



Ministry of Health, Welfare and Sport

Decree of 24 November 2014 containing rules for compulsory insurance in medical research involving human subjects

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477

Decree of 24 November 2014 containing rules for compulsory insurance in medical research involving human subjects (Medical Research (Human Subjects) Compulsory Insurance Decree 2015)¹

We Willem-Alexander, by the grace of God King of the Netherlands, Prince of Orange-Nassau, etc., etc., etc.

On the recommendation of Our Minister of Security and Justice of 10 October 2014, no. 570755, made in agreement with Our Minister of Health, Welfare and Sport;

Having regard to section 7, subsections 1 and 3 of the Medical Research (Human Subjects) Act;

Having heard the Advisory Division of the Council of State (report no. Wo3.14.0366/II of 12 November 2014);

Having seen the further report of Our Minister of Security and Justice of 20 November 2014, no. 585831, issued in agreement with Our Minister of Health, Welfare and Sport;

Have approved and decreed:

Article 1

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

- a. *Act*: the Medical Research (Human Subjects) Act;
- b. *insurance*: the insurance referred to in section 7, subsection 1 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 subjected to interventions or is no longer required to conduct himself in a certain manner.

Article 2

1. Insurance must be taken out and maintained with a financial undertaking that may carry on the business of insurance in the Netherlands pursuant to the Financial Supervision Act.
2. If the insurance is taken out with an insurer that has its registered office outside the Netherlands, the policy must designate a loss adjuster with a registered office in the Netherlands to deal with and settle insurance claims.

¹ In the event of any dispute on the interpretation of this Decree, the Dutch version of this Decree will prevail.

Article 3

1. The sums insured must be at least €650,000 per subject and at least €5,000,000 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, must be at least €7,500,000 in respect of damage that manifests itself during the insurance year. For the purposes of the previous sentence, damage is deemed to have manifested itself when it is reported to the insurer.
2. If a clinical trial is conducted at more than one institution, whoever performs the clinical trial must ensure that the damage suffered by all subjects participating in the trial is covered by the same insurance agreement. The insured sum for the clinical trial must be at least €5,000,000.
3. Upon cancellation of an insurance agreement, the damage referred to in the first sentence of article 4, paragraph 1 suffered by subjects who were participating or were about to participate in the clinical trial before the agreement was cancelled must in any event be covered. For the purposes of the previous sentence, the clinical trial is deemed to commence on the day that the committee responsible for assessing the trial protocol in question approves that protocol. With due regard for the insurer's liability per clinical trial if more than one clinical trial is insured, the cover provided by a cancelled insurance agreement for damage that manifests itself after the cancellation must be at least €7,500,000.
4. Notwithstanding paragraph 3, upon cancellation of an insurance agreement the damage referred to in the first sentence of article 4, paragraph 1 suffered by subjects need not be covered in so far as the sponsor has concluded another insurance agreement to cover that damage.
5. If more than one subject has suffered damage and the total amount of the compensation payable exceeds the sum insured, the subjects' claims vis-à-vis the insurer must be proportionally reduced to the amount of the sum insured. Nevertheless, 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 portion to which he was entitled is not obliged to pay the others more than the remainder of the sum insured.

Article 4

1. Having regard to article 5, the insurance must cover damage caused by the death or injury of a subject as a result of the materialisation of risks attached to the clinical trial that the subject had not been informed of in writing in accordance with section 6, subsection 5 (b) of the Act and also of risks attached to the clinical trial that the subject had been informed of in writing but which materialised to a more serious degree than foreseen and of risks that the subject had been informed of in writing but whose materialisation had been considered during the drafting and assessment of the protocol in question to be so improbable in an individual case that it did not prevent the committee from approving the protocol. The damage referred to in the previous sentence must be covered if it manifests itself 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, damage is deemed to have manifested itself when it is reported to the insurer.
2. The insurance need not cover damage that manifests itself in the offspring of the subject as a result of the clinical trial having an adverse effect on the subject or the offspring.

Article 5

If a right to compensation can be derived from another insurance policy or from any law or other provision but full compensation cannot be obtained therefrom, the insurance must cover the damage caused by the subject's death or injury in so far as this is necessary to compensate the subject for such damage in full. Notwithstanding the first sentence, if someone is liable for damage caused by the subject's death or injury, the insurance must cover this damage as though that liability does not exist.

Article 6

1. An insurer may not invoke invalidity, defence or lapse against the subject if such arises from statutory provisions concerning the insurance agreement or from the agreement itself. Defence or lapse 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 apply only to the amount or amounts for which the insurance must be taken out. The provisions of the first sentence do not apply to damage that, pursuant to article 3, paragraph 4, is not covered.
2. An insurer which, pursuant to the provisions of paragraph 1, compensates a subject in whole or in part for damage suffered, even though the damage was not covered by an agreement concluded with him, may recover the amount of the compensation from the person with whom it concluded the agreement.

Article 7

1. Before requesting the consent referred to in section 6 of the Act, the investigator must ensure that the person whose consent is required is informed in writing of the sums insured, the 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 case 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 must be informed thereof in writing by the investigator.
2. Before consent is requested, the investigator must also ensure that the subjects are informed in writing in Dutch about the obligations imposed on them by the insurance agreement. A similar requirement applies to the other persons whose consent is required pursuant to section 6 of the Act.

Article 8

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

Article 9

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

Article 10

The Medical Research (Human Subjects) Compulsory Insurance Decree is repealed.

Article 11

This Decree enters into force on 1 July 2015.

Article 12

This Decree may be cited as the Medical Research (Human Subjects) Compulsory Insurance Decree 2015.

We order and command that this Decree and the explanatory memorandum pertaining to it be published in the Bulletin of Acts and Decrees.

Wassenaar, 24 November 2014

Willem-Alexander

I.W. Opstelten

Minister of Security and Justice

E.I. Schippers

Minister of Health, Welfare and Sport

Published on the *ninth* of December 2014

I.W. Opstelten

Minister of Security and Justice

Explanatory Memorandum

General

1. Introduction

This Decree arises from the obligation laid down in section 7, subsection 1 of the Medical Research (Human Subjects) Act ('the Act') to conclude a direct non-life insurance agreement for human subjects. It contains further rules that the insurance must satisfy. The rules relate mainly to the sums that must be insured, the duration of the insurance and the relationship between the subject covered by the insurance and the insurer.

The Decree replaces the Medical Research (Human Subjects) Compulsory Insurance Decree of 1 September 2003. It enters into force on 1 July 2015. The Decree was amended principally in the light of the report on the Propatria study issued by the Healthcare Inspectorate (IGZ), the Central Committee on Research Involving Human Subjects (CCMO) and the Food and Consumer Product Safety Authority (VWA), which found that not all subjects were insured,¹ and the second evaluation report concerning the Act, which specifically considered the insurance decree.² The evaluation report in particular highlighted several problems that needed to be resolved. Together with the parties involved in such research and the relevant insurance, a working party of the Dutch Clinical Trial Foundation looked for solutions. The amendments to the Decree therefore derive directly from the working party's deliberations on how to improve the cover. The problems and preferred solutions are explained below.

2. Problems in the evaluation report and in practice

For medical research purposes, patients and healthy volunteers are asked to participate in clinical trials. It is of great importance that the trials are carried out on condition that the subjects are not left with adverse consequences and are guaranteed compensation for any damage arising from their participation. This is a key principle in developing a system to compensate subjects for any damage they suffer. The Act therefore requires the sponsor of a clinical trial to take out direct non-life insurance for the subjects. In addition, section 7, subsections 8 and 9 of the Act ensure that liability obligations can be fulfilled, in accordance with article 3 of Directive 2001/20/EC.³

1 Parliamentary Papers, House of Representatives, 2009/10, 32 123-XVI, no. 103 plus annexes; for the government's response, see Parliamentary Papers, House of Representatives, 2009/10, 32 123-XVI, no. 130 plus annexe.

2 Parliamentary Papers, House of Representatives, 2011/12, 29 963, no. 5, annexe; for the government's response see Parliamentary Papers, House of Representatives, 2011/12, 29 963, no. 7.

3 Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ 2001, L 121).

An initial problem regarding direct non-life insurance was revealed by the Propatria study carried out jointly by the IGZ, CCMO and VWA. It found that not all subjects were insured. The study was carried out in several hospitals. As a rule, the hospitals had their own continuous policies to insure subjects, under which every trial had to be notified separately so that the premium could be calculated on the basis of the number of subjects involved in the clinical trial at a particular hospital. As a result, multi-centre research had to be insured separately for each centre. This was a labour-intensive procedure for the investigators, who repeatedly had to collect the data, the insurers, who repeatedly had to issue proof of cover, and the assessment committees, which had to determine whether each centre had taken out insurance. The system was prone to error, which created the possibility that not every centre would be insured when the research commenced and not all subjects provided with the cover required under the Act.

The second evaluation report highlighted a second problem, relating to the exclusions permitted by article 5 of the previous Decree that arose from the Act. The exclusion relating to the non-alleviation of a subject's health problems or a deterioration in the health of a patient with a disease or condition that was the subject of the trial came in for particular criticism. The evaluators thought that in practice this exclusion allowed too much freedom to not provide compensation for damage suffered during the clinical trial.

Furthermore, the evaluation report stated that the burden of proof resting on the subjects should be reduced.⁴

It also recommended that in article 3, paragraphs 3 and 4 the cover provided for a clinical trial that commences during the policy period be extended to the end of the trial so that insurance is guaranteed throughout the trial regardless of which party cancels the policy.

3. Main amendments to the Decree in force until 30 June 2015

To address these problems and bring the cover up to date, the Decree that was in effect until 30 June 2015 has been amended on several points:

- a. the sums insured have been brought into line with market practice (article 3, paragraph 1);
- b. the cover provided for all subjects in multi-centre clinical trials must be provided under a single insurance agreement (article 3, paragraph 2);
- c. the run-off provided by the insurance under article 3, paragraphs 3 and 4 has been clarified and simplified;
- d. unnecessary exclusions in the old article 5 have been scrapped;
- e. the restrictions on the cover provided for specific losses and costs under the old article 6, paragraph 1 have been scrapped.

Amendments a, b, c and e

These amendments are explained in so far as necessary in the notes on individual articles. The restrictions on the cover provided for specific losses and costs by the old article 6, paragraph 1 have been scrapped as they proved unnecessary in practice.

⁴ M.J. Stukart et al., *Tweede evaluatie Wet medisch-wetenschappelijk onderzoek met mensen* (Second Evaluation of the Medical Research (Human Subjects) Act), The Hague, ZonMw, March 2012, p. 175.

Amendment d

Article 5, paragraph 2 of the previous Decree (now article 4) included specific exclusions to clarify that damage that would have been suffered even if a subject had not taken part in the clinical trial need not be covered.

Such damage included complications caused by the clinical trial that would probably have occurred if the subject had undergone an established treatment method. An option to exclude damage that would have occurred even if the subject had not taken part in the trial is unnecessary. The first sentence of article 4, paragraph 1 already provides for such a restriction. If the insurer wishes to invoke this provision, it need only make a reasonable case that the damage would also have occurred without the clinical trial.

The previous Decree also contained an exemption from the compulsory cover for damage that is due to the subject's health being impaired if the subject participates in a clinical trial intended to compare procedures that are commonly used in the medical profession and it is likely that the damage is the outcome of the procedure that the subject undergoes. The exemption related to damage that would also have been suffered if the subject had undergone the procedure outside the context of the comparative trial. This exemption is therefore covered by the principle that only damage caused by the materialisation of risks attached to the clinical trial is covered; see article 4, paragraph 1 of the Decree.

Another provision allowed the exclusion of damage due to the subject's health problems not being alleviated or the subject's health problems deteriorating, if he participated in the clinical trial with a view to those problems. This exclusion had 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. By allowing every deterioration in the subject's health during his participation in the clinical trial to be excluded – provided the trial was carried out with a view to that illness – the exemption placed the burden of proof entirely on the – already ill – subject. It inadequately respected the principle that the compulsory insurance must cover damage caused by the death or injury of a subject as a result of the materialisation of risks attached to the clinical trial.⁵ The exemption has therefore been scrapped. This does not mean that every deterioration in the subject's health or failure to improve his health as expected is automatically due to participation in the clinical trial. In principle, the subject must demonstrate a possible connection between participation in the clinical trial and the damage alleged to have arisen from it. The allocation of the burden of proof is a critical factor in this regard and is considered further below.

4. Burden of proof

The second evaluation report revealed that the burden of proof created practical problems for the subjects. The evaluators proposed examining whether application of the rules of objective attribution could resolve this issue.⁶

The allocation of the burden of proof is a critical factor in insurance law. Fair allocation is essential to take adequate account of the interests of the parties concerned. It is generally accepted that the person submitting a claim must also substantiate it, unless a special rule or

⁵ Ibid, p. 103.

⁶ Ibid, p. 175.

the requirements of reasonableness and fairness require the burden of proof to be allocated differently. There is no reason for the insurance of human subjects in general to depart from this principle. An important factor in this regard, however, is the extent to which the subject should be deemed able to demonstrate that the damage is the result of the clinical trial.

The solution proposed by the evaluators of applying the civil law theory of objective attribution is not appropriate as it is based on the attribution of damage according to liability. It means that a court first considers whether there is a condition without which the damage would not have arisen and, if so, then examines whether the damage can reasonably be attributed to the party that created the condition. In doing so, it considers the purpose of the rules infringed and the nature of the infringement. This is not relevant to human subjects, however, as rules have not been infringed. What is relevant is whether participation in the clinical trial constitutes a condition without which the damage would not have been suffered.⁷

In certain circumstances, however, the requirements of reasonableness and fairness may require a reduction in the burden of proof resting on the subject, on account of the nature of the subject's insurance and of the clinical trial (article 150, Code of Civil Procedure). The court decides whether this is the case. In principle, a subject must adequately demonstrate that the damage could be due to participation in the clinical trial. If the insurer claims that the damage would also have occurred if the subject had not participated in the clinical trial, it must prove that the damage was not and could not have been due to participation in the trial.

In practice, we expect that the problem of demonstrating causality could largely be remedied by having a group of independent experts assess subjects' claims on a voluntary basis, as proposed by insurers. Insurers are willing to include provisions on such assessments in their policies. If there is a difference of opinion between the subject and the insurer, minor claims could then be put to independent experts for a binding third-party ruling. We will follow developments in this area closely.

5. Relationship to liability

The insurance referred to in section 7, subsection 1 of the Act provides compensation in the event of the subject's death or injury resulting from participation in a clinical trial, regardless of whether or not the trial was conducted in a culpably negligent manner. The cover is not unlimited; as is also customary in liability insurance, the cover is limited if, for instance, the damage is so great that it exceeds the sum insured or if the damage manifests itself when it is no longer covered. The insurance does not absolve the investigator, the sponsor or the institution that facilitates the clinical trial (cf. section 7, subsection 8 in conjunction with section 1 (e), (f) and (g) of the Act) of liability for any damage that arises. However, if the clinical trial was conducted in a culpably negligent manner, the investigator is liable for all or part of the damage suffered by the subject. This may be important to the subject if the insurance does not cover the damage in full. He can then claim the uninsured damage from the investigator. If the investigator is liable, the sponsor is also liable under section 7, subsection 8 of the Act. The subject therefore has several avenues to claim compensation. Section 7, subsection 9 of the Act also lays down a duty to take out liability insurance or otherwise offer sufficient guarantees that liability obligations can be fulfilled. The present Decree does not pertain to liability insurance but only to the insurance referred to in section 7, subsection 1 of the Act.

⁷ Parliamentary Papers, House of Representatives, 2012/13, 29 538, no. 148, p. 6.

6. Consultation

This Decree was drafted in consultation with a working party of the Dutch Clinical Trial Foundation consisting of parties in the field. The working party included representatives of the Dutch Association of Insurers, the two largest mutual assurance companies providing insurance cover to hospitals in the Netherlands (MediRisk and Centramed), the Netherlands Federation of University Medical Centres (NFU), the Association of Tertiary Medical Teaching Hospitals (STZ) and other stakeholders, such as the Dutch Association of Medical Research Ethics Committees (NVMETC), Nefarma, the Central Committee on Research Involving Human Subjects (CCMO) and patients associations.

7. Regulatory burden

This Decree replaces the Medical Research (Human Subjects) Compulsory Insurance Decree. In comparison with the previous Decree it simplifies the applicable rules in several respects, mainly by scrapping exemptions to the obligation to take out insurance and simplifying the rules on compulsory cover after the insurance agreement has been cancelled. The Decree therefore has no impact on the administrative burden.

The increase in the minimum cover and the amended run-off after the insurance agreement has been cancelled may increase insurers' compliance costs. Consultation with the insurers showed that the potential increase in their compliance costs could not yet be calculated. Whether such an increase would also lead to higher premiums for compulsory insurance is also not yet known. The matter has been discussed, however, by the Dutch Clinical Trial Foundation's working party. To date, the premium has proved more than adequate to cover the compensation that has been paid out. All payments without exception were comfortably within the maximum cover. The insurers and their reinsurers will accordingly have to decide whether an increase in the maximum sums will also lead to an increase in premiums, taking into account the cost of reinsurance.

Notes on individual articles

Article 2

This article has been adopted without change from the previous Decree.

Paragraph 1 states that insurance must be taken out and maintained with an insurer that satisfies the requirements of the Financial Supervision Act regarding access to the Dutch insurance market. This should ensure as far as possible that the insurer fulfils its contractual obligations to a subject who has suffered damage.

If insurance is taken out with a foreign insurer, paragraph 2 prevents a subject who has suffered damage from having to have his claim settled outside the Netherlands. In such cases, paragraph 2 requires the policy to name a loss adjuster registered in the Netherlands.

Article 3

This article lays down the minimum amounts for which the insurance must be taken out. Section 8 of the Act requires the sponsor of a clinical trial to ensure that insurance is taken out. The sponsor is usually a pharmaceutical manufacturer or a care or research institution. In many cases, the trials themselves are conducted in a hospital or other care institution. Clinical trials can relate to new medicines but may also relate to diagnostics, treatments or other methods or techniques, or contributions to the advancement of medical knowledge.

The amounts stated in paragraph 1 of this article are amounts for which cover can be obtained in the current insurance market: €650,000 per subject, €5,000,000 per clinical trial and €7,500,000 per insurance year. The 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 can be required to be more than €5,000,000. The statutory provisions do not preclude insurance being taken out for a higher sum or sums (cf. article 8 of the Decree).

The sums insured are higher than in the previous Decree. It had been feared that the limited premium income would be inadequate to build up sufficient reserves to provide cover, but this fear has proved unfounded and the sums can be increased.

With regard to the limit per insurance year, it should be noted that the pharmaceutical industry and hospitals usually take out continuous insurance to cover all clinical trials within the meaning of the Act. In any particular year, therefore, damage might arise as a result of several clinical trials, some of which are still ongoing while others have already ended. To avoid discussion about the insurance year in which damage manifests itself, the second sentence of paragraph 1 states that damage is deemed to manifest itself when it is reported to the insurer.

Paragraph 2 requires the sponsor to ensure that a clinical trial carried out jointly at several institutions is insured with a single insurer. The second sentence requires such multi-centre trials to be insured for at least €5,000,000.

Paragraphs 3 and 4 provide for the run-off after a policy has been cancelled. The rule on the run-off relates to a continuous policy covering one or more clinical trials that is cancelled before the clinical trials are completed.

The first sentence of paragraph 3 states that on cancellation of the insurance policy, cover must be provided for at least the damage referred to in the first sentence of article 4, paragraph 1 that is suffered by subjects who had started or are about to start participating in a clinical trial that commenced before the insurance was cancelled. Subjects must therefore remain insured, and therefore not suffer adverse consequences, if new cover has not been arranged when the insurance is cancelled. It is uncertain whether a new insurer would be willing to insure the subjects because the insured risk may already have materialised without the damage having manifested itself.

This continued cover makes sense because the insurance premium is usually paid in full before the clinical trial begins. Despite the cancellation, cover will therefore be provided for damage suffered by subjects who participate in the clinical trial after the insurance is cancelled. 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 will also consider the insurance required for the clinical trial. It should be noted that a change of insurer might create significant practical problems, particularly for long-term clinical trials involving several institutions and many subjects.

If an insurance agreement for a single clinical trial is cancelled, under paragraph 1 the insurance must still provide cover to an amount of €5,000,000. It is not relevant whether damage manifests itself before or after the cancellation. If a cancelled insurance agreement provided cover for several clinical trials, the third sentence of paragraph 3 states that it must still provide cover to an amount of €7,500,000 for damage that manifests itself 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 €3,500,000 in respect of one clinical trial and €2,500,000 in respect of another. Upon cancellation, therefore, the insurer's maximum liability is €1,500,000 in respect of the first clinical trial and €2,500,000 in respect of the second. In respect of these clinical trials, the insurer's total liability for damage that manifests itself after the cancellation therefore cannot exceed €4,000,000 in this example.

Paragraph 4 provides that, notwithstanding paragraph 3, the run-off of a cancelled insurance policy is unnecessary if a new policy has been taken out to cover the risk. This is consistent with current practice. Insurance can be cancelled or transferred for financial reasons. Under section 8 of the Act, the sponsor must ensure that the new insurance covers damage suffered by subjects who are still participating in the clinical trial when the insurance is cancelled. Such a transfer of risks is in line with standard practice in the pharmaceutical industry.

Paragraph 5, which is derived from section 6, subsection 2 of the Civil Liability Insurance (Motor Vehicles) Act (WAM), provides for situations in which more than one subject suffers damage 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 also applies if the sponsor has taken out insurance for 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 under the first sentence is not obliged to pay the other subjects more than the remainder of the sum insured.

Article 4

Article 4, paragraph 1 has been adopted without change from the previous Decree.

Section 7, subsection 1 of the Act provides that the insurance must cover the death or injury of a subject due to a clinical trial. Article 4, paragraph 1 of this Decree describes which damage that subjects might suffer is covered and specifies the minimum period of the cover.

The first sentence of paragraph 1 first states that damage arising from the materialisation of a risk attached to a clinical trial is covered. These are risks that are specifically related to the clinical trial and participation in it. This means that damage suffered by a subject because, for example, he stumbled in the institution where the clinical trial is held or fainted when a blood sample was taken, is not covered. The damage must be due specifically to participation in the clinical trial. Patients already undergoing treatment who are included in a clinical trial may be exposed to additional risks that are covered by the insurance. The risks inherent in an existing illness or condition or the treatment provided for it are not covered by the insurance because the risks are not created by the clinical trial. If an existing risk inherent in a treatment is increased by the clinical trial, the insurance must cover the increased portion attributable to participation in the trial.

Damage caused by the materialisation of risks inherent in a clinical trial is therefore covered. It is not the intention to cover damage that is reasonably certain to occur and does not impede the approval and conduct of the clinical trial. The physical damage caused by a muscle biopsy performed as part of a clinical trial is foreseen and taken into account when considering whether the clinical value of the trial outweighs the risks and burden on the subjects. Such damage falls outside the scope of the insurance. The subject must, of course, be informed of this.

Damage caused by the materialisation of a risk attached to the clinical trial that was not explained to the subject during the informed consent procedure is always covered. A clinical trial can entail certain unforeseen risks that could not have been explained to the subject. The resultant damage is covered by the insurance.

Informing subjects of possible damage does not always mean that the damage is excluded from the cover. If a risk is known and explained to the subject but proves to be more serious than expected, the adverse consequences of this unforeseen factor are covered by the insurance. In such cases, the conduct of the clinical trial will probably have to be suspended under section 10, subsection 1 of the Act.

The insurance also covers damage caused by the materialisation of risks which are known (and are explained to the subject) but which the sponsor and subsequently the assessment committee consider so unlikely to materialise in an individual case that the clinical trial is approved. In a clinical trial on a medicine to treat cancer, for example, the medicine might be known to very occasionally cause liver damage. Since such damage is unlikely in an individual case, it need not prevent the clinical trial from being approved, on account of its importance. Where such damage does occur, the subject concerned will be covered by the insurance.

Under the second sentence of paragraph 1, the insurance must cover damage that manifests itself during the subject's participation in the clinical trial and damage that manifests itself within four years of the end of his participation in the clinical trial. Damage may manifest itself before the subject has actually suffered it, for example future damage that can be claimed under article 105 of Book 6 of the Civil Code provided it is 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

on 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. Under article 1 (c) this is when a subject within the meaning of section 1, subsection 1 (b) of the Act is no longer subjected to interventions or is no longer required to conduct himself in a certain manner.

To prevent damage that manifests itself during this period from being reported to the insurer some considerable time thereafter, damage is deemed to have manifested itself when it is reported to the insurer. It is not relevant who reports the damage but the insurer must be informed in a timely manner.

Paragraph 2 allows the cover to exclude damage suffered by the subject's offspring owing to the clinical trial's adverse effect on the subject or his offspring. The adverse effect will usually relate to the subject's or his offspring's genetic material but there may be other adverse effects, as was the case with thalidomide. This provision, however, does not prevent an insurance agreement from providing cover for the damage (see also article 8 of the Decree). In some cases that will also be desirable, for example if the trial involves pregnant women.

If, under this article, the insurance agreement does not cover the damage suffered by a subject, the subject can recover the damage from the investigator if that investigator acted in a culpably negligent manner. Reference is made here to the general part of this explanatory memorandum, which considers the relationship with section 7, subsection 9 of the Act.

Article 5

Article 5 is based on article 6, paragraph 2 of the previous Decree.

It follows from article 5 that the insurance covers the damage referred to in the first sentence of article 4, paragraph 1 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 damage 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 of Book 6 of the Civil Code, which applies *mutatis mutandis* to this situation. For the subject, this provision has the advantage 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 that does not provide full compensation for loss of income, the loss that is not compensated is covered to an amount of €650,000. The total loss of income may therefore be insured to a considerably higher amount. The first sentence is worded so as to ensure that the compensation paid to the subject does not exceed the total loss incurred.

The second sentence provides an exception in so far as, for instance, the investigator is liable for the damage suffered by the subject. The insurance must cover such damage irrespective of whether the investigator (or another person) is liable. The second sentence is necessary to prevent the possibility of the subject being denied entitlement to cover in the event of, for instance, the investigator being liable for damage 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 6

This article is based on the article 8 of the previous Decree.

Within the limits of the cover, compulsory insurance must ensure that subjects who serve science and thus, in general, the public interest need not bear the damage that may be caused by the clinical trial. 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. Under the third sentence of paragraph 1, the protection thus offered to subjects does not exceed the minimum amount or amounts for which the insurance must be concluded.

Under article 3, paragraph 3 the insurance agreement must provide cover for any damage suffered by subjects who participate in a clinical trial after the insurance is cancelled. Article 3, paragraph 4 contains an exception to this main rule for cases in which the insurance agreement has been cancelled and the sponsor has arranged alternative insurance that covers this damage. In such cases, the premium is usually reduced in an equitable fashion (article 939 of Book 7 of the Civil Code). Since the insurer cannot be required to provide compensation for damage suffered by subjects in such cases, the fourth sentence of paragraph 1 states that the first sentence does not apply in such cases.

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 damage to the insurer within a reasonable period 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 damage caused by the non-fulfilment of an obligation within the meaning of article 101 of 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 of Book 6 of the Civil Code, the policy is in conflict in this respect with the Act and this Decree. In such cases, article 6 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 damage 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 easily qualifies such conditions as unreasonably onerous (cf. article 233 of Book 6 of the Civil Code). Finally it should be noted that pursuant to article 7, 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 damage that is not covered from the person who sponsors the clinical trial. This article has been adopted without change from the previous Decree.

A similar provision to this article can be found in section 11, subsection 1 of the 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 damage 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 7

This article has been adopted without change from the previous Decree.

Before the subject (or another person as set out in 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 must be informed of the sums insured and the applicable exclusions before he gives his consent. The subject must also be informed of the insurer's name and address or, pursuant to article 2, paragraph 2, the loss adjuster's since this is whom the subject must contact in the event of damage.

This information must be provided in writing with a view to the subject's informed consent concerning 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. Under paragraph 1, the investigator is obliged to inform the subject in writing before seeking his consent.

Before seeking the subject's consent, the investigator must 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 such an obligation will be subject to a sanction, for example the lapse of a claim. Since the insurance may be concluded outside the Netherlands, a provision has been included stating that the subject must be informed in writing in Dutch. Article 7, paragraph 2 also states that this information must be provided to the subject even if, under 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 8

This article has been adopted without change from the previous Decree.

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 type of damage, 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 damage may be recovered from the sponsor, which in certain cases already follows from article 6, paragraph 2.

Article 9

This is a transitional clause. Without it, the provisions of this Decree would apply without exception, under section 7, subsection 1 of the Act, to all clinical trials that commence on or after the date on which this Decree enters into force, i.e. 1 July 2015. Under section 7, subsection 7 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 under 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. At issue is the primary assessment of the protocol, not the assessment of changes to it. Since the previous Decree will cease to apply as from 1 July 2015, 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 previous Decree will remain in force.

As it can be ruled out that there are still clinical trials ongoing that were subject to the previous temporary Medical Research (Human Subjects) Compulsory Insurance Decree, the transitional clause makes no allowance for them.

Article 11

Under section 7, subsection 3 of the Act, the Decree will enter into force no earlier than eight weeks after the date of its publication in the Bulletin of Acts and Decrees. Publication will take account of this requirement.

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