(19) The measures necessary for the implementation of this Directive should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission [1],

HAVE ADOPTED THIS DIRECTIVE:

Article 1

Scope

1. This Directive establishes specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products as defined in Article 1 of Directive 65/65/EEC, in particular relating to the implementation of good clinical practice. This Directive does not apply to non-interventional trials.

2. Good clinical practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible.

3. The principles of good clinical practice and detailed guidelines in line with those principles shall be adopted and, if necessary, revised to take account of technical and scientific progress in accordance with the procedure referred to in Article 21(2).

These detailed guidelines shall be published by the Commission.

4. All clinical trials, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of good clinical practice.

Article 2

Definitions

For the purposes of this Directive the following definitions shall apply:

(a) 'clinical trial': any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy;

This includes clinical trials carried out in either one site or multiple sites, whether in one or more than one Member State;

(b) 'multi-centre clinical trial': a clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries;

(c) 'non-interventional trial': a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data;

(d) 'investigational medicinal product': a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form;

(e) 'sponsor': an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial;

(f) 'investigator': a doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator;

(g) 'investigator's brochure': a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects;

(h) 'protocol': a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments;

(i) 'subject': an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control;

[1] OJ L 184, 17.7.1999, p. 23.

(j) 'informed consent': decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.

(k) 'ethics committee': an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent;

(l) 'inspection': the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect;

(m) 'adverse event': any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment;

(n) 'adverse reaction': all untoward and unintended responses to an investigational medicinal product related to any dose administered;

(o) 'serious adverse event or serious adverse reaction': any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect;

(p) 'unexpected adverse reaction': an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

Article 3

Protection of clinical trial subjects

1. This Directive shall apply without prejudice to the national provisions on the protection of clinical trial subjects if they are more comprehensive than the provisions of this Directive and consistent with the procedures and time-scales specified therein. Member States shall, insofar as they have not already done so, adopt detailed rules to protect from abuse individuals who are incapable of giving their informed consent.

2. A clinical trial may be undertaken only if, in particular:

(a) the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored;

(b) the trial subject or, when the person is not able to give informed consent, his legal representative has had the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted and has also been informed of his right to withdraw from the trial at any time;

(c) the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with Directive 95/46/EC are safeguarded;

(d) the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial; if the individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation;

(e) the subject may without any resulting detriment withdraw from the clinical trial at any time by revoking his informed consent;

(f) provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.

3. The medical care given to, and medical decisions made on behalf of, subjects shall be the responsibility of an appropriately qualified doctor or, where appropriate, of a qualified dentist.

4. The subject shall be provided with a contact point where he may obtain further information.

Article 4

Clinical trials on minors

In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if:

(a) the informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor;

(b) the minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits;

(c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except compensation;

(e) some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors;

(f) the corresponding scientific guidelines of the Agency have been followed;

(g) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored;

(h) the Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol; and

(i) the interests of the patient always prevail over those of science and society.

Article 5

Clinical trials on incapacitated adults not able to give informed legal consent

In the case of other persons incapable of giving informed legal consent, all relevant requirements listed for persons capable of giving such consent shall apply. In addition to these requirements, inclusion in clinical trials of incapacitated adults who have not given or not refused informed consent before the onset of their incapacity shall be allowed only if:

(a) the informed consent of the legal representative has been obtained; consent must represent the subject's presumed will and may be revoked at any time, without detriment to the subject;

(b) the person not able to give informed legal consent has received information according to his/her capacity of understanding regarding the trial, the risks and the benefits;

(c) the explicit wish of a subject who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except compensation;

(e) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods and relates directly to a life-threatening or debilitating clinical condition from which the incapacitated adult concerned suffers;

(f) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress shall be specially defined and constantly monitored;

(g) the Ethics Committee, with expertise in the relevant disease and the patient population concerned or after taking advice in clinical, ethical and psychosocial questions in the field of the relevant disease and patient population concerned, has endorsed the protocol;

(h) the interests of the patient always prevail over those of science and society; and

(i) there are grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risk at all.

Article 6

Ethics Committee

1. For the purposes of implementation of the clinical trials, Member States shall take the measures necessary for establishment and operation of Ethics Committees.

2. The Ethics Committee shall give its opinion, before a clinical trial commences, on any issue requested.

3. In preparing its opinion, the Ethics Committee shall consider, in particular:

(a) the relevance of the clinical trial and the trial design;

(b) whether the evaluation of the anticipated benefits and risks as required under Article 3(2)(a) is satisfactory and whether the conclusions are justified;

(c) the protocol;

(d) the suitability of the investigator and supporting staff;

(e) the investigator's brochure;

(f) the quality of the facilities;

(g) the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent as regards the specific restrictions laid down in Article 3;

(h) provision for indemnity or compensation in the event of injury or death attributable to a clinical trial;

(i) any insurance or indemnity to cover the liability of the investigator and sponsor;

(j) the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial subjects and the relevant aspects of any agreement between the sponsor and the site;

(k) the arrangements for the recruitment of subjects.

4. Notwithstanding the provisions of this Article, a Member State may decide that the competent authority it has designated for the purpose of Article 9 shall be responsible for the consideration of, and the giving of an opinion on, the matters referred to in paragraph 3(h), (i) and (j) of this Article.

When a Member State avails itself of this provision, it shall notify the Commission, the other Member States and the Agency.

5. The Ethics Committee shall have a maximum of 60 days from the date of receipt of a valid application to give its reasoned opinion to the applicant and the competent authority in the Member State concerned.

6. Within the period of examination of the application for an opinion, the Ethics Committee may send a single request for information supplementary to that already supplied by the applicant. The period laid down in paragraph 5 shall be suspended until receipt of the supplementary information.

7. No extension to the 60-day period referred to in paragraph 5 shall be permissible except in the case of trials involving medicinal products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms. In this case, an extension of a maximum of 30 days shall be permitted. For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or a committee in accordance with the regulations and procedures of the Member States concerned. In the case of xenogenic cell therapy, there shall be no time limit to the authorisation period.

Article 7

Single opinion

For multi-centre clinical trials limited to the territory of a single Member State, Member States shall establish a procedure providing, notwithstanding the number of Ethics Committees, for the adoption of a single opinion for that Member State.

In the case of multi-centre clinical trials carried out in more than one Member State simultaneously, a single opinion shall be given for each Member State concerned by the clinical trial.

Article 8

Detailed guidance

The Commission, in consultation with Member States and interested parties, shall draw up and publish detailed guidance on the application format and documentation to be submitted in an application for an ethics committee opinion, in particular regarding the information that is given to subjects, and on the appropriate safeguards for the protection of personal data.

Article 9

Commencement of a clinical trial

1. Member States shall take the measures necessary to ensure that the procedure described in this Article is followed for commencement of a clinical trial.

The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion and inasmuch as the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance. The procedures to reach these decisions can be run in parallel or not, depending on the sponsor.

2. Before commencing any clinical trial, the sponsor shall be required to submit a valid request for authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial.

3. If the competent authority of the Member State notifies the sponsor of grounds for non-acceptance, the sponsor may, on one occasion only, amend the content of the request referred to in paragraph 2 in order to take due account of the grounds given. If the sponsor fails to amend the request accordingly, the request shall be considered rejected and the clinical trial may not commence.

4. Consideration of a valid request for authorisation by the competent authority as stated in paragraph 2 shall be carried out as rapidly as possible and may not exceed 60 days. The Member States may lay down a shorter period than 60 days within their area of responsibility if that is in compliance with current practice. The competent authority can nevertheless notify the sponsor before the end of this period that it has no grounds for non-acceptance.

No further extensions to the period referred to in the first subparagraph shall be permissible except in the case of trials involving the medicinal products listed in paragraph 6, for which an extension of a maximum of 30 days shall be permitted. For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or a committee in accordance with the regulations and procedures of the Member States concerned. In the case of xenogenic cell therapy there shall be no time limit to the authorisation period.

5. Without prejudice to paragraph 6, written authorisation may be required before the commencement of clinical trials for such trials on medicinal products which do not have a marketing authorisation within the meaning of Directive 65/65/EEC and are referred to in Part A of the Annex to Regulation (EEC) No 2309/93, and other medicinal products with special characteristics, such as medicinal products the active ingredient or active ingredients of which is or are a biological product or biological products of human or animal origin, or contains biological components of human or animal origin, or the manufacturing of which requires such components.

6. Written authorisation shall be required before commencing clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms. No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity.

7. This authorisation shall be issued without prejudice to the application of Council Directives 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms [1] and 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms [2].

8. In consultation with Member States, the Commission shall draw up and publish detailed guidance on:

(a) the format and contents of the request referred to in paragraph 2 as well as the documentation to be submitted to support that request, on the quality and manufacture of the investigational medicinal product, any toxicological and pharmacological tests, the protocol and clinical information on the investigational medicinal product including the investigator's brochure;

(b) the presentation and content of the proposed amendment referred to in point (a) of Article 10 on substantial amendments made to the protocol;

(c) the declaration of the end of the clinical trial.

Article 10

Conduct of a clinical trial

Amendments may be made to the conduct of a clinical trial following the procedure described hereinafter:

(a) after the commencement of the clinical trial, the sponsor may make amendments to the protocol. If those amendments are substantial and are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the sponsor shall notify the competent authorities of the Member State or Member States concerned of the reasons for, and content of, these amendments and shall inform the ethics committee or committees concerned in accordance with Articles 6 and 9.

On the basis of the details referred to in Article 6(3) and in accordance with Article 7, the Ethics Committee shall give an opinion within a maximum of 35 days of the date of receipt of the proposed amendment in good and due form. If this opinion is unfavourable, the sponsor may not implement the amendment to the protocol.

If the opinion of the Ethics Committee is favourable and the competent authorities of the Member States have raised no grounds for non-acceptance of the abovementioned substantial amendments, the sponsor shall proceed to conduct the clinical trial following the amended protocol. Should this not be the case, the sponsor shall either take account of the grounds for non-acceptance and adapt the proposed amendment to the protocol accordingly or withdraw the proposed amendment;

(b) without prejudice to point (a), in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the Ethics Committee is notified at the same time;

(c) within 90 days of the end of a clinical trial the sponsor shall notify the competent authorities of the Member State or Member States concerned and the Ethics Committee that the clinical trial has ended. If the trial has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

Article 11

Exchange of information

1. Member States in whose territory the clinical trial takes place shall enter in a European database, accessible only to the competent authorities of the Member States, the Agency and the Commission:

(a) extracts from the request for authorisation referred to in Article 9(2);

(b) any amendments made to the request, as provided for in Article 9(3);

[1] OJ L 117, 8.5.1990, p. 1. Directive as last amended by Directive 98/81/EC (OJ L 330, 5.12.1998, p. 13).
[2] OJ L 117, 8.5.1990, p. 15. Directive as last amended by Commission Directive 97/35/EC (OJ L 169, 27.6.1997, p. 72).

(c) any amendments made to the protocol, as provided for in point a of Article 10;

(d) the favourable opinion of the Ethics Committee;

(e) the declaration of the end of the clinical trial; and

(f) a reference to the inspections carried out on conformity with good clinical practice.

2. At the substantiated request of any Member State, the Agency or the Commission, the competent authority to which the request for authorisation was submitted shall supply all further information concerning the clinical trial in question other than the data already in the European database.

3. In consultation with the Member States, the Commission shall draw up and publish detailed guidance on the relevant data to be included in this European database, which it operates with the assistance of the Agency, as well as the methods for electronic communication of the data. The detailed guidance thus drawn up shall ensure that the confidentiality of the data is strictly observed.

Article 12

Suspension of the trial or infringements

1. Where a Member State has objective grounds for considering that the conditions in the request for authorisation referred to in Article 9(2) are no longer met or has information raising doubts about the safety or scientific validity of the clinical trial, it may suspend or prohibit the clinical trial and shall notify the sponsor thereof.

Before the Member State reaches its decision it shall, except where there is imminent risk, ask the sponsor and/or the investigator for their opinion, to be delivered within one week.

In this case, the competent authority concerned shall forthwith inform the other competent authorities, the Ethics Committee concerned, the Agency and the Commission of its decision to suspend or prohibit the trial and of the reasons for the decision.

2. Where a competent authority has objective grounds for considering that the sponsor or the investigator or any other person involved in the conduct of the trial no longer meets the obligations laid down, it shall forthwith inform him thereof, indicating the course of action which he must take to remedy this state of affairs. The competent authority concerned shall forthwith inform the Ethics Committee, the other competent authorities and the Commission of this course of action.

Article 13

Manufacture and import of investigational medicinal products

1. Member States shall take all appropriate measures to ensure that the manufacture or importation of investigational medicinal products is subject to the holding of authorisation. In order to obtain the authorisation, the applicant and, subsequently, the holder of the authorisation, shall meet at least the requirements defined in accordance with the procedure referred to in Article 21(2).

2. Member States shall take all appropriate measures to ensure that the holder of the authorisation referred to in paragraph 1 has permanently and continuously at his disposal the services of at least one qualified person who, in accordance with the conditions laid down in Article 23 of the second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products [1], is responsible in particular for carrying out the duties specified in paragraph 3 of this Article.

3. Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 21 of Directive 75/319/EEC, without prejudice to his relationship with the manufacturer or importer, is responsible, in the context of the procedures referred to in Article 25 of the said Directive, for ensuring:

(a) in the case of investigational medicinal products manufactured in the Member State concerned, that each batch of medicinal products has been manufactured and checked in compliance with the requirements of Commission Directive 91/356/EEC of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use [2], the product specification file and the information notified pursuant to Article 9(2) of this Directive;

(b) in the case of investigational medicinal products manufactured in a third country, that each production batch has been manufactured and checked in accordance with standards of good manufacturing practice at least equivalent to those laid down in Commission Directive 91/356/EEC, in accordance with the product specification file, and that each production batch has been checked in accordance with the information notified pursuant to Article 9(2) of this Directive;

(c) in the case of an investigational medicinal product which is a comparator product from a third country, and which has a marketing authorisation, where the documentation certifying that each production batch has been manufactured in conditions at least equivalent to the standards of good manufacturing practice referred to above cannot be obtained, that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality in accordance with the information notified pursuant to Article 9(2) of this Directive.

Detailed guidance on the elements to be taken into account when evaluating products with the object of releasing batches within the Community shall be drawn up pursuant to the good manufacturing practice guidelines, and in particular Annex 13 to the said guidelines. Such guidelines will be adopted in accordance with the procedure referred to in Article 21(2) of this Directive and published in accordance with Article 19a of Directive 75/319/EEC.

[1] OJ L 147, 9.6.1975, p. 13. Directive as last amended by Council Directive 93/39/EC (OJ L 214, 24.8.1993, p. 22).
[2] OJ L 193, 17.7.1991, p. 30.

Insofar as the provisions laid down in (a), (b) or (c) are complied with, investigational medicinal products shall not have to undergo any further checks if they are imported into another Member State together with batch release certification signed by the qualified person.

4. In all cases, the qualified person must certify in a register or equivalent document that each production batch satisfies the provisions of this Article. The said register or equivalent document shall be kept up to date as operations are carried out and shall remain at the disposal of the agents of the competent authority for the period specified in the provisions of the Member States concerned. This period shall in any event be not less than five years.

5. Any person engaging in activities as the qualified person referred to in Article 21 of Directive 75/319/EEC as regards investigational medicinal products at the time when this Directive is applied in the Member State where that person is, but without complying with the conditions laid down in Articles 23 and 24 of that Directive, shall be authorised to continue those activities in the Member State concerned.

Article 14

Labelling

The particulars to appear in at least the official language(s) of the Member State on the outer packaging of investigational medicinal products or, where there is no outer packaging, on the immediate packaging, shall be published by the Commission in the good manufacturing practice guidelines on investigational medicinal products adopted in accordance with Article 19a of Directive 75/319/EEC.

In addition, these guidelines shall lay down adapted provisions relating to labelling for investigational medicinal products intended for clinical trials with the following characteristics:

— the planning of the trial does not require particular manufacturing or packaging processes;

— the trial is conducted with medicinal products with, in the Member States concerned by the study, a marketing authorisation within the meaning of Directive 65/65/EEC, manufactured or imported in accordance with the provisions of Directive 75/319/EEC;

— the patients participating in the trial have the same characteristics as those covered by the indication specified in the abovementioned authorisation.

Article 15

Verification of compliance of investigational medicinal products with good clinical and manufacturing practice

1. To verify compliance with the provisions on good clinical and manufacturing practice, Member States shall appoint inspectors to inspect the sites concerned by any clinical trial conducted, particularly the trial site or sites, the manufacturing site of the investigational medicinal product, any laboratory used for analyses in the clinical trial and/or the sponsor's premises.

The inspections shall be conducted by the competent authority of the Member State concerned, which shall inform the Agency; they shall be carried out on behalf of the Community and the results shall be recognised by all the other Member States. These inspections shall be coordinated by the Agency, within the framework of its powers as provided for in Regulation (EEC) No 2309/93. A Member State may request assistance from another Member State in this matter.

2. Following inspection, an inspection report shall be prepared. It must be made available to the sponsor while safeguarding confidential aspects. It may be made available to the other Member States, to the Ethics Committee and to the Agency, at their reasoned request.

3. At the request of the Agency, within the framework of its powers as provided for in Regulation (EEC) No 2309/93, or of one of the Member States concerned, and following consultation with the Member States concerned, the Commission may request a new inspection should verification of compliance with this Directive reveal differences between Member States.

4. Subject to any arrangements which may have been concluded between the Community and third countries, the Commission, upon receipt of a reasoned request from a Member State or on its own initiative, or a Member State may propose that the trial site and/or the sponsor's premises and/or the manufacturer established in a third country undergo an inspection. The inspection shall be carried out by duly qualified Community inspectors.

5. The detailed guidelines on the documentation relating to the clinical trial, which shall constitute the master file on the trial, archiving, qualifications of inspectors and inspection procedures to verify compliance of the clinical trial in question with this Directive shall be adopted and revised in accordance with the procedure referred to in Article 21(2).

Article 16

Notification of adverse events

1. The investigator shall report all serious adverse events immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.

2. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.

3. For reported deaths of a subject, the investigator shall supply the sponsor and the Ethics Committee with any additional information requested.

4. The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the Member States in whose territory the clinical trial is being conducted, if they so request.

Article 17

Notification of serious adverse reactions

1. (a) The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

(b) All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor.

(c) Each Member State shall ensure that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are recorded.

(d) The sponsor shall also inform all investigators.

2. Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

3. (a) Each Member State shall see to it that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are immediately entered in a European database to which, in accordance with Article 11(1), only the competent authorities of the Member States, the Agency and the Commission shall have access.

(b) The Agency shall make the information notified by the sponsor available to the competent authorities of the Member States.

Article 18

Guidance concerning reports

The Commission, in consultation with the Agency, Member States and interested parties, shall draw up and publish detailed guidance on the collection, verification and presentation of adverse event/reaction reports, together with decoding procedures for unexpected serious adverse reactions.

Article 19

General provisions

This Directive is without prejudice to the civil and criminal liability of the sponsor or the investigator. To this end, the sponsor or a legal representative of the sponsor must be established in the Community.

Unless Member States have established precise conditions for exceptional circumstances, investigational medicinal products and, as the case may be, the devices used for their administration shall be made available free of charge by the sponsor.

The Member States shall inform the Commission of such conditions.

Article 20

Adaptation to scientific and technical progress

This Directive shall be adapted to take account of scientific and technical progress in accordance with the procedure referred to in Article 21(2).

Article 21

Committee procedure

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use, set up by Article 2b of Directive 75/318/EEC (hereinafter referred to as the Committee).

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period referred to in Article 5(6) of Decision 1999/468/EC shall be set at three months.

3. The Committee shall adopt its rules of procedure.

Article 22

Application

1. Member States shall adopt and publish before 1 May 2003 the laws, regulations and administrative provisions necessary to comply with this Directive. They shall forthwith inform the Commission thereof.

They shall apply these provisions at the latest with effect from 1 May 2004.

When Member States adopt these provisions, they shall contain a reference to this Directive or shall be accompanied by such reference on the occasion of their official publication. The methods of making such reference shall be laid down by Member States.

2. Member States shall communicate to the Commission the text of the provisions of national law which they adopt in the field governed by this Directive.

Article 23

Entry into force

This Directive shall enter into force on the day of its publication in the Official Journal of the European Communities.

Article 24

Addressees

This Directive is addressed to the Member States.

Done at Luxembourg, 4 April 2001.

For the European Parliament	*For the Council*
The President	*The President*
N. FONTAINE	B. ROSENGREN

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 03/12/2009
ENTR/F/2/SF/dn D(2009) 35810

Detailed guidelines on good clinical practice specific to advanced therapy medicinal products

Please note: These guidelines have been developed to address specific issues related to good clinical practice for clinical trials involving advanced therapy medicinal products.

The final adoption of these guidelines by the College of Commissioners is foreseen once more practical experiences have been gained with the specificities of clinical trials involving advanced therapy medicinal products.

Pending the final adoption of this guideline, it is recommended to apply the rules and principles set out in this text.

1. INTRODUCTION AND SCOPE

1. Article 4(2) of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004[1] requires the Commission to draw up detailed guidelines on good clinical practice ("**GCP**") specific to advanced therapy medicinal products ("**ATMP**").

2. These guidelines do not replace but supplement the principles and detailed guidelines set out in the Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.[2] They should be read in conjunction with the detailed guidelines set out in Volume 10 of the Rules Governing Medicinal Products in the European Union[3], including in particular the Note for guidance on Good Clinical Practice[4], as well as other guidelines specific to advanced therapies.[5]

2. DEFINITIONS

3. The definitions set out in Directive 2005/28/EC and in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the

---

1 OJ L 324, 10.12.2007, p. 121.
2 OJ L 91, 9.4.2005, p. 13.
3 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm
4 CPMP/ICH/135/95
5 http://www.emea.europa.eu/htms/human/mes/advancedtherapies.htm

laws, regulation 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[6] apply.

4. Moreover, for the purpose of these guidelines, the following definitions shall apply:

- 'advanced therapy investigational medicinal product' ("**ATIMP**") means a ATMP as defined in Article 2(1) of Regulation 1394/2007 which is tested or used in accordance with Article 2(d) of Directive 2001/20/EC;

- 'procurement organisation' means a health care establishment or a unit of a hospital or another body that undertakes the procurement of human tissues and cells and that may not be accredited, designated, authorised or licensed as a tissue establishment;[7]

- 'traceability' means the ability to locate and identify each individual unit of tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal and vice versa. This also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storing the tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying the tissue/cells to the recipient(s); traceability also covers the ability to locate and identify all relevant data relating to products and materials coming into contact with those tissues/cells;[8]

- 'tissue establishment' means a tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells;[9]

- 'procurement' means a process by which tissue or cells are made available;[10]

- 'human application' means the use of tissues or cells on or in a human recipient and extracorporeal applications;[11]

- 'blood establishment' means any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components,

---

6 OJ L 121, 1.5.2001, p. 34.

7 Cf. Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells (OJ L 204, 25.10.2009, p. 32).

8 Idem.

9 Cf. Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety fort he donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L 102, 7.4.2004, p. 48).

10 Idem.

11 Idem.

whatever their intended purpose, and their processing, storage, and distribution when intended for transfusion. This does not include hospital blood banks;[12]

- 'animal facility' means a facility where the activities as described in the guideline on xenogenic cell-based medicinal products[13] are carried out;

- 'clinical follow-up' shall mean a follow-up of individual subjects conducted by healthcare professionals. It includes prevention, screening, monitoring, diagnosis and treatment of diseases, injuries, complications, adverse reactions and medical errors;[14]

- 'safety follow-up' shall mean any systematic collection and collation of data that is designed in a way that enables learning about safety of a medicinal product. It may include passive or active surveillance, observational studies, or clinical trials;[15]

- 'efficacy follow-up' shall mean any systematic collection and collation of data that is designed in a way that enables learning about efficacy or effectiveness of a medicinal product. It may include passive or active surveillance, observational studies, or clinical trials;[16]

- 'donor' shall mean any human or animal source, whether living or deceased, of human cells or tissues;

- 'donation' shall mean donating human or animal tissues or cells intended for human applications.

3. DONATION, PROCUREMENT AND TESTING OF ATIMPS

5. As regards ATIMPs, apart from the sponsor, investigator and manufacturer/importer, other actors have to be considered, including tissue/blood establishments, procurement organisations, animal facilities and donors. It is important to put the role of these parties, and the applicable legislation, in the context of the roles and responsibilities for clinical trials.

6. The donation, procurement and testing of human cells and tissues used for the manufacturing of an ATIMP are carried out in accordance with the

- Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety fort he donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells;[17] and

---

12 Cf. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (OJ L 33, 8.2.2003, p. 30).

13 EMEA/CHMP/CPWP/83508/2009.

14 EMEA/149995/2008.

15 Idem.

16 Idem.

17 OJ L 102, 7.4.2004, p. 48.

- Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC,[18]

7. as well as their implementing acts:

- Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells[19] ;

- Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells[20]

- Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components.[21]

- Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events[22]; and

- Commission Directive 2005/62/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments[23]

8. In particular, where an ATIMP to be used in a clinical trial contains human cells or tissues, the legal obligations in relation to the donors (e.g. consent, eligibility of donors, compensation, data protection and confidentiality, selection, evaluation and procurement) are laid down in Directive 2004/23/EC (Articles 12, 13, 14 and 15) and its implementing Directives, . Regarding human blood cells, they are laid down in Directive 2002/98/EC (Articles 16- 24) and its implementing Directives.

9. Where tissues or cells are sourced from an animal origin for the manufacture of an ATIMP the processes related to donation are covered by the Annex 2 to the Good Manufacturing Practice ("**GMP**") Guidelines[24] and the guideline on xenogenic cell-based medicinal products.[25]

---

18 OJ L 33, 8.2.2003, p. 30.
19 OJ L 38, 9.2.2006, p. 40.
20 OJ L 32, 25.102.2006, p. 294.
21 OJ L 91, 30.3.2004, p. 25.
22 OJ L 256, 10.2.2005, p. 32.
23 OJ L 256, 1.10.2005, p. 41.
24 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm
25 EMEA/CHMP/CPWP/83508/2009.

4. TISSUE OR BLOOD ESTABLISHMENTS AND ANIMAL FACILITIES

10. The responsibilities of the tissue or blood establishment and procurement organization with respect to donation, procurement, testing, traceability requirements, and other technical requirements (e.g. processing, preservation, storage and distribution) of human tissues and cells, including blood cells, to be used for the manufacture of an ATIMP are set out in the Directives referred to in section 3.

11. When tissues or cells of animal origin are used in the manufacture of ATIMPs the requirements for sourcing/donation, procurement and testing are set out in Annex 2 to the GMP Guidelines and in the guideline on xenogenic cell-based medicinal products.

5. MANUFACTURING AND IMPORTATION OF ATIMP

12. The requirements for the manufacture and import of ATIMPs are laid down in Article 13 of Directive 2001/20/EC.

6. OVERARCHING PRINCIPLES

13. The use of each ATIMP should be traceable. The individual product should be traceable through the sourcing, manufacturing, packaging, storing, transport, delivery to the hospital/institution/private practice, administration to the subjects, reconciliation and destruction or final disposition.

14. The number of links in the chain of custody (from donation to subject application) should be no more than necessary. If the product or part of it originates from a donor, records should contain sufficient detail to allow linking from the donor to the individual subject who received the product and vice versa.

15. Subjects should be followed-up during and, if necessary, after the end of the clinical trial both for their own care and to allow data collection as needed. The nature of follow-up and, if applicable, long-term follow-up after the end of the trial should be determined based on the nature of the ATIMP, the current state of knowledge regarding that ATIMP and a risk analysis. Processes should be established to enable contact with subjects to be maintained throughout the required follow up period.

16. In some situations, e.g. human embryonic stem cells, tissue establishments may also need to undertake significant processing activities to derive stem cell lines to the point that they have clinical value before their transfer to a manufacturer of the ATIMP.

17. Where tissues or cells of animal origin are used in the manufacture of an ATIMP, the sourcing procurement and testing should be carried out in accordance with the Annex 2 to the GMP Guidelines and the guideline on xenogenic cell-based medicinal products, unless for some specific cells and tissues of animal origin (e.g. cell lines used for production of viral vectors) other guidelines have become available in the light of experience and further developments.

18. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or a qualified dentist.[26] However there may be circumstances where a representative of the sponsor experienced in the administration of the ATIMP needs to be present during the application of the ATIMP to the subject. This expert may provide advice and information to the investigator/responsible physician but the investigator/responsible physician remains responsible for any decision to halt or modify the application procedure.

7. TRACEABILITY

7.1. General requirements

19. Where an ATIMP contains human cells or tissues, the sponsor of the trial, the manufacturer and the investigator/institution where the product is used should ensure that there is a traceability system in place complementary to, and compatible with, the requirements laid down in the Directives referred in section 3, which already set out the traceability requirements for tissue and blood establishments. Where the tissues or cells are of animal origin the same requirements for traceability apply as indicated in the guideline on xenogenic cell-based medicinal products.

20. This means that at the tissue establishment/animal facility there has to be a link between the donor/animal source and the donation, at the manufacturing site there has to be a link between donation and product and at the investigator/institution site there has to be a link between the product and the subject. The traceability has to work in both directions from source to subject and from subject to source.

21. GCP contains requirements for accountability of IMPs. These requirements contribute significantly to the traceability of an IMP from the point of release of the IMP from the manufacturer onwards. The requirements for traceability may be achieved by ensuring that the systems established for traceability and for IMP accountability are integrated so that the special requirements of each are addressed.

22. Traceability requirements should also be compatible with the requirements in Annexes 2 to the GMP Guidelines and 13 to the GMP Guidelines as amended for the specific requirements of ATIMPs.

23. The guideline on traceability referred to in Article 15(7) of the Regulation 1394/2007 should also be applicable to clinical trials on ATIMPs.

24. In the event that the clinical trial is suspended or prematurely ended or the product development discontinued, the sponsors retains their obligations to ensure that the traceability system is maintained. If the ownership of the ATIMP is transferred to another legal entity, the new owner should take responsibilities for maintaining the traceability. In case of bankruptcy or liquidation of the sponsor, and in the event that the ownership is not transferred to another legal entity, the traceability records shall be transferred to the national competent authority.

---

[26] Principle 2.7 of CPMP/ICH/135/95.

25. The traceability procedures and the documentation process should be described in the clinical trial protocol and amended as needed.

26. The requirements for traceability are without prejudice to the provision of Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.[27] Therefore the system should allow full traceability from the donor to the recipient through anonymous coding systems ensuring that:

- The identities of the human donors are protected and that they are only identified by code numbers that can be linked to their full identity by the tissue/blood establishments; and

- The subject identity is protected and is only identified by code numbers that can be linked to their full identity by the investigator/institution where the product is used.

7.2. Responsibilities

7.2.1. Responsibility of the sponsor

27. The sponsor of a clinical trial with an ATIMP is responsible for ensuring that a traceability system is established and maintained. The system should ensure that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the investigator/institution where the product is used, application of the product to the subject or other final reconciliation, disposal or destruction of the product.

28. Where multiple parties are involved the sponsor should ensure that the role of each is clear (*e.g.* where the surgeon obtaining the tissue or cells from an autologous donor prior to the manufacturing of the ATIMP is located at the same site as the investigator responsible for its administration to the subject) and that the integrity of the traceability is maintained.

29. The sponsor should guarantee the establishment and maintenance of the traceability system through contractual agreements with the tissue or blood establishment or animal facility, the manufacturer and the investigator/institution, ensuring that the ATIMP can be linked via the procurement organisation to the donor/donation and via the investigator/institution where the product is used to the subject, and *vice versa*.

7.2.2. Responsibility of the tissue/blood establishment, procurement organisations, or animal facility

30. The tissue or blood establishment or procurement organisation or animal facility is responsible for implementing a traceability system with respect to the donation and procurement of the cell or tissue material needed for the manufacturing of the ATIMP, up to the delivery of that material to the manufacturer. These activities are addressed in the Directives referred to in section 3 for human tissues, cells and blood

---

[27] OJ L 281, 23.11.1995, p. 31,.

and in Annex 2 to the GMP Guideline, and in the guideline on xenogenic cell-based medicinal products for cells/tissues of animal origin. The Directives referred to in section 3 also cover the data protection and confidentiality of the human donors.

7.2.3. Responsibility of the manufacturer of the ATIMP

31. The manufacturer is responsible for implementing a traceability system during the manufacturing process from receipt from the procurement organisation, tissues/cell/blood establishment or animal facility up to the release of the finished ATIMP to the sponsor for use in the clinical trial and its delivery to the clinical trial site, where the latter is also undertaken by the manufacturer or under their control. Where the sponsor takes care of the delivery of the ATIMP from the manufacturer to the clinical trial site the sponsor is responsible for ensuring traceability through that step of the process.

7.2.4. Responsibility of the investigator/institution

32. The investigator or pharmacist or other individual who is designated by the investigator is responsible for implementing a system for subject and product traceability at the clinical site. That system should contain sufficient detail to allow linking of each product delivered to the investigator to the subject receiving it and *vice versa.*

7.3. Archiving by the sponsor, manufacturer and the investigator/institution for traceability

33. The sponsor of the trial, the tissue establishments/procurement organization, the animal facility, the manufacturer and the investigator/institution where the ATIMP is used, should keep their parts of the traceability records for a minimum of 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by the agreement with the sponsor. In the case of the tissue establishments, if that period is longer than provided in the Directives referred to in section 3, the sponsor should ensure through contractual agreements that the traceability records are kept for that longer period.

34. The minimum data set to be kept by each party is outlined in the Annex.

8. SAFETY REPORTING AND LONG TERM FOLLOW-UP

8.1. Notification of Adverse Events and Reactions

35. The requirements for notification of adverse events and adverse reactions by the investigator and the sponsor in the context of clinical trials are laid down in Articles 16 and 17 of Directive 2001/20/EC and their implementing guidelines.[28] New events related to the conduct of the trial or the development of the ATIMP and likely to affect the safety of the subjects should be reported according to the existing timelines for expedited reporting. This includes:

---

28 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm

- serious adverse events which could be associated with the trial procedures and which could require modification of the conduct of the trial;

- significant hazard to the subject population.

36. The sponsor should provide information and training to the investigator on any additional protocol and/or product specific requirements for the reporting of adverse events and this reporting process should be outlined clearly in the clinical trial protocol. The following safety issues are of particular concern:

- Adverse events related to the product application process (surgical or other);

- Suspected or confirmed cases of infection;

- Unexpected reactions (e.g. hypersensitivity, immunological, toxic or other as consequence of a change in the construction or function of the viral vector (e.g. generation of replication competent virus);

- Adverse events related to product failure (including lack of efficacy);

- Adverse events related to mandatory concomitant medication (e.g. immunosuppression);

- Adverse events related to medical devices which form part of the product or are used for application of the product.

37. Differentiated causality assessment concerning the safety issues mentioned above should be described in the clinical trial protocol and implemented in the adverse event reporting system.

38. The national competent authority of the Member State where a serious adverse reaction occurs in a clinical trial with an ATIMP containing cells or tissues or a combined ATIMP should inform the relevant national authorities responsible for the implementation of the Directives referred to in section 3 (only applicable to ATIMP containing human cells or tissues) and the relevant national authority responsible for the Directives on medical devices (applicable to both, ATIMP containing human or animal cells or tissues).

8.2. Follow up

39. The need for, the duration and the nature of follow up should be determined by the sponsor for each clinical trial based on the nature of the ATIMP, the current state of knowledge regarding that ATIMP and a risk analysis, including the risk for close contacts and offspring. The sponsor should also take into account any Community guidance on risk assessment and follow-up of subjects treated with particular types of ATIMPs which may provide more details on the follow up period and kind of follow up to be expected.

40. The sponsor may wish to discuss the duration of follow up with the concerned national competent authority. This follow up should be aligned with the specific requirements of the product under development, should be described in the protocol, and amended as needed in accordance with the evolving experience with the ATIMP,

and should make clear which follow up activities should take place prior to and after the end of the clinical trial. The rationale for the chosen follow up, including the available supporting information, should be documented and kept as an essential clinical trial document as indicated in section 15.

41. The follow up should be considered from the following aspects:

- follow up for the protection of the subject i.e. clinical follow up;
- follow up for the purpose of collection of specific data (which might not involve all subjects) i.e. safety follow up and efficacy follow up.

42. All subjects participating in a clinical trial with an ATIMP should receive from the investigator an alert card, which has been previously agreed by the sponsor and approved by the Ethics Committee, containing as minimum the name of the subject, the investigator contact number and information regarding the medical treatment received.

43. The protocol should define the end of the trial and which follow up should take place after the end of the trial. The safety and efficacy follow up involving active data collection (study visits etc.) should form part of the clinical trial whereas clinical follow up and passive data collection may take place after the end of the trial.

44. Where follow up after the end of the trial is required, in particular when this occurs over a long term, the sponsor needs to ensure that there is a process in place for follow up of the subjects treated with the product even in cases where the product development is discontinued or the (former) sponsor ceases to exist as a legal entity. This process should be described in the protocol, which should be amended as needed, and may be achieved, for instance, by:

- appropriate information about follow up of the subjects after the end of the clinical trial provided to healthcare establishments that served as centres for the particular clinical trial;
- websites/phone-lines that provide data/consultation in case of complications;
- subject alert cards that inform treating physicians about the product used and any independent registries or other sources of data available in case of safety/efficacy issues, and of the need to inform the national competent authority, the investigational sites and the sponsor in the event of certain serious adverse reactions. These alert cards should contain as minimum the name of the subject, a physician contact number and information regarding the medical treatment received. They should have been previously agreed by the sponsor and approved by the Ethics Committee. This may be the same as the one used for the clinical trial if changes or additional information is not required to address further follow up after the end of the trial.

45. Where a subject is withdrawn from a trial at their own request or based on a decision of the investigator the follow up should be maintained, subject to the consent of the subject.

9. NATIONAL COMPETENT AUTHORITIES

46. The national competent authorities when assessing the request for authorisation of a clinical trial involving an ATIMP should consider in particular the adequateness of traceability arrangements and the follow up strategy, including the definition of the end of the trial and risk-assessment.

10. ETHICS COMMITTEE

47. As regards clinical trials involving an ATIMP, the Ethics Committee should in particular check:

(a) The arrangements for traceability as regards provisions for subject data protection and confidentiality (see section 7);

(b) The arrangements for follow up before and after the end of the trial, including after subjects withdraw from the study and including the information (alert card) to be provided to each subject for use in the event of problems arising after the end of the trial (see section 8.2);

(c) The arrangement when follow up needs to include close contact and offspring of the recipients;

(d) The written informed consent as regards ethical concerns of particular relevance for ATIMPs. (see informed consent issues in section 10;

(e) The circumstances where a representative of the sponsor experienced in the administration of the ATIMP needs to be present during the application of the ATIMP to the subject.

48. The following should be taken into account by the Ethics Committees when assessing the ethics of a clinical trial involving an ATIMP:

- The irreversible nature of certain ATIMP applications, and the information provided to subjects in that context;
- The peculiarities of situations where the donor is a relative of the subject to be included in the trial, in particular the protection from "sibling/parent" pressure.

11. INVESTIGATOR

49. In the context of clinical trials with ATIMPs, investigators should:

(a) establish and maintain a system for traceability at the clinical site (see section 7.1 and 7.2.4);

(b) keep their part of the traceability records for the required period (see section 7.3 and 15);

(c) be aware of the adverse event and adverse reaction reporting process, including reactions related to application of the ATIMP (see section 8.1);