Good practice in observational epidemiological research: guidelines for biostatisticians on Ethics Committees

SISMEC Working Group on Observational Studies[1]

[1] Members of the SISMEC Working Group on Observational Studies: Simone Accordini (Verona), Francesco Bamfi (Verona), Iacopo Baussano (Turin), Flavia Carle (Ancona), Roberto de Marco (Verona), Adriano Decarli (Milan), Anna Chiara Frigo (Padua), Gianmichele Galassi (Siena), Dario Gregori (Turin), Francesco Grigoletto (Padua), Alessandra Marinoni (Pavia), Franco Merletti (Turin), Cristina Montomoli (Pavia), Francesca Patarnello (Verona), Gabriella Serio (Bari), Lucia Simoni (Modena), Giovanni Sotgiu (Sassari), Antonietta Stendardo (Messina), Annarita Vestri (Rome), Simona Villani (Pavia), Sandra Volpato (Padua), Mauro Zucchetto (Padua)

Preamble

The problem of defining and approving observational studies has attracted growing attention in the clinical and epidemiological research sector since the Italian Ministry of Health's publication, on 2 September 2002, of its circular n.6 on the work of ethics committees. It is known that observational studies are not covered by the implementing legislation of European directive 2001/20/EC on good clinical practice in the conduct of clinical trials, as defined by Italian Legislative Decree n. 211 of 24 June 2003. Following the publication of the abovementioned circular there was a significant increase in the number of "observational" (or "non-interventional") study protocols submitted to ethics committees for evaluation.

The considerable problems ethics committees faced in interpreting and implementing the existing legislation underlined the need for better definition and regulation of these studies.

The promotion of epidemiological research, and of instruments that may improve its quality, is one of our association's primary objectives. We therefore see it as our duty to seek to remove obstacles and barriers of all kinds, administrative, regulatory and cultural, and to develop opportunities for discussion, as well as training and study programmes targeting methodological issues.

These various considerations prompted SISMEC to set up a special working group on observational studies, appointed by the board of the association, and to entrust it with drawing up guidelines aimed at biostatisticians who sit on ethics committees. The resulting guidelines, presented in this paper, are an elaboration of an initial document devoted to this topic, published on the SISMEC website in October 2005.

KEY WORDS: *observational studies, Ethics Committees, guidelines, biostatisticians, research protocol*.

Introduction

European Union member states are now subject to legislation on clinical research (European Parliament and Council Directive 2001/20/EC, which came into force in 2004) that makes it compulsory to obtain ethics committee approval for research protocols. However, this legal requirement extends only to pharmacological research, with the result that there exist no uniform provisions for research conducted in other areas (research relating to surgery, medical devices, biological material of human origin, and non-interventional studies generally), for which the US, instead, has clearly defined guidelines (1, 2).

Yet, if read correctly, the terms of the Helsinki Declaration, which states that research protocols involving human subjects "*should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence*", like those of the Italian law on the protection of personal data (Italian Legislative Decree n. 196, 30/06/03, and subsequent modifications and additions), seem to suggest that any research protocol in-

volving people should be submitted to an independent body, such as an ethics committee. This is, indeed, becoming an obligatory requirement of research studies published in international journals, and also when applying for sponsorship and funding (in Italy as elsewhere).

Given the importance of epidemiological research, both in increasing awareness of the frequency of diseases and of their natural history, and in study of the effects of healthcare interventions on populations, it has been deemed useful to put together, in this paper, a series of recommendations, particularly aimed at biostatisticians who sit on ethics committees, that might encourage the application of common definitions, methodologies and criteria to observational epidemiological studies, thereby increasing the quality of these studies for the benefit of patients and of the general population.

Aims of the paper

This paper aims:

a) to give an overview of the different types of observational research protocol that are submitted to ethics committees in Italy;

b) to identify the critical aspects, for SISMEC, of current legislation on good practice in clinical research and on the activity of ethics committees;

c) to furnish some recommendations, aimed at biostatisticians and epidemiologists sitting on ethics committees, to facilitate correct evaluation of the said protocols.

Operational setting: the different types of observational study

There are many types of observational study. Drawing on the experience of some of the members of the working group (ethics committee biostatisticians), we have classified, as set out below, this particular category of studies, which in the three-year period considered (2004-2006) accounted for around a third of all the protocols examined.

a) Studies in **clinical epidemiology**: in these studies subjects are not treated according to schemes established in the research protocol, but according to the decisions of their own doctors, independently of the investigator, whose only role is to observe what happens "naturally". Depending on the objectives, these studies can be divided into:

– long-term assessments of the efficacy of interventions (pharmacological, surgical, prosthesic, psychotherapeutic, rehabilitative, etc.) administered in the course of routine healthcare delivery;

– validation studies of diagnostic and screening procedures.

b) Studies in **healthcare management and health economics**: these studies evaluate programmes of healthcare, management modalities, organisational aspects and healthcare and/or social costs.

c) Studies in **general epidemiology** (population studies): here, the aim is to study the natural history of diseases, to identify risk and/or causal factors and the dynamics of the spread of diseases, and to estimate their prevalence and incidence, using classical epidemiological study designs: cross-sectional, case-control, cohort and ecological.

d) Studies in **genetic epidemiology**: these studies are conducted with the aim of identifying mechanisms underlying the hereditary transmission of diseases, of resistance and of susceptibility to drugs, etc., through specific study designs, the construction of genealogical trees, patient typing, etc.

e) **Anatomical-physiological** research: in this case the aim is to identify relations between stimuli and reactions of the organism (e.g. in sports medicine), and of biological material (e.g. stem cells, assessment of biological material *in vitro*, etc.).

f) Studies of **complementary medicine**: these are conducted to assess the effects of these treatments (acupuncture, spa treatments, homeopathy, etc.).

Legislation and its critical aspects

The appendix to this paper sets out, in chronological order, a selection of the various decrees, directives and circulars, issued at national and at regional level in Italy, as well as at European level, regulating ethics committees, observational studies and clinical trials. We decided to include legislation on clinical trials since it might provide a useful source of reference and some indications for the evaluation of observational studies.

From a close reading of the various provisions, it is clear that one of the first problems is the definition of "observational study", a term that is open to a range of different interpretations, given that it can be applied to studies with widely differing designs and objectives. Current legislation includes the following:

1) The Italian Ministry of Health circular n. 6, 2002, which defines non-interventional (observational) trials;
2) The Italian Legislative Decree (Dlgs) n. 211/2003 on clinical trials of medicinal products, which also gives a definition of the "non-interventional" trial (observational study);
3) The 20 March 2008 ruling of the Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) which gives guidelines for the classification and conduct of observational drug trials.

The Ministry of Health circular n. 6 of September 2, 2002 defines non-interventional trial as "*the study of problems or pathologies in whose ambit medicinal products are prescribed in the normal way, in compliance with the conditions established when the marketing of the drug was authorised. The patient's assignment to a given therapeutic strategy is not decided in advance in the study protocol, but is part of normal clinical practice and the decision to prescribe the medicinal product is entirely independent of the decision to include the patient in the study*".

Similarly, according to Dlgs n. 211/2003, a non-interventional trial is "*a study in which medicinal products are prescribed in accordance with the indications of the marketing authorisation. A patient's assignment to a given therapeutic strategy is not decided in advance by a study protocol, it is part of normal clinical practice, and the decision to prescibe the medicinal product is entirely independent of the decision to include the patient in the study". The text goes on, affirming that "No supplementary diagnostic or monitoring procedure is applied to the patients, and the data collected are analysed using epidemiological methods*".

It is clear, on reading this decree, that in order for a clinical drug trial to be defined "observational" it has to concern patients who are using an already authorised drug and doing so in accordance with the approved indications. Consequently, this leaves the circular as our sole source of reference for all other kinds of observational study, such as studies of medical devices or biological materials, and risk factor evaluations. The recent AIFA ruling (20 March 2008), very opportunely extends the definition of current clinical practice to procedures such as follow-up visits (if provided for in current practice or by national or international guidelines), the administration of questionnaires, and the use of interviews and diaries, health economics and pharmacoeconomics investigations, subjective assessments of perceived health status, assessment scales and blood chemistry tests, providing they are justified by the rationale of the study, in compliance with the provisions of the European Commission in its Rules Governing Medicinal Products in the European Union (Chapter 7.1, p. 87) (3). Other procedures, such as radiological investigations and biopsies, continue to be excluded: this seems questionable but is perhaps justified by the different level of invasiveness of these procedures. Pharmacogenetics and pharmacogenomics studies, on the other hand, are not to be considered observational studies. According to the same ruling, all prospective cohort observational studies of medicinal products must be submitted to an ethics committee, whereas other types of observational study, such as retrospective cohort, case-control, case cross-over and case series, or cross-sectional studies, must be notified to the researcher's local ethics committee. In these cases, the single ethics committee, depending on its institutional statute, may either approve the study formally, or simply register it (in accordance with art. 2.4 of the circular of September 2, 2002). It is SISMEC's hope that all ethics committees will, uniformly, favour a formal act of approval, not least in order to guarantee that the AIFA register of observational studies is sufficiently exhaustive.

Observational studies must also comply with the same rules as clinical trials with regard to:

– transparency over sponsorship, funding and other financial aspects;
– ownership of the data and transparency of the results;
– respect for the study participants' rights to be fully informed about the research and to have their personal data protected (where applicable);
– the possibility of forming a scientific committee responsible for managing/conducting the study, all of which are aspects that the legislator took into account

in the circular of September 2, 2002, with the affirmation that "*it is the task and responsibility of the ethics committees to ascertain (if necessary requesting additional documentation) that the proposers mentioned in points a) e b) have effective autonomy, vis-à-vis industrial sponsors, with regard to the planning and general management of the research and its results*".
Without jeopardising the freedom of the individual organisations to fix their charges for examining the study protocols submitted to them, it is worth pointing out the need to apply restraint and reasonable criteria in this regard, even making provision for exemption from payment for studies conducted by investigators operating within the ambit of the national health service and for studies sponsored by scientific societies and/or no-profit institutions and associations. This consideration applies particularly in the case of multicentre studies, as the need to pay fees to a number of ethics committees could make it difficult or even impossible to proceed with the study.
Due to the inherent nature of observational studies of all kinds, which are based on normal clinical practice, no provision need be made for specific insurance cover, given that the insurance cover already in place in the institutes where the study is conducted extends to the medical procedures that the study will involve.
For completeness of information in this regard, the Italian Ministry of Health circular n. 6 of September 2, 2002 states that:
"*Research protocols for observational studies must adhere to a rigorous methodology, given that their results are not protected by procedures of randomised allocation of patients and/or interventions. As with randomised clinical trials, the following must be unequivocally and consistently defined:*
a) the rationale of the research and its hypotheses;
b) the expectations of the study;
c) the criteria to be applied for the analysis and interpretation of the results (whether these are intended as descriptive, or as data that may suggest, document or confirm relations of causality);
d) appropriate statistical analyses".
According to the ruling of 20 March 2008, observational studies can be conducted not only at public health institutions or by GPs and paediatricians of patients' own free choice, but also at private health institutions and by medical doctors working on a freelance basis.

Definition of observational study

A study is defined as observational when the investigator considers the variables of interest without his action in any way influencing the condition of the subject or subjects studied. If the variables being observed relate to the effect of a treatment, the decision to include a patient in a given therapeutic strategy must be taken as part of routine clinical practice, and the decision to prescribe the treatment must be entirely independent of the decision to include the patient in the study.
Should the study include measures for the gathering of specific data, such as the administration of a questionnaire, blood chemistry tests or instrumental examinations, and these interventions do not modify the condition being studied, then the design of the study retains its observational character. From this perspective, however, observational studies cannot merely be defined as "non-interventional".

Assessment of protocols

Even at the feasibility study stage – a feasibility assessment is a prerequisite of any research –, it is important to ensure that the type of study chosen is compatible with the objective of the study itself, so as to ensure the achievement of that objective. The choice of study type should never be based on practical, economic, time or legislative considerations. The investigator must appreciate how important it is to avoid generating false conclusions through the use of an incorrect or inappropriate study design or analysis method.
A detailed study protocol must be drawn up in order to plan an observational study that produces scientifically reliable results that might ultimately benefit the health of the general population.
The protocol must be fully defined before the start of the research and might include the following sections, to be evaluated by the ethics committee:
• a title indicating the main aim of the study, its design and the population to be investigated;
• the date and identification number of the final version of the protocol;
• the organisational structure of the study: sponsor(s), coordinating centre and participating centres, and the names of the individuals in charge of them;
• a summary of the protocol;

• an introduction and rationale, which will include the scientific bases of the study, the characteristics of the population to be investigated, reference to previous studies, the relevance of the research hypothesis to the field of public health, etc.;
• the general and specific aims;
• the study design:
– the type of design (cross-sectional, case-control, cohort, ecological, etc.):
– the population (characteristics of the subjects, selection criteria);
– the size of the sample and the criteria applied in its definition, as well as justification should its calculation not be possible;
– definition of the variables of the study (main and secondary endpoints, exposures, potential modifiers of effects, confounding factors);
– measures taken to avoid sources of bias;
– means and instruments used to gather data, with details of their validation;
– sources of data;
– description of data management (data collection and storage systems, transmission, quality control of data);
• data analysis methods (planned statistical analysis, including techniques to neutralise sources of bias);
• organisational aspects (stages of the research, programme and scheduled completion date);
• ethical aspects, including the submission of the study to the ethics committee;
• economic aspects (if the study includes interventions that are not part of routine clinical practice, it is necessary to state how the additional cost is to be met);
• funding and, if necessary, insurance;
• protection and ownership of data;
• policies regarding publication and notification of the results;
• bibliography;
• protocol approval form with the signatures and qualifications/roles of each participant;
• attachments (data collection sheets, informed consent forms where appropriate, maybe the letter informing patients' own doctors, etc.).

Recommendations

We draw attention to the opportuneness of an *ad hoc* legislative provision covering all observational studies (including those that are not related to the use of medicinal products) which uses universally recognised definitions and terms, and also makes reference to international guidelines (1-5).
There is a need, in particular, to clarify aspects relating to:
a) insurance cover, should the observational study make provision for additional diagnostic procedures;
b) notification of the Ministry of Health. The ruling of 20 March, 2008, which provides for the setting up by AIFA of a national observational studies register, implies that the said register should include prospective studies – these require ethics review board approval – while it does not distinguish between or make specific reference to the different types of observational study;
c) the informed consent and privacy of personal data statement: it is necessary to establish the minimum essential information patients should be given.
We also underline that the AIFA draft guidelines are aimed only at drug trials and that they do not cover the full breadth of observational research. In particular, they do not cover investigations that involve the use of medical devices, for which the opinion of the ethics committee sometimes has to be sought, irrespectively of the obligation to notify the Ministry of Health (Ministry of Health Circular – February 26, 2007 and Dlgs 46/97).
An ethics committee is required to examine and express an opinion on all the protocols submitted to it, whether the studies in question set out to evaluate a drug or other health-related issues. In any case, simple notification and registration of a study, as provided for by Circular n. 6 of September 2, 2002, seems inadequate, for the following reasons:
1. the protocol must in any case be read in order for its content to be evaluated;
2. the simple registration or taking note of a protocol produces an ambiguous document that could be taken as formal approval by the proposers of the research, even though it does not amount to such;
3. even studies of this kind demand methodological rigour, not least to avoid the diffusion of inaccurate scientific information;
4. if all studies submitted to ethics committees were routinely submitted to a rigorous evaluation procedure and properly registered, this would result in the creation of a wealth of useful information not only

on experimental but also on observational research, the results of which could be combined to produce better evidence.

In the course of observational studies, as well as on their completion, the investigator should submit reports to the ethics committee, to be included in the register recently instituted by AIFA, informing it of how the research is progressing. Such interim reports should describe the stage reached in the project and detail the results thus far obtained, any changes made to the protocol, and the objectives still to be reached. In particular, the report should make it possible to evaluate the compatibility of the research with the study's rationale, objectives and available resources. The report should give the date on which the work began and the date of its expected completion, the number of subjects expected to be involved and the number actually involved at the time the report was compiled, the procedures under investigation and any modification of them, and finally the results of interim analyses that make it possible to judge whether it is opportune to continue with the study.

The final report, instead, must clearly indicate what new knowledge has been generated by the research, also giving a full account of the limitations of the study, its generalisability, and the interpretation of the results. To facilitate its evaluation of ongoing research projects, the ethics committee may compile a checklist of critical points to help researchers present the results of their work in a coherent and exhaustive manner.

Conclusions

In view of the increasingly frequent recourse to observational studies in the clinical setting and the fact that incomplete or inadequate transmission of information precludes proper critical assessment and appropriate interpretation of the results of such studies, complicating evidence-based treatment and prevention, we feel that there is an urgent need for legislation that will encourage well-designed and well-conducted observational studies. Finally, we feel that biostatisticians sitting on ethics committees have a moral obligation to express an opinion on the research methodology, in view of the repercussions it will clearly have on the results of the study and therefore on the clinical management of patients.

References

1. International Society for Pharmacoepidemiology "Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the United States", 1996 (www.hsph.harvard.edu/Organizations/DDIL/gep_PE.html).
2. American College of Epidemiology. Ethics Guidelines. Annals of Epidemiology 2000; 10: 487-497 (http://www.acepidemiology2.org/policystmts/EthicsGuide.pdf).
3. European Commission - Enterprise and Industry Directorate General - Consumer goods - Pharmaceuticals - Volume 9A – Pharmacovigilance for Medicinal Products for Human Use (version April 2007) (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9_2007-07_upd07.pdf)
4. Declich et al. Proposta di linee guida per una buona pratica epidemiologica, Epidemiologia e Prevenzione, 2001; 25: 206-209.
5. International Epidemiological Association "Good Epidemiological Practice (GEP): proper conduct in epidemiologic research", 2007 (http://www.dundee.ac.uk/iea/download/ GEPjan07.pdf).

APPENDIX

PUBLICATION DATE	TYPE OF PROVISION	TITLE
20.3.2008	AIFA ruling, 20.3.2008, *Gazzetta Ufficiale* n. 76, 31.3.2008	Guidelines for the classification and conduct of observational drug trials
6.11.2007	Italian Legislative Decree *Gazzetta Ufficiale* n. 261, 9.11.2007, (*Suppl. Ordinario* n. 228)	Implementation of the directive 2005/28/EC which lays 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.
6.11.2007	Italian Legislative Decree *Gazzetta Ufficiale* n. 261, 9.11.2007, (*Suppl. Ordinario* n. 228)	Implementation of the directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.
26.2.2007	Circular of the Italian Ministry of Health	Administrative procedures relating to the conduct of clinical investigations using devices carrying the CE mark
13.12.2006	D.G.R. n. 8/3780, 13.12.2006 (Decree of the Council of Lombardy, Italy)	Guidelines on the institution, organisation and funding of ethics committees for the clinical experimentation of drugs implementing Italian Ministerial Decree 12.5.2006. Repeal of D.G.R. n. 40368/1998 (Decree of the Council of Lombardy, Italy)
12.5.2006	Italian Health Ministry Decree *Gazzetta Ufficiale* n. 194, 22.8.2006	Minimum requirements for the institution, organisation and funding of ethics committees for clinical drug trials
21.4.2006	Document of the Italian National Committee for Bioethics (under the Italian presidency of the EU Council of Ministers)	From Pharmacogenetics to Pharmacogenomics
19.4.2006	Document of the Italian National Committee on Bio-security and Biotechnologies (under the Italian presidency of the EU Council of Ministers)	Guidelines for the institution and certification of biobanks
15.3.2006	Adopted by the Committee Ministers on 15.3.2006 at the 958th meeting of Ministers' Deputies	Recommendation of Committee Ministers to Member States on Research on Biological Materials of Human Origin
14.12.2005	Ministry of Health letter to ethics committees	Clinical investigations using medical devices
2.8.2005	Italian Ministerial Decree *Gazzetta Ufficiale* n. 210, 9.9.2005	Procedure for presenting documents notifying of clinical investigations using medical devices
8.4.2005	Commission Directive 2005/28/EC of 8.4.2005 *OJ L 91, 9.4.2005, p. 13-19*	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
17.3.2005	EMEA	Concept paper on the Development of Guideline on Biobanks Issues relevant to Pharmacogenetics

PUBLICATION DATE	TYPE OF PROVISION	TITLE
9.2.2005	EMEA - Updates	Concept paper on the Development of Guideline on Biobanks Issues relevant to Pharmacogenetics
2004	EN ISO 14155-2:2004	Clinical investigation of medical devices for human subjects. Part 2: Clinical investigation plans
22.12.2004	Direttiva regionale n. 4049 - Regione Veneto (Directive of the Region of Veneto, Italy)	Interventions in bioethics. Institutionalisation of the regional bioethics committee. Guidelines for the establishment and operation of ethics committees for experimentation. Guidelines for the establishment and operation of ethics committees for clinical practice.
17.12.2004	Italian Ministerial Decree *Gazzetta Ufficiale* n. 43, 22.2.2005. Italy – Ministry of Health	General provisions and conditions relating to the conduct of clinical drug trials, with special reference to those geared at improving clinical practice, as an integral part of healthcare.
13.7.2004	Decreto Direzione Generale Sanità n. 11960 – Regione Lombardia (Decree of the Directorate-General for Health, Region of Lombardy, Italy)	Approval of guidelines on "observational studies" or "non-interventional studies", the drawing up of periodic reports and the institution of a regional register of "observational" or "non-interventional studies" conducted in the region of Lombardy.
23.2.2004	Direttiva Regionale n. 158, Bollettino Ufficiale della Regione Toscana, n. 11 (Directive of the Region of Tuscany, Italy)	General directives on the authorisation and procedures for the validation of observational studies
2003	EN ISO 14155-1	Clinical investigation of medical devices for human subjects. Part 1: General requirements
24.6.2003	Italian Legislative Decree n. 211 *Gazzetta Ufficiale* n. 184, 9.8.2003	Implementation of the directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials of medicinal products for human use
8.5. 2003	Italian Ministerial Decree *Gazzetta Ufficiale* n. 173, 28.7.2003	Therapeutic use of medicinal products under clinical trials
2.9.2002	Italian Ministerial Circular n. 6 *Gazzetta Ufficiale* n. 214, 12.9.2002 Italy – Ministry of Health	Activity of ethics committees instituted in accordance with Italian Ministerial Decree 18.3.1998 (*)
1.2.2002	D.G. n. 187 (7ª legislatura) Council Resolution (7th legislature) n. 187 – Region of Veneto Direzione Generale Sanità n. 2384 - Regione Veneto (Decree of the Directorate-General for Health, Region of Veneto, Italy)	Regional guidelines implementing Italian Ministry of Health Decree 10.5.2001 on controlled clinical trials conducted by general practitioners or by paediatricians of patients' own free choice
21.11.2001	Decree n. 27931 Direzione Generale Sanità n. 2384 - Regione Lombardia (Decree of the Directorate-General for Health, Region of Lombardy , Italy)	Regional guidelines implementing Italian Ministry of Health Decree 10.5.2001 on controlled clinical trials conducted by general practitioners or by paediatricians of patients' own free choice
21.9.2001	Italian Presidential Decree n. 439 *Gazzetta Ufficiale* n. 294, 19.12.2001	Ruling simplifying the procedures for the assessment and monitoring of new experimental treatment systems and protocols

PUBLICATION DATE	TYPE OF PROVISION	TITLE
30.5.2001	Italian Decree *Gazzetta Ufficiale* n. 216, 17.9.2001	Inspections to verify the observance of good manufacturing practice and good clinical practice regulations
10.5.2001	Italian Decree *Gazzetta Ufficiale* n. 139, 18.6.2001	Controlled clinical trials conducted by general practitioners or by paediatricians of patients' own free choice
4.4.2001	Directive 2001/20/EC of the European Parliament and of the Council *OJ L 121, 1.5.2001, p. 34–44*	Approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
December 2000	ICH Harmonised Tripartite Guideline	Guidance for Industry-E11 Clinical Investigation of Medicinal Products in the Paediatric Population
October 2000	Circular 05 n. 15 *Gazzetta Ufficiale* n. 262, 9.11.2000 (general series), (*Suppl. Ordinario* n. 184)	Update of Italian ministerial circular n. 8, 10.7.1997 relating to clinical drug trials
25.5.2000	Italian Ministerial Decree *Gazzetta Ufficiale* n. 133, 9.6.2000	Telematic transmission of data relating to clinical drug trials
23.11.1999	Italian Ministerial Decree *Gazzetta Ufficiale* n. 21, 27.1.2000	Composition and functions of the Italian National Ethics Committee for Clinical Drug Testing, in accordance with the terms of the Italian Legislative Decree n. 229, 19.6.1999
12.10.1999	Circular n. 16 *Gazzetta Ufficiale* n. 225 of 29.10.1999	Irregularities in authorisation procedures and in the conduct of clinical drug trials
19.6.1999	Italian Legislative Decree n. 229 *Gazzetta Ufficiale* n. 165 of 16.7.1999 (Suppl. Ordinario n. 132/L)	Provisions to streamline the Italian National Health Service in conformity with art. 1 of the Italian Law n. 419, 30.11.1998, (art. 11; art. 13, new art. 15-quinquies of the Italian Legislative Decree n. 502 30.12.1992)
13.5.1999	Italian Ministerial Decree *Gazzetta Ufficiale* n. 174, 27.7.1999	Integrations to Italian Ministerial Decree 18.3.1998 on: "Procedures exempting from assessment drugs used in clinical trials" and to the Italian Ministerial Decree 19.3.1998 on: "Recognition of the suitability of centres for the conduct of clinical drug trials"
8.4.1999	Circular n. 6 *Gazzetta Ufficiale* n. 90, 19.4.1999	Explanations of the Italian Ministerial Decrees 18.3.1998 and 19.3.1998 published in Gazzetta Ufficiale n. 123, 28.5.1998
20.1.1999	Italian Ministerial Decree *Gazzetta Ufficiale* n. 31, 8.2.1999	Provisions on the marketing and clinical testing of medicinal products containing materials of bovine origin
7.10. 1998	Italian Ministerial Decree *Gazzetta Ufficiale* n. 274, 23.11.1998	Integration to the Annex to the Italian Ministerial Decree 19.3.1998 on: "Procedures exempting from assessment drugs used in clinical trials"
15.9.1998	Italian Ministerial Decree *Gazzetta Ufficiale* n. 222, 23.9.1998	Integration to the Italian Ministerial Decree 18.3.1998: "Procedures exempting from assessment drugs used in clinical trials"
19.3.1998	Italian Ministerial Decree *Gazzetta Ufficiale* n. 122, 28.5.1998	Recognition of the suitability of centres for the conduct of clinical drug trials

PUBLICATION DATE	TYPE OF PROVISION	TITLE
18.3.1998	Italian Ministerial Decree *Gazzetta Ufficiale* n. 122, 28.5.1998	Procedures for exempting from assessment, pursuant to Italian Presidential Decree n. 274, 21.9.1994, drugs used in clinical trials
18.3.1998	Italian Health Ministry Decree *Gazzetta Ufficiale* n. 122, 28.5.1998	Guidelines for the institution and working of ethics committees
21.11.1997	Italian Ministerial Decree *Gazzetta Ufficiale* n. 57, 10.3.1998	Establishment of procedures for submitting requests for approval of clinical research protocols involving the exposure of people to ionising radiation
15.7.1997	Italian Ministerial Decree *Gazzetta Ufficiale* n. 191, 18.8.1997 (Suppl. Ordinario n. 162)	Assimilation of the European Union's good clinical practice guidelines for the conduct of clinical drug trials (The annexes to this decree replace entirely the annexes to the Italian Ministerial Decree 27.4.1992)
10.7.1997	Circular n. 8 *Gazzetta Ufficiale* n. 168, 21.7.1997	Clinical drug testing
24.2.1997	Italian Legislative Decree n. 46 *Gazzetta Ufficiale* n. 54, 6.3.1997, (Suppl. Ordinario n. 49)	Implementation of Directive 93/42/EEC concerning medical devices
1995	EN 540	Clinical investigation of medical devices for human use
24.6.1993	ICH Harmonised Tripartite Guideline	Studies in Support of Special Populations: Geriatrics
14.12.1992	Italian Legislative Decree n. 507 *Gazzetta Ufficiale* n. 305, 30.12.1992	Implementation of Directive 90/385/EEC concerning the approximation of the laws of the Member States relating to active implantable medical devices
27.4.1992	Italian Ministerial Decree *Gazzetta Ufficiale* n. 139, 15.6.1992, (*Suppl. Ordinario* n. 86)	Provisions on the technical documentation that must accompany applications for marketing authorisation for medicinal products for human use, also implementing directive 91/507/EEC
4.12.1990	Italian Ministerial Decree *Gazzetta Ufficiale* n. 297, 21.12.1990	Modifies the Italian Ministerial Decree 23.6.1981 on the regulation of scientific information on pharmaceuticals
25.8.1977	Italian Ministerial Decree *Gazzetta Ufficiale* n. 238, 1.9.1977	Correction of the Italian Ministerial Decree 28.7.1977 concerning ruling on ascertaining the composition and innocuousness of new pharmaceutical products prior to their clinical testing on humans
28.7.1977	Italian Ministerial Decree *Gazzetta Ufficiale* n. 216, 9.8.1977	Ruling on ascertaining the composition and innocuousness of new pharmaceutical products prior to their clinical testing on humans

(*) The Italian Ministerial Decree 18.3.1998 "Procedures exempting from assessment drugs used in clinical trials" was repealed by the Italian Ministerial Decree 12.5.2006 as regards articles: 1, 2, points 1 to 6, 3, 4, 5, 9, 10 point 1 letter b and annexes 1 and 2.