage that the insurance pays out only in so far as the loss suffered by the subject is not covered by any other insurance agreement or provision, which again increases the insurability of this risk. A subject may have taken out, for example, medical insurance, funeral insurance or incapacity insurance or may be entitled to statutory incapacity benefit. The first sentence can therefore be seen as a statutory "if not insured elsewhere" clause. It can also be seen as a specific amplification of article 100, Book 6 of the Civil Code, which is applicable *mutatis mutandis* to this situation. For the subject, the words "in addition to the compensation" have the benefit that the right to compensation from the insurance is in addition to any compensation received from another source. If, for instance, the subject is entitled to statutory incapacity

benefit or has taken out incapacity insurance but it does not provide full compensation for loss of income, the loss that is not compensated is covered to an amount of €60,000 per annum. The total loss of income may therefore be insured to a considerably higher amount than €60,000 per annum. The first sentence is formulated so that the compensation paid to the subject is not higher than the total loss incurred.

The second sentence of paragraph 2 makes an exception in so far as, for instance, the investigator is liable for the loss suffered by the subject. The insurance should cover such losses irrespective of whether the investigator or another person is liable. The second sentence of paragraph 2 is necessary to prevent the subject from being denied a right to cover in the event of, for instance, the investigator being liable for a loss suffered by the subject, which might also seriously delay the settlement of the claim. In such a case the insurer is subrogated to the subject's rights and may thus have recourse against the person who is liable.

Article 7

Section 7, subsection 2 of the Act lays down that Book 6, Title 1, Part 10 of the Civil Code is applicable *mutatis mutandis* to the insurer's obligation to provide compensation for a loss in so far as the purpose of the provisions concerned does not require otherwise owing to the nature of the obligation. Uncertainty has arisen about which provisions of this Part are applicable in view of the nature of the insurer's obligation. Not only article 6 but also this present article provides clarification on this point. This is provided for under section 7, subsection 3 of the Act.

Articles 99, 103 and 104, Book 6 of the Civil Code do not apply because the purpose of these provisions is not compatible with the nature of the insurer's obligation. In addition, article 98, Book 6 of the Civil Code does not apply. The cover provided by the insurance is not determined by whether the loss can be imputed to the insurer pursuant to this article but by whether the Act and this Decree require the loss to be insured. If there is any doubt, the nature of the insurance is decisive in accordance with the requirements of reasonableness and fairness. Article 107a, paragraph 2, Book 6 of the Civil Code is also excluded. It should be noted in this respect that this exclusion has little independent meaning in addition to article 5, paragraph 3 of this Decree but this provision has been included to prevent a natural person who is an employer having recourse against the insurance.

A question that has arisen in practice is how the applicable provisions of Book 6, Title 1, section 10 of the Civil Code relate to the provisions of insurance law. The provisions can be applied alongside each other but if they conflict, the Act and thus Book 6, Title 1, Part 10 of the Civil Code take precedence over the provisions of insurance law. This means, for instance, that article 101, Book 6 of the Civil Code has precedence over article 276 of the Commercial Code. This is not the case with regard to the reimbursement of costs incurred to prevent or mitigate losses. Such costs, as referred to in article 96, paragraph 2 (a), Book 6 of the Civil Code, are not named in article 6 because, in our opinion, it would be incorrect to include costs incurred to mitigate damage in the cover. This means that such costs can be reimbursed on the grounds of article 283 of the Commercial Code.

Article 8

Within the limits of the cover, compulsory insurance should ensure that subjects who serve science and thus in general, the public interest need not bear losses caused by the research. The first sentence of paragraph 1 prevents a situation where the sponsor takes out insurance but the subject has no right to compensation because the insurer can invoke invalidity, counterclaim or dissolution against him. This ensures, for example, that a subject is not disadvantaged by the suspension of cover because the sponsor fails to pay a periodic premium. Pursuant to the third sentence of paragraph 1, the protection offered to subjects extends only to the minimum amount or amounts for which the insurance must be concluded.

Since the insurer usually cannot be forced to reimburse losses incurred by subjects who start to participate in a clinical trial after the end of the insurance agreement, the fourth sentence of paragraph 1 states that the first sentence of this paragraph is not applicable to subjects who start to participate in a clinical trial after the end of the insurance agreement or cover. This is again illustrated by the situation in which the insurer cancels the agreement because a periodic premium is not paid and the sponsor nevertheless allows new subjects to take part in the clinical trial. It should be borne in mind that in such cases the sponsor is not observing section 7 of the Act and is accordingly committing an offence under section 33 of the Act. An exception is made if the insurance agreement, after it has ended, continues to cover losses suffered by subjects who start to participate in a clinical trial after the agreement has been cancelled. Article 3, paragraph 4, for example, provides for run-off cover.

Pursuant to the second sentence of paragraph 1, counterclaim or dissolution may be invoked against a subject if it arises from the subject's failure to fulfil an obligation and the insurer's reasonable interests are harmed as a result. An example is the obligation to notify a loss to the insurer within a reasonable period of time and to provide the insurer with the necessary information and documents. Policies often include an obligation, moreover, to follow instructions. It should be noted here that losses caused by the non-fulfilment of an obligation within the meaning of article 101, Book 6 of the Civil Code, can be imputed to the subject. If the policy states that the sanction for the non-fulfilment of such an obligation is cancellation of the benefit and the benefit is at most reduced pursuant to article 101, Book 6 of the Civil Code, the policy is in conflict in this respect with the Act and this Decree. In such cases, article 10 prevents the insurer from successfully invoking this sanction.

It should also be noted that in practice policies sometimes include obligations or conditions that are unreasonably onerous for or disadvantageous to the subject. If a loss is suffered, for instance, a subject might be obliged to have himself admitted to a medical institution designated by the insurer or submit a dispute with the insurer to arbitration. It should be borne in mind that a subject is not involved in the formulation of such conditions, which is one circumstance that quickly qualifies such conditions as unreasonably onerous (compare article 233, Book 6 of the Civil Code). Finally it should be noted that pursuant to article 9, the subject must be informed in writing in Dutch of the obligations arising from the insurance agreement before he gives his consent.

This article may result in the insurer having to offer a subject greater cover than it is obliged to offer the policyholder. This is again illustrated by the situation in which the cover is suspended because the sponsor fails to pay a periodic premium. Paragraph 2 of this article therefore states that the insurer can recover the amount of the loss that is not covered from the person who sponsors the clinical trial.

A similar provision to this article can be found in section 11, subsection 1 of the Motor Insurance Liability Act (WAM). In comparison with that provision, this article is more urgent because if compulsory liability insurance does not provide cover the injured party can claim compensation from the liable party. In the case of direct non-life insurance, as in this Act, however, a particular person need not necessarily be liable for the loss suffered by a subject. The WAM also includes a direct right to take legal action against the insurer. This is not necessary in this Decree

because the subject is the insured person in a direct non-life insurance agreement and the insurer is accordingly obliged to pay the subject directly.

Article 9

Before the subject (or another person pursuant to section 6 of the Act) gives his consent, he must be fully informed of whether insurance has been taken out on his behalf. If so, he should be informed of the sum insured and the applicable exclusions before he gives his consent. The subject should also be informed of the insurer's name and address or, pursuant to article 2, paragraph 2, the loss adjuster's since this is the person the subject must contact in the event of a loss.

This information must be provided in writing with a view to the subject's informed consent as to his participation in the clinical trial. The subject can then consider the information before personally deciding whether or not to participate in the clinical trial. Pursuant to paragraph 1, the investigator is obliged to inform the subject in writing before seeking his consent. Before seeking the subject's consent, the investigator should also ensure that the subject is informed in writing about the insurance obligations resting upon him. It is particularly important that the subject knows about the obligations if his failure to fulfil an obligation will be subject to a sanction, for example the lapse of a claim. Since the insurance may be concluded outside the Netherlands, the subject must be informed in writing in Dutch. Paragraph 2 of article 9 also states that this information must be provided to the subject even if, pursuant to section 6 of the Act, the consent of another person is required because the subject will usually be the person who must fulfil the obligations.

Article 10

This provision is intended to prevent any policy clauses that are contrary to this Decree being invoked against the subject. Examples include a sum insured that is too low or a run-off period that is too short. Any departures in the cover, such as uninsured risks or the exclusion of a specific loss, agreed between the insurer and the sponsor, may not be to the detriment of the subject. In such cases, the insurer and the sponsor might agree that a loss may be recovered from the sponsor, which in certain cases already follows from article 8, paragraph 2.

Article 11

This provision is a transitional right. It follows from section 7, subsection 1 of the Act that the provisions of this Decree will apply without exception to all clinical trials that commence on or after the date on which this Decree enters into force, i.e. 1 September 2003. Pursuant to section 7, subsection 4 of the Act, however, the way in which the duty to provide insurance is implemented must already be laid down in the trial protocol. Hence the need for a transitional provision pursuant to which this Decree is not applicable to clinical trials that were approved by the relevant committee on the basis of the trial protocol before this Decree entered into force. Since the Interim Decree will no longer be in force as from 1 September 2003, it is necessary to indicate what regime will be applicable to clinical trials that were approved before this Decree entered into force. The second sentence provides for this and states that the provisions of the Interim Decree will remain in force.

The Minister of Justice,
J.P.H. Donner

The State Secretary for Health, Welfare and Sport,
C.I.J.M. Ross-van Dorp

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