

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (Text with EEA relevance)

CHAPTER V

**PROTECTION OF SUBJECTS AND INFORMED CONSENT**

*Article 28*

**General rules**

- 1 A clinical trial may be conducted only where all of the following conditions are met:
- a the anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences and compliance with this condition is constantly monitored;
  - b the subjects, or where a subject is not able to give informed consent, his or her legally designated representative, have been informed in accordance with Article 29(2) to (6);
  - c the subjects, or where a subject is not able to give informed consent, his or her legally designated representative, have given informed consent in accordance with Article 29(1), (7) and (8);
  - d the rights of the subjects to physical and mental integrity, to privacy and to the protection of the data concerning them in accordance with Directive 95/46/EC are safeguarded;
  - e the clinical trial has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects and both the risk threshold and the degree of distress are specifically defined in the protocol and constantly monitored;
  - f the medical care provided to the subjects is the responsibility of an appropriately qualified medical doctor or, where appropriate, a qualified dental practitioner;
  - g the subject or, where the subject is not able to give informed consent, his or her legally designated representative has been provided with the contact details of an entity where further information can be received in case of need;
  - h no undue influence, including that of a financial nature, is exerted on subjects to participate in the clinical trial.

2 Without prejudice to Directive 95/46/EC, the sponsor may ask the subject or, where the subject is not able to give informed consent, his or her legally designated representative at the time when the subject or the legally designated representative gives his or her informed consent to participate in the clinical trial to consent to the use of his or her data outside the protocol of the clinical trial exclusively for scientific purposes. That consent may be withdrawn at any time by the subject or his or her legally designated representative.

The scientific research making use of the data outside the protocol of the clinical trial shall be conducted in accordance with the applicable law on data protection.

3 Any subject, or, where the subject is not able to give informed consent, his or her legally designated representative, may, without any resulting detriment and without having to provide any justification, withdraw from the clinical trial at any time by revoking his or her informed consent. Without prejudice to Directive 95/46/EC, the withdrawal of the informed consent shall not affect the activities already carried out and the use of data obtained based on informed consent before its withdrawal.

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## Article 29

### Informed consent

1 Informed consent shall be written, dated and signed by the person performing the interview referred to in point (c) of paragraph 2, and by the subject or, where the subject is not able to give informed consent, his or her legally designated representative after having been duly informed in accordance with paragraph 2. Where the subject is unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness. In that case, the witness shall sign and date the informed consent document. The subject or, where the subject is not able to give informed consent, his or her legally designated representative shall be provided with a copy of the document (or the record) by which informed consent has been given. The informed consent shall be documented. Adequate time shall be given for the subject or his or her legally designated representative to consider his or her decision to participate in the clinical trial.

2 Information given to the subject or, where the subject is not able to give informed consent, his or her legally designated representative for the purposes of obtaining his or her informed consent shall:

- a enable the subject or his or her legally designated representative to understand:
  - (i) the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial;
  - (ii) the subject's rights and guarantees regarding his or her protection, in particular his or her right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification;
  - (iii) the conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial; and
  - (iv) the possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical trial is discontinued;
- b be kept comprehensive, concise, clear, relevant, and understandable to a layperson;
- c be provided in a prior interview with a member of the investigating team who is appropriately qualified according to the law of the Member State concerned;
- d include information about the applicable damage compensation system referred to in Article 76(1); and
- e include the EU trial number and information about the availability of the clinical trial results in accordance with paragraph 6.

3 The information referred to in paragraph 2 shall be prepared in writing and be available to the subject or, where the subject is not able to give informed consent, his or her legally designated representative.

4 In the interview referred to in point (c) of paragraph 2, special attention shall be paid to the information needs of specific patient populations and of individual subjects, as well as to the methods used to give the information.

5 In the interview referred to in point (c) of paragraph 2, it shall be verified that the subject has understood the information.

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6 The subject shall be informed that the summary of the results of the clinical trial and a summary presented in terms understandable to a layperson will be made available in the EU database, referred to in Article 81 (the ‘EU database’), pursuant to Article 37(4), irrespective of the outcome of the clinical trial, and, to the extent possible, when the summaries become available.

7 This Regulation is without prejudice to national law requiring that both the signature of the incapacitated person and the signature of his or her legally designated representative may be required on the informed consent form.

8 This Regulation is without prejudice to national law requiring that, in addition to the informed consent given by the legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her, shall also assent in order to participate in a clinical trial.

### *Article 30*

#### **Informed consent in cluster trials**

1 Where a clinical trial is to be conducted exclusively in one Member State, that Member State may, without prejudice to Article 35, and by way of derogation from points (b), (c), and (g) of Article 28(1), Article 29(1), point (c) of Article 29(2), Article 29(3), (4) and (5), points (a), (b) and (c) of Article 31(1) and points (a), (b) and (c) of Article 32(1), allow the investigator to obtain informed consent by the simplified means set out in paragraph 2 of this Article, provided that all of the conditions set out in paragraph 3 of this Article are fulfilled.

2 For clinical trials that fulfil the conditions set out in paragraph 3, informed consent shall be deemed to have been obtained if:

- a the information required under points (a), (b), (d) and (e) of Article 29(2) is given, in accordance with what is laid down in the protocol, prior to the inclusion of the subject in the clinical trial, and this information makes clear, in particular, that the subject can refuse to participate in, or withdraw at any time from, the clinical trial without any resulting detriment; and
- b the potential subject, after being informed, does not object to participating in the clinical trial.

3 Informed consent may be obtained by the simplified means set out in paragraph 2, if all the following conditions are fulfilled:

- a the simplified means for obtaining informed consent do not contradict national law in the Member State concerned;
- b the methodology of the clinical trial requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products in a clinical trial;
- c the clinical trial is a low-intervention clinical trial and the investigational medicinal products are used in accordance with the terms of the marketing authorisation;
- d there are no interventions other than the standard treatment of the subjects concerned;
- e the protocol justifies the reasons for obtaining informed consent with simplified means and describes the scope of information provided to the subjects, as well as the ways of providing information.

4 The investigator shall document all refusals and withdrawals and shall ensure that no data for the clinical trial are collected from subjects that refuse to participate in or have withdrawn from the clinical trial.

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### Article 31

#### **Clinical trials on incapacitated subjects**

1 In the case of incapacitated subjects who have not given, or have not refused to give, informed consent before the onset of their incapacity, a clinical trial may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:

- a the informed consent of their legally designated representative has been obtained;
- b the incapacitated subjects have received the information referred to in Article 29(2) in a way that is adequate in view of their capacity to understand it;
- c the explicit wish of an incapacitated subject who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator;
- d no incentives or financial inducements are given to the subjects or their legally designated representatives, except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial;
- e the clinical trial is essential with respect to incapacitated subjects and data of comparable validity cannot be obtained in clinical trials on persons able to give informed consent, or by other research methods;
- f the clinical trial relates directly to a medical condition from which the subject suffers;
- g there are scientific grounds for expecting that participation in the clinical trial will produce:
  - (i) a direct benefit to the incapacitated subject outweighing the risks and burdens involved; or
  - (ii) some benefit for the population represented by the incapacitated subject concerned when the clinical trial relates directly to the life-threatening or debilitating medical condition from which the subject suffers and such trial will pose only minimal risk to, and will impose minimal burden on, the incapacitated subject concerned in comparison with the standard treatment of the incapacitated subject's condition.

2 Point (g)(ii) of paragraph 1 shall be without prejudice to more stringent national rules prohibiting the conduct of those clinical trials on incapacitated subjects, where there are no scientific grounds to expect that participation in the clinical trial will produce a direct benefit to the subject outweighing the risks and burdens involved.

3 The subject shall as far as possible take part in the informed consent procedure.

### Article 32

#### **Clinical trials on minors**

1 A clinical trial on minors may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:

- a the informed consent of their legally designated representative has been obtained;
- b the minors have received the information referred to in Article 29(2) in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children;

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- c the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator;
- d no incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial;
- e the clinical trial is intended to investigate treatments for a medical condition that only occurs in minors or the clinical trial is essential with respect to minors to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;
- f the clinical trial either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;
- g there are scientific grounds for expecting that participation in the clinical trial will produce:
  - (i) a direct benefit for the minor concerned outweighing the risks and burdens involved; or
  - (ii) some benefit for the population represented by the minor concerned and such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition.

2 The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity.

3 If during a clinical trial the minor reaches the age of legal competence to give informed consent as defined in the law of the Member State concerned, his or her express informed consent shall be obtained before that subject can continue to participate in the clinical trial.

### *Article 33*

#### **Clinical trials on pregnant or breastfeeding women**

A clinical trial on pregnant or breastfeeding women may be conducted only where, in addition to the conditions set out in Article 28, the following conditions are met:

- (a) the clinical trial has the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, outweighing the risks and burdens involved; or
- (b) if such clinical trial has no direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, it can be conducted only if:
  - (i) a clinical trial of comparable effectiveness cannot be carried out on women who are not pregnant or breastfeeding;
  - (ii) the clinical trial contributes to the attainment of results capable of benefitting pregnant or breastfeeding women or other women in relation to reproduction or other embryos, foetuses or children; and
  - (iii) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the pregnant or breastfeeding woman concerned, her embryo, foetus or child after birth;

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- (c) where research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child; and
- (d) no incentives or financial inducements are given to the subject except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial.

#### *Article 34*

#### **Additional national measures**

Member States may maintain additional measures regarding persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical trials, or persons in residential care institutions.

#### *Article 35*

#### **Clinical trials in emergency situations**

1 By way of derogation from points (b) and (c) of Article 28(1), from points (a) and (b) of Article 31(1) and from points (a) and (b) of Article 32(1), informed consent to participate in a clinical trial may be obtained, and information on the clinical trial may be given, after the decision to include the subject in the clinical trial, provided that this decision is taken at the time of the first intervention on the subject, in accordance with the protocol for that clinical trial" and that all of the following conditions are fulfilled:

- a due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the subject is unable to provide prior informed consent and to receive prior information on the clinical trial;
- b there are scientific grounds to expect that participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition;
- c it is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative;
- d the investigator certifies that he or she is not aware of any objections to participate in the clinical trial previously expressed by the subject;
- e the clinical trial relates directly to the subject's medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative and to supply prior information, and the clinical trial is of such a nature that it may be conducted exclusively in emergency situations;
- f the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition.

2 Following an intervention pursuant to paragraph 1, informed consent in accordance with Article 29 shall be sought to continue the participation of the subject in the clinical trial, and information on the clinical trial shall be given, in accordance with the following requirements:

- a regarding incapacitated subjects and minors, the informed consent shall be sought by the investigator from his or her legally designated representative without undue delay and the information referred to in Article 29(2) shall be given as soon as possible to the subject and to his or her legally designated representative;

- b regarding other subjects, the informed consent shall be sought by the investigator without undue delay from the subject or his or her legally designated representative, whichever is sooner and the information referred to in Article 29(2) shall be given as soon as possible to the the subject or his or her legally designated representative, whichever is sooner.

For the purposes of point (b), where informed consent has been obtained from the legally designated representative, informed consent to continue the participation in the clinical trial shall be obtained from the subject as soon as he or she is capable of giving informed consent.

3 If the subject or, where applicable, his or her legally designated representative does not give consent, he or she shall be informed of the right to object to the use of data obtained from the clinical trial.

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