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MINISTERIAL DECREE of 17th December, 2004

Prescriptions and conditions of a general nature referring to the conduct of clinical trials of medicines, with special reference to those designed to enhance clinical practice as an integral part of health and medical care.

(Italian Official Journal no. 43 of 22nd February, 2005)

THE MINISTER OF HEALTH

Having regard to legislative decree no. 211 of 24 June 2003 implementing Directive 2001/20/EC governing the application of good clinical practice in the clinical testing of medicines for clinical use;

Having regard in particular to article 20 paragraph 4 of the foresaid legislative decree no. 211 of 24 June 2003 in which provision is made for establishing by decree of the Minister of Health, with full respect of the directives and recommendations of the European Union, conditions and prescriptions of a general nature governing the execution of clinical trials of medicines;

Having regard to section no. 14 of Directive 2001/20/EC which establishes that non commercial clinical trials can be of great utility for the patients concerned and that it is advisable to take account of the specific nature of such clinical trials;

Having regard to Ministerial Decree of 15 July 1997 published in the Ordinary Supplement to the *Official Journal* no. 191 of 18 August 1997 implementing the transposition of the European Union guidelines governing good clinical practice in the execution of a clinical trials of medicines;

Having regard to the Council of Europe convention on the protection of human rights and human dignity in the application of biology and medicine signed at Oviedo on 4 April 1997;

Whereas in the framework of the activities of the non-profit National Health Service clinical trials of medicines aimed at enhancing clinical practice that as such are an integral part of health and medical care;

Also having regard to the need to identify operating modes facilitating the execution of the trials;

After hearing the State-Regions Conference at the session of 11 November 2004;

HEREBY ISSUES:

Art. 1

1. The present decree lays down conditions and establishes prescriptions of a general nature referring to the execution of clinical trials intended to enhance clinical practice as an integral part of health and medical care and not for industrial purposes.

2. Any trial included in the definition contained in article 2, paragraph 1, section a) of legislative decree no. 211 of 2003 shall be deemed to be included among the trials defined in paragraph 1 provided it satisfies all the following requirements:

- a) that the promoter mentioned in article 2 paragraph 1, section e) of legislative decree no. 211 of 2003 is a research or healthcare structure or public entity or institution or the equivalent or a foundation or moral entity or a non profit scientific or research association/society or a scientific hospital and treatment Institute or a person belonging to one of these structures and which performs the role of promoter within the framework of its statutory tasks;
- b) that the promoter is not the owner of the patent of the trial drug or the holder of the authorization to market it and has no economic co-interest in the company manufacturing the trial drug;
- c) that the ownership of the data referring to the trial, its performance and its results belong to the promoter mentioned in section a), without prejudice to current legislation governing the publication of the data;
- d) that the trial is not aimed at or used for the industrial development of the drug and in any case not for profit;
- e) that it should be aimed at enhancing clinical practice and be recognized for this purpose by the competent Ethics Committees as a significant trial and, as such, an integral part of health and medical care.

Art. 2

1. The expenditure on medicines authorized for introduction on the market (AIC) used within the scope of this authorization and considered as chargeable to the National Health Services continues to be borne by the latter if used by patients involved in the clinical trials described in article 1.
2. Any additional expenditure, including the cost of the trial drug, required for the clinical trials described in article 1, unless covered by *ad hoc* research funds, may be charged to the funds mentioned in paragraph 3 within the constraints imposed by the financial resources of the competent health care structure and compatible with the economic planning of the structure itself.
3. The Directors General of the Local Healthcare Authorities and of the Hospital Organizations, as well as the governing bodies of the structures mentioned in section a) paragraph 1, article 1, wherever applicable, in accordance with the indications given by the Autonomous Regions and Provinces, shall take the necessary steps to set up a fund for the trials described in article 1 promoted by the structure itself. This fund may comprise funds possessed by the health care structure, including any deriving from contracts with pharmaceutical companies as mentioned in paragraph 6, article 6 of legislative decree no 211 of 2003, as well as part of the revenue from the charges made for issuing the single opinion of the Ethics Committee, for the acceptance or rejection of this opinion by other Ethics Committees, for the issue of the permit of the competent Authority mentioned in article 2, paragraph 1, section t), number 1 and articles 6 and 7, paragraphs 1 and 3, respectively, of legislative decree no. 211 of 2003.
4. The Directors General of the local Health Care and Hospital Organizations as well as the governing bodies of the structures mentioned in section a), paragraph 1, article 1, wherever applicable, in accordance with the indications given by the Autonomous Regions and Provinces, shall take the necessary steps to ensure that, for the trials envisaged in article 1, the relative insurances mentioned in article 3, paragraph 1, section f) of legislative decree no. 211 of 2003 are included in the general insurance framework envisaged for the structure's general clinical or research activity.
5. The trials specified in article 1 are not subject to the payment of the charge for the issue of the single opinion by the Ethics Committee, for the acceptance or rejection of such an opinion by other Ethics Committee, for the authorization of the competent local or national Authority mentioned in article 2, paragraph 1, section t), and articles 6 and 7, paragraphs 1 and 3, respectively, of legislative decree no. 211 of 2003.
6. For the trials mentioned in article 1, any use of funds, equipment, drugs, material or services made available by drug companies or in any case by third parties must be notified at the time of the request for the opinion of the Ethics Committee and for the authorization of the competent Authority specified in legislative decree no. 211 of 2003.
7. The use of the support or contributions specified in paragraph 6, must not alter the requirements and conditions specified in article 1, or affect the scientific, technical and procedural autonomy of the experimenters.
8. The General Directions of the Health Care and Hospital Organizations, as well as the governing bodies of the structures mentioned in article 1, paragraph 2, section a), shall communicate to the Autonomous Regions and Provinces to which they belong, whenever requested, the data specified in article 2, paragraphs 1, 2, 3, 4 and 6 in accordance with the procedure laid down by the Autonomous Regions and Provinces themselves.

Art. 3

1. In the case of multicentre trials as specified in article 2, paragraph 1, section *b*) of legislative decree no. 211 of 2003, whenever several structures or persons delegated to performing the various tasks of the promoter are present, a single promoter must be selected from among them as referent and who is responsible for the tasks of pharmacovigilance and the communication of the beginning, end, and interruption of the trial as well as of the relative results as specified in legislative decree no. 211 of 2003, as well as for the presentation of the request for the single opinion of the Ethics Committee for the authorization of the Ministry of Health and of the National Health Institute in the cases specified in article 2 paragraph 1, section *t*), numbers 2) and 3) of legislative decree no. 211 of 2003. The foresaid single promoter is obliged to report to the holder of the authorization to market the product or the person responsible for the development of the drug any events and adverse reactions as specified in article 16, paragraphs 1 and 2, and article 17, paragraphs 3 and 5 of legislative decree no. 211 of 2003.

Art. 4

1. Prior to the coming into force of the decree of the Minister of Health mentioned in article 1, paragraph 3, of legislative decree no. 211 of 2003 transposing into national legislation the principles of good clinical practice adopted by the European Commission laying down detailed guidelines in compliance with these principles, the clinical trials mentioned in article 1 must be conducted having due regard to the rules of Good Clinical Practice specified in annex 1 to Ministerial Decree of 15 July 1997 cited in the introduction as regards the applicable parts and not related to the authorizations for marketing, without prejudice to the obligation to follow the principles of good clinical practice mentioned in paragraph 2 of the same annex 1.

2. In the case of the trials mentioned in article 1 the Drug Companies are obliged to make available to the single promoter mentioned in article 3, paragraph 1, the pharmacovigilance data for subsequent communication by the promoter itself to the Ethics Committee(s) concerned and for the decisions for which it is responsible, as well as a copy of the updated versions of the experimenter's dossiers, without prejudice to the confidentiality of data referring to the industrial aspects. The availability and transmission of the above data may be defined in the ways indicated on the web site of the Italian Monitoring Centre for Clinical Trials (OsSC).

Art. 5

1. The medical and health care personnel involved in the trials as specified in article 1 are eligible for the Continuing Medical Education (CME) provided for by the National Continuing Education Commission pursuant to article 16 of legislative decree no. 229 of 19 June 1999 in accordance with the relevant provisions contained in the agreements reached in the State-Regions Conference.

Art. 6

1. The provisions of the present decree, with the exception of article 2, paragraphs 1 and 2, have been extended to cover also trials that, although not aimed at the enhancement of clinical practice, nevertheless satisfy the requirements specified in art.1, paragraph 1, sections *a*), *b*), *c*), *d*).

Art. 7

1. The Italian Monitoring Centre for Clinical Trials mentioned in article 11, paragraph 4 of legislative decree no. 211 of 2003, lays down the operating procedures for the digital communication of data referring to the trials mentioned in article 1 to the Italian Medicines Agency (AIFA) as well as the Autonomous Regions and Provinces concerned.

2. The Italian Medicines Agency (AIFA) and Autonomous Regions and Provinces concerned shall receive from the single promoter provided for in article 3, paragraph 1 a copy of the communication specified in paragraph 1, including the self-certification of the compliance of the clinical trial with the requirements laid down in article 1, paragraph 1, requesting, wherever necessary, supplementary preliminary information from the promoters and the Ethics Committee.

Art. 8

1. The type of reference, the requirements and the criteria regarding identification by the Ethics Committees of the types of trial as mentioned in article 1, are set out in annex 1.
2. The reference elements required by the Ethics Committee to evaluate the economic co-interests mentioned in article 1, paragraph 1, section *b*) are set out in annexes 1 and 2.

Art. 9

1. Annexes 1 and 2 are an integral part of the present decree.

Art. 10

1. The provisions contained in paragraphs 1, 2 and 3 of article 2 of the present decree, at the preliminary implementation stage, are applied to enhancing clinical practice as an integral part of health care although limited to the trials in which drugs already approved for introduction to the market are used, even when employed for different therapeutic purposes and in a different dosage or pharmaceutical form.
2. The Autonomous Regions and Provinces of Trento and Bolzano shall take the necessary steps to apply the provisions contained in the present decree.

Art. 11

1. The present decree shall come into effect on the ninetieth day after its publication in the *Official Journal* of the Italian Republic.

The present decree shall be transmitted to the control bodies for registration.

Rome, 17th December 2004

Sirchia, Minister of Health

Annex 1

A. Types of trial

1. Trials not for private interest or profit but in the public interest.
2. Trials that may be denoted as significant for the enhancement of clinical practice and, as such, an integral part of health and medical care.
3. Trials aimed not at the medicine as such or at its development but at therapeutic strategies.

e.g.

- *to define the best therapeutic regime (risks/benefits) of approved drugs;*
- *enhancement of the therapeutic use of drugs (e.g. by laying down improved therapeutic protocols, identifying associations or sequential use of drugs or drugs plus other more effective action – surgery, radiotherapy, etc.).*

4. Trials of importance for public health, pursuing objectives:

- having a clear benefit for patients and/or for the cost effectiveness of the health care system;
- capable of providing opportunities in addition to the patients' therapeutic and health prospects;
- capable of optimizing the quality of the health care benefits

5. Trials in which the objective of a real enhancement of clinical practice is guaranteed by:

- the significance of the protocol
- the specific nature of the pathology
- the type of treatment

B. Requirements

1. Trials, the methodology of which is a guarantee of scientific/methodological reliability and of objectivity of the results (controlled, preferably randomized).
2. Trials for which suitable measures are envisaged to ensure the quality of their execution and of the data produced; these measures (including a form of monitoring predefined in the research protocol, the extent and typology of which should be commensurate with the objective, purpose, complexity and characteristics of the trial) may be:

- a) either ad hoc for the trial;
- b) or provided for by the quality system of the structure for trials promoted by the structure itself.

C. Checklist of the conditions envisaged in the Decree articles.

Necessary verifications by ECs for the definition of a study aimed at enhancing clinical practice as an integral part of health and medical care which is non profit vis-à-vis the drugs tested:

	Proposed trials pursuant to art. 1	Proposed trials pursuant to art. 6
<i>a)</i> is the trial promoter a public institution or the equivalent or, in the case of associations or private cooperatives, clearly defined in the by-laws of the non-profit structure itself?	YES	YES
<i>b)</i> is it envisaged that the ownership of the data referring to the trial, its performance, its results belong to the structure mentioned in section a) acting as promoter?	YES	YES
<i>c)</i> is it envisaged that the results of the trial will be published by independent decision of the promoter mentioned in section a)?	YES	YES
<i>d)</i> is the trial promoter the owner of the patent for the trial drug or the holder of the authorization to market the drug?	NO	NO
<i>e)</i> is the trial aimed at the industrial development of the drug or in any case for profit?	NO	NO

	Proposed trials pursuant to art. 1	Proposed trials pursuant to art. 6
<p>j) does the trial at least comply with all 13 of the principles of the Rules of Good Clinical Practice specified in paragraph 2 of annex 1 to Ministerial Decree of 15 July 1997 indicated below?</p> <p>2. PRINCIPLES OF THE RULES OF GOOD CLINICAL PRACTICE</p> <p>2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with GCP and the applicable regulatory requirement(s).</p> <p>2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial participant and society. A trial should be initiated and continued only if the benefits justify the risks.</p> <p>2.3 The rights, security and well-being of the trial participants are the most important consideration and should prevail over the interests of science and society.</p> <p>2.4 The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.</p> <p>2.5 Clinical studies should be scientifically sound and described in a clear detailed protocol.</p> <p>2.6 The trial should be conducted in compliance with the protocol that has received prior approval/favourable opinion of an Institutional Review Board (IRB)/Independent Ethics Committee (IEC).</p> <p>2.7 The medical care given to, and medical decisions made on behalf of, participants should always be the responsibility of a qualified physician or, when appropriate, a qualified dentist.</p> <p>2.8 Each individual involved in conducting a trial should be qualified by education, training and experience to perform his or her respective task(s).</p> <p>2.9 Freely given informed consent should be obtained from every participant prior to clinical trial participation.</p> <p>2.10 All clinical trial information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.</p> <p>2.11 The confidentiality of records that could identify participants should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).</p> <p>2.12 Investigational products should be manufactured, handled and stored in accordance with Good Manufacturing Practice (GMP). They should be used in accordance with the approved protocol.</p> <p>2.13 Systems with procedures that ensure the quality of every aspect of the trial should be implemented.</p>	<p>YES</p>	<p>YES</p>

Annex 2

PUBLIC DECLARATION CONCERNING CONFLICT OF INTEREST

Name:

Qualifications:

Affiliation:

Please list below any interest in the pharmaceutical industry (*use several forms if necessary*)

Employment in the pharmaceuticals industry over the last five years:

All activities carried on (directly or indirectly) for drug companies (or on their behalf; in this case, specify one's role and the activities performed and indicate the name of the product and the nature of the work performed), whether or not such activities involved regular or occasional remuneration, in money or in kind, including:

Participation in the decision-making process inside a drug company (e.g. sitting on the board of directors, executive or non executive management);

Permanent or temporary membership of the staff of a drug company. Other activities carried on inside a drug company (e.g. training) should also be declared;

Consultancy or other work contracted out by drug companies

Financial shareholding in a drug manufacturing company:

Name of company:

Type of share:Number of shares:.....

Other relations with the pharmaceutical industry:

Any kind of assistance and support received from the industry in the preceding 5 years, including any pecuniary or material benefits, whether direct or indirect, of the following type:

Study or research grants offered by the industry;

Fellowships or sponsorships subsidized by the drug industry.

Any other interests or facts deemed worthy of note, including elements referring to members of one's own family nucleus (the components of the family nucleus are: spouse, partner and dependent children living under the same roof as the person concerned. It is not necessary to mention the name of such persons):

.....
.....

The undersignedhereby declares that, to the best of his or her knowledge, he or she does not hold any other direct or indirect interests in the pharmaceuticals industry in addition to those mentioned above.

He or she also declares the commitment to present a new public declaration of interest should any new or further interests emerge to which attention needs to be drawn.

In witness whereof:Date: