Medicines for Human Use (Clinical Trials Regulations) 2004

Informed consent in clinical trials

Introduction

1. This information note summarises the statutory requirements for informed consent of participants in clinical trials of investigational medicinal products (CTIMPs). The requirements are set out in Schedule 1 to the Medicines for Human Use (Clinical Trials) Regulations 2004 (S.I.2004:1031) as amended by S.I.2006:1928, S.I.2006:2984 and S.I.2008:941. The Regulations transpose the provisions of the European Clinical Trials Directive (EC2001/20) into UK law.

2. In particular, the note describes the provisions relating to giving informed consent on behalf of ***minors and adults who are unable to consent for themselves*** (referred to in this note as "incapacitated adults"), including the role and responsibilities of ***legal representatives***.

3. The statutory responsibilities of ethics committees when reviewing trials involving minors and incapacitated adults are also summarised.

4. Any queries should be sent to queries@nres.npsa.nhs.uk. Where complex questions of interpretation arise, NRES will seek further advice from legal advisers at the Department of Health. Queries relating to the distinct Scottish provisions on adults with incapacity will be referred to the Scottish Executive Health Department.

Principles of the EU Directive

5. Paragraphs 3-5 of the preamble to the EU Directive set out fundamental principles relating to the inclusion of minors and incapacitated adults in clinical trials:

> "(3) Persons who are incapable of giving legal consent to clinical trials should be given special protection. It is incumbent on the Member States to lay down rules to this effect. Such persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent.

Normally these persons should be included in clinical trials only when there are grounds for expecting that the administering of the medicinal product would be of direct benefit to the patient, thereby outweighing the risks. However, there is a need for clinical trials involving children to improve the treatment available to them. Children represent a vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development-related research important for their benefit. Medicinal products, including vaccines, for children need to be tested scientifically before widespread use. This can only be achieved by ensuring that medicinal products which are likely to be of significant value for children are fully studied. The clinical trials for this purpose should be carried out under conditions affording the best possible protection for the subjects. Criteria for the protection of children in clinical trials therefore need to be laid down.

(4) In the case of other persons incapable of giving their consent, such as persons with dementia, psychiatric patients, etc, inclusion in clinical trials in such cases should be on an even more restrictive basis. Medicinal products for trial may be administered to all such individuals only where there are grounds for assuming that the direct benefit to the patient outweighs the risks. Moreover, in such cases the written consent of the patient's legal representative, given in co-operation with the treating doctor, is necessary before participation in any such clinical trial.

(5) The notion of legal representative refers back to existing national law and consequently may include natural or legal persons, an authority and/or a body provided for in national law."

Definition of a legal representative – general points

6. Under Article 5 of the EU Directive, the definition of a legal representative is a matter for national legislation in each member state. Under the UK Regulations, the definition depends on whether the subject is a minor or an adult with incapacity. The definition also varies where the subject is an adult with incapacity in Scotland. The detailed provisions are set out in the tables at paragraphs 15 and 18 of this note.

7. Common to the definition of the legal representative in any scenario is that the individual concerned must not be “a person connected with the conduct of the trial”. This is defined for the purpose of Schedule 1 of the Regulations as:

(a) the sponsor of the trial,
(b) a person employed or engaged by, or acting under arrangements with, the sponsor and who undertakes activities connected with the management of the trial,
(c) an investigator for the trial,
(d) a health care professional who is a member of an investigator’s team for the purposes of the trial, or
(e) a person who provides health care under the direction or control of a person referred to in paragraphs (c) and (d) above, whether in the course of the trial or otherwise.

Definition of informed consent

8. Paragraph 3(1) of Part 1 of Schedule 1 to the Regulations, implementing Article 2(j) of the EU Directive, gives the following definition of informed consent:

A person gives informed consent to take part in a clinical trial only if his decision:

(a) is given freely after that person is informed of the nature, significance, implications and risks of the trial; and

(b) either:

(i) is evidenced in writing, dated and signed, or otherwise marked, by that person so as to indicate his consent, or

(ii) if the person is unable to sign or to mark a document so as to indicate his consent, is given orally in the presence of at least one witness and recorded in writing.

9. The same definition applies to the giving of informed consent by a person with parental responsibility, or a legal representative, on behalf of the trial subject.

Capable adults

10. Under Part 3 of Schedule 1 to the Regulations (implementing Article 3(2) to the EU Directive) the following conditions apply to the giving of informed consent by a capable adult:

    1. *The subject has had an interview with the investigator, or another member of the investigating team, in which he has been given the opportunity to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted.*

    2. *The subject has been informed of his right to withdraw from the trial at any time.*

    3. *The subject has given his informed consent to taking part in the trial.*

    4. *The subject may, without being subject to any resulting detriment, withdraw from the clinical trial at any time by revoking his informed consent.*

    5. *The subject has been provided with a contact point where he may obtain further information about the trial.*

11. If a capable adult gives informed consent to take part in a CTIMP in accordance with these conditions, and subsequently becomes unable to give informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid.

12. If a capable adult refuses informed consent, and subsequently becomes unable to give informed consent, the refusal is legally binding. He or she cannot be entered into the trial by seeking consent from a legal representative.

Minors

13. The following guidance applies to England, Wales, Scotland and Northern Ireland without distinction.

Definition of a minor

14. Under the Regulations a minor is a person under the age of 16 years.

Hierarchy of consent

15. The Regulations prescribe a hierarchy for determining who should be approached to give informed consent on behalf of a minor prior to their inclusion in the trial. The provisions for informed consent by a legal representative only apply if by reason of the emergency nature of the treatment provided as part of the trial no person with parental responsibility can be contacted prior to the proposed inclusion of the minor. (See also paragraph [ ] on situations where it is also not possible to contact a legal representative.)

Table 1: Hierarchy of informed consent for a minor

	Person who may give consent	*Definition*	*Commentary*
1.	Parent	A parent or person with parental responsibility.	Should always be approached if available.
2.	Personal legal representative	A person not connected with the conduct of the trial who is: (a) suitable to act as the legal representative by virtue of their relationship with the minor, and (b) available and willing to do so.	May be approached if no person with parental responsibility can be contacted prior to the proposed inclusion of the minor, by reason of the emergency nature of the treatment provided as part of the trial.
3.	Professional legal representative	A person not connected with the conduct of the trial who is: (a) the doctor primarily	May be approached if no person suitable to act as a personal legal representative is available. Informed consent must be given before the minor is entered into

		responsible for the medical treatment of the minor, or (b) a person nominated by the relevant health care provider (e.g. an acute NHS Trust or Health Board).	the trial.

Emergency situations

16. The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality Amendment) Regulations 2008 made additional provision relating to trials involving minors in emergency situations. Where the treatment to be given to a minor as part of the trial needs to be administered urgently, time may not allow for the written consent of a person with parental responsibility or a legal representative to be obtained first. The amendment allows minors to be entered into a trial prior to informed consent being obtained provided that:

- Having regard to the nature of the trial and the particular circumstances of the case, it is necessary to take action for the purpose of the trial as a matter of urgency but
- It is not reasonably practicable to obtain informed consent prior to entering the subject, and
- The action to be taken is carried out in accordance with a procedure approved by the ethics committee.

17. Where a minor is recruited in an emergency situation without prior informed consent, steps must be taken to seek informed consent from a person with parental responsibility or a legal representative as soon as practicable after the initial emergency has passed. Where consent is withheld, the subject must be withdrawn from the trial.

Conditions and principles applying to minors

18. All the conditions and principles listed in Annex A must normally be satisfied if a minor is to be included in a clinical trial. These relate mainly to the justification for inclusion of minors in the trial and to the informed consent procedure. Where the emergency provisions apply (see paragraphs 16-17 above), sub-paragraphs 1-5 of Annex A do not apply until the emergency has passed.

Incapacitated adults

Definition

19. The term used in the Regulations is *"an adult unable by virtue of physical or mental incapacity to give informed consent"*.

Hierarchy of consent

20. Table 2 sets out the hierarchy prescribed in the Regulations for determining what type of legal representative should be approached to give informed consent on behalf of an incapacitated adult prior to inclusion of the subject in the trial. The provisions in England, Wales and Northern Ireland differ from those in Scotland.

Table 2: Hierarchy of informed consent for an incapacitated adult

England, Wales and Northern Ireland	***Scotland***
1. Personal legal representative A person not connected with the conduct of the trial who is: (a) suitable to act as the legal representative by virtue of their relationship with the adult, *and* (b) available and willing to do so.	*1. Personal legal representative* 1A. Any guardian or welfare attorney who has power to consent to the adult's participation in research. 1B. If there is no such person, the adult's nearest relative as defined in section 87(1) of the Adults with Incapacity (Scotland) Act 2000.
2. Professional legal representative	*2. Professional legal representative*

A person not connected with the conduct of the trial who is: (a) the doctor primarily responsible for the adult's medical treatment, or (b) a person nominated by the relevant health care provider (e.g. an acute NHS Trust or Health Board). A professional legal representative may be approached if no suitable personal legal representative is available.	A person not connected with the conduct of the trial who is: (a) the doctor primarily responsible for the adult's medical treatment, or (b) a person nominated by the relevant health care provider. A professional legal representative may be approached if it is not reasonably practicable to contact either 1A or 1B before the decision to enter the adult into the trial is made. Informed consent must be given before the subject is entered into the trial.

Emergency situations

21. The Medicines for Human Use (Clinical Trials) (Amendment No.2) Regulations 2006 made additional provision relating to trials involving incapacitated adults in emergency situations. Where the treatment to be given to an incapacitated adult as part of the trial needs to be given urgently, time may not allow for the written consent of a legal representative to be obtained first. The amendment allows incapacitated adults to be entered into a trial prior to consent being obtained from a legal representative provided that:

- Having regard to the nature of the trial and the particular circumstances of the case, it is necessary to take action for the purpose of the trial as a matter of urgency but

- It is not reasonably practicable to obtain informed consent prior to entering the subject, and

- The action to be taken is carried out in accordance with a procedure approved by the ethics committee.

22. Where an incapacitated adult is recruited in an emergency situation without prior informed consent, steps must be taken to seek informed consent either from the subject (if capacity has been recovered) or from a legal representative as soon as practicable after the initial emergency has passed. Where consent is withheld, the subject must be withdrawn from the trial.

Conditions and principles applying to incapacitated adults

23. All the conditions and principles listed in Annex B must normally be satisfied if an incapacitated adult is to be included in a clinical trial. They relate mainly to the justification for inclusion of incapacitated adults in the trial and to the informed consent procedure. Where the emergency provisions apply (see paragraphs 21-22 above), sub-paragraphs 1-5 of Annex B do not apply until the emergency has passed.

Responsibilities of ethics committees in trials involving minors or incapacitated adults

Ethical issues to be considered

24. An application to an ethics committee under the Regulations must include:

- The procedures for obtaining informed consent
- A copy of all written information to be given to a potential subject or their legal representative prior to seeking informed consent, and
- A copy of the form to be used to record consent.

25. The ethics committee that reviews a clinical trial (referred to in this note as "the main REC") must consider various matters before giving its opinion. These include:

- The adequacy and completeness of the written information to be given, and the procedures to be followed, for the purpose of obtaining informed consent to the subjects' participation in the trial.

- If the subjects are to include incapacitated adults, whether the research is justified having regard to the conditions and principles specified in Annex B.

Expertise

26. If the main REC does not have a member with suitable expertise, it must obtain expert advice before giving its opinion on a clinical trial involving minors or incapacitated adults.

27. In the case of a minor, where the REC does not have a member with professional expertise in paediatric care, it must obtain advice on the clinical, ethical and psychosocial problems that may arise in relation to the trial.

28. In the case of an incapacitated adult, where the REC does not have a member with professional expertise in:

    (i) the treatment of the disease to which the trial relates ***and***
    (ii) the treatment of the patient population suffering that disease

    it must obtain advice on the clinical, ethical and psychosocial problems in the field of that disease and patient population that may arise in relation to the trial.

29. Procedures for consulting expert referees are set out in section 2 of the COREC Standard Operating Procedures for Research Ethics Committees.

National Research Ethics Service
National Patient Safety Agency
4-8 Maple Street
London W1T 5HD

1 May 2008

ANNEX A

Conditions and principles which apply to the inclusion of a minor in a clinical trial

The following conditions and principles are listed in Part 4 of Schedule 1 to the Regulations and implement Article 4 of the EU Directive.

Conditions

1. The parent or legal representative has had an interview with the investigator, or another member of the investigating team, in which opportunity has been given to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted.

2. The parent or legal representative has been provided with a contact point where further information about the trial may be obtained.

3. The parent or legal representative has been informed of the right to withdraw the minor from the trial at any time.

4. The parent or legal representative has given informed consent to the minor taking part in the trial.

5. The parent or legal representative may, without the minor being subject to any resulting detriment, withdraw the minor from the trial at any time by revoking the informed consent.

[Note: Paragraphs 1-5 do not apply where treatment is being, or is about to be provided for a minor as a matter of urgency and, having regard to the nature of the clinical trial and of the particular circumstances of the case:

(a) It is also necessary to take action for the purposes of the trial as a matter of urgency, but

(b) It is not reasonably practicable to meet the conditions set out in paragraph 1-5, and

(c) The action taken is carried out in accordance with a procedure approved by the ethics committee.]

6. The minor has received information, according to his or her capacity of understanding, about the trial and its risks and benefits. The information must be given by staff with experience with minors.

7. The investigator must consider the explicit wish of a minor capable of forming an opinion and assessing the information provided. This applies both to the wish of a minor to refuse to take part, or to withdraw from the trial at any time.

8. No incentives or financial inducements are given either to the minor or to the parent or legal representative, except the provision of compensation for injury or loss.

9. The clinical trial relates directly to a condition from which the minor suffers or is of such a nature that it can only be carried out on minors.

10. Some direct benefit for the group of patients involved in the trial is to be obtained from the trial.

11. The trial is necessary to validate data obtained (a) in other clinical trials involving persons able to give informed consent, or (b) by other research methods.

12. The corresponding scientific guidelines of the European Medicines Agency (EMEA) are followed.

Principles

13. Informed consent by a parent or legal representative shall represent the minor's presumed will.

14. The trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and the minor's stage of development.

15. The risk threshold and the degree of distress have to be specially defined and constantly monitored.

16. The interests of the patient always prevail over those of science and society.

ANNEX B

Conditions and principles which apply to the inclusion of an incapacitated adult in a clinical trial

The following conditions and principles are listed in Part 5 of Schedule 1 to the Regulations and implement Article 5 of the EU Directive.

1. The legal representative has had an interview with the investigator, or another member of the investigating team, in which opportunity has been given to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted.

2. The legal representative has been provided with a contact point where further information about the trial may be obtained.

3. The legal representative has been informed of the right to withdraw the subject from the trial at any time.

4. The legal representative has given informed consent to the subject taking part in the trial.

5. The legal representative may, without the subject being subject to any resulting detriment, withdraw the subject from the trial at any time by revoking the informed consent.

[Note: Paragraphs 1-5 do not apply where treatment is being, or is about to be provided for a subject who is an incapacitated adult as a matter of urgency and, having regard to the nature of the clinical trial and of the particular circumstances of the case:

(d) It is also necessary to take action for the purposes of the trial as a matter of urgency, but

(e) It is not reasonably practicable to meet the conditions set out in paragraph 1-5, and

(f) The action taken is carried out in accordance with a procedure approved by the ethics committee.]

6. The subject has received information, according to his or her capacity of understanding, about the trial and its risks and benefits.

7. The investigator must consider the explicit wish of a subject capable of forming an opinion and assessing the information provided. This applies both to the wish of a subject to refuse to take part, or to withdraw from the trial at any time.

8. No incentives or financial inducements are given either to the subject or to the legal representative, except the provision of compensation for injury or loss.

9. There are grounds for expecting that administering the medicinal product to be tested in the trial will produce a benefit.

10. The trial is essential to validate data obtained (a) in other clinical trials involving persons able to give informed consent, or (b) by other research methods.

11. The clinical trial relates directly to a life-threatening or debilitating clinical condition from which the subject suffers.

Principles

12. Informed consent given by a legal representative shall represent the presumed will of an incapacitated adult.

13. The trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and the cognitive abilities of the patient.

14. The risk threshold and the degree of distress have to be specially defined and constantly monitored.

15. The interests of the patient always prevail over those of science and society.