



The EFGCP Report on
The Procedure for the Ethical Review of Protocols
for Clinical Research Projects in Europe
(Update: March 2008)

Italy

1. What laws or regulations apply to an application for conducting a clinical trial in Italy?

Ministerial Decree of November 6 2007: “Transposition of Directive 2005/28/EC relating to principles and guidelines for good clinical practice for medicines in experimental phase for human use, and requirements for the authorization to produce and to import these medicines”.

Ministerial Decree of May 12, 2006 “Minimum requirements for the institution, organization and functioning of Ethical Committee for clinical trials with medicines”.

Ministerial Decree of December 17, 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.”

Legislative Decree no.211 of June 24, 2003 “Transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use.”

Decree of the President of the Republic of September 21, 2001 ”Regulations to simplify the Procedures and to Verify and Check New Systems and Experimental Therapeutic Protocols”.

Ministerial Decree of May 10, 2001 “Controlled clinical trials conducted by General Practitioners and Paediatricians”.

Ministerial Circular no. 15 of 5 October 2000, “Updating of the ministerial circular n. 8 of 10 July 1997 relating clinical trials with medicines.”

Decree of the Director General of the Department of medicines evaluation and pharmacovigilance of the Ministry of Health, of May 25, 2000, “Electronic transmission of data concerning clinical trials.”

Ministerial Decree of March 18, 1998 “Procedure for the exemption from assessment on medicines used in clinical trials”.

Ministerial Decree of 15 July 1997, “Transposition of guidelines of the European Union in good clinical practice for the conduction of clinical trials with medicines”
Prime Minister’s Decree of March 28, 1990 establishing the National Bioethics Committee.

2. Which government, legal or authoritative body or bodies is or are responsible for the establishment and/or accreditation of (research) ethics committees for reviewing clinical trials for investigational medicinal products, their supervision and quality? Are there different (research) ethics committees reviewing other projects?

In Italy, according to the Ministerial Decree of May 12, 2006 “Minimum requirements for the institution, organization and functioning of Ethical Committee for clinical trials with medicines”, local Ethics Committees are established by the organ of administration of the public health facilities in which clinical trials are conducted. The Regional Authorities are responsible for the accreditation of the Ethics Committees working within their regions and for the transmission of the list of them to the Italian Medicines Agency.

Regional bioethics committees may act as co-ordinators for local ethics committees and also as a link between them and the National Bioethics Committee. In some regions where there is only a Regional bioethics committee, it will act as a local ethics committee and review research proposals.

The National Bioethics Committee acts as a consultative body of the Council of Ministers. Parliament, research centres, local ethics committees and individuals can approach it for advice. It may present proposals of laws.

3. What is the process for achieving clinical trial authorisation from the competent authority in Italy?

In Italy, in most cases to obtain an authorisation to conduct a clinical trial with medicines, the sponsor must apply to the local competent Authority, the legal Officer of each clinical site (eg: director general of the health facility). The competent Authority can authorise the trial within 60 days. If the competent Authority has not informed the sponsor of any grounds for non-acceptance within 60 days, the trial is considered authorised.

Only for clinical trials with gene therapy, somatic cells therapy and medicines containing OGM (phase II, III, IV, Bioequivalence/Bioavailability) and, for first-in-man use trials the authorisation is granted by a central competent Authority is required. In the first case, the competent authority is the Agenzia Italiana del Farmaco – AIFA (Italian Medicines Agency); in the second case, (first-in-man use, in general phase I studies) the authorisation is granted by the National Institute of Health

(Istituto Superiore di Sanità). Information are available at the following site:
<http://www.iss.it/scf1/>

In any case, in order to start a clinical trial, a sponsor must enter the data into web-based database of the "Osservatorio Nazionale per la Sperimentazione Clinica" (National Monitoring Centre for Clinical Trials) established at. At the end of the electronic procedure, it is possible to print the data entered into the *OsSC* and the result will be a Clinical Trial Application (CTA) form in Italian language, to submit to the competent Authority and Ethics Committee, respectively for authorization and opinion.

4. What is the process for obtaining ethical review of a clinical trial protocol by a competent (research) ethics committee in Italy?

For all the trials, even for those authorised by a central Competent Authority, the sponsor needs to obtain:

1. the single opinion released, within 30 days from the receipt of the clinical trial application, by the Ethics Committee of the clinical site of the coordinating investigator and then, the acceptance or refusal of the single opinion released by the Ethics Committees of the satellite clinical sites, within 30 days from the receipt of the single opinion;
2. the financial agreement between the Legal Officer of each clinical site, or a person appointed by him, and the sponsor.

In order to start a clinical trial, a sponsor must enter the data into the web-based database of the "*Osservatorio Nazionale per la Sperimentazione Clinica*" (National Monitoring Centre for Clinical Trials)

[http://oss-sper-clin.agenziafarmaco.it/normative_ingl.htm]

established at the Italian Medicines Agency. At the end of the electronic procedure it is possible to print the data entered into the *OsSC* and the result will be a Clinical Trial Application (CTA) form, in Italian, to submit to the Competent Authority and the Ethics Committee, respectively, for authorization and opinion.

5. Is there a single organisation to which to apply for ethical review of a clinical trial for an investigational medicinal product, regardless of whether this is for a single site or multiple sites?

No.

6. What is the website for the organisation that issues guidelines on the ethical review of a clinical trial for an investigational medicinal product?

In the website of the National Monitoring Centre for Clinical Trials established at the Italian Medicines Agency, http://oss-sper-clin.agenziafarmaco.it/normativa_ingl.htm, a list of all the laws and regulations concerning clinical trials with IMPs is available.

The website of the National Bioethics Committee (Comitato Nazionale per la Bioetica) is at <http://www.palazzochigi.it/bioetica>.

The website of the National Federation of Ethics Committees (Federazione Nazionale dei Comitati di Etica) can be consulted at <http://www.unich.it/fnace>.

7. Is there a procedural interaction between the national or local competent authority and the (research) ethics committee during the approval process?

Each single health facility adopts its own internal procedures autonomously as for this matter.

8. Does the application to the EC and to the competent authority have to be submitted in parallel, or, if not, in which order?

According to the Legislative Decree no. 211 of 23 June 2003, the clinical trial application to the competent Authority and to the Ethics Committee/s may be submitted in parallel.

9. How many (research) ethics committees are there in Italy?

According to the Italian Register of Ethics Committees, a section of the database of the National Monitoring Centre of Clinical Trials (*OsSC*), there are 264 Ethics Committees in Italy. They are continually developing after the Ministerial Decree that has given the minimum requirements for Ecs and the following transposition to Regional Laws. The number at regional level are: Valle D'Aosta (0), Piemonte (7), Lombardia (62), Trentino-AltoAdige (3), Veneto (11), Friuli-Venezia Giulia (7), Liguria (10), Emilia-Romagna (9), Toscana (13), Marche (9), Umbria (10), Lazio (34), Abruzzo (6), Campania (25), Puglia (12), Basilicata (4), Calabria (13) Sicilia (28), Sardegna (10).

10. How are ECs funded in Italy? Do they charge fees? If yes what is their scale of fees?

The Ethics Committees are funded by the institution or health facility in which they are funded. The Ethics Committees usually charge fees to the sponsors for the performance of their tasks according to the directives of the Regional Authorities with a range between €1,500 and €4,000 per trial.

11. Who is responsible for submitting the request for ethical review to the competent ethics committee for single-site and for multi-site clinical trials?

According to the Legislative Decree no.211, June 23, 2004, the sponsor or an applicant appointed by the sponsor is responsible for submitting the request.

12. How is a "single opinion" achieved for multi-site studies?

The single opinion is expressed by the Ethics Committee of the facility in which the co-ordinating investigator works and will either be: a) favourable; or b) not favourable.

In the case of b) the sponsor of clinical trial cannot apply to another Ethics Committee. If the sponsor modifies the elements of the clinical trial application in accordance with the reasons of the Ethics Committee for non-approval, he/she may apply again to the same Ethics Committee in order to obtain a new opinion. If the sponsor intends to conduct a multi-centre trial, application has to be made to the Competent Authorities and the Ethics Committees of the sites involved. The Ethics Committees of the collaborating sites have to send their comments, favourable or not favourable, within 30 days to the coordinating Ethics Committee without making any changes regarding the protocol. The Ethics Committees of the participating sites may only change the informed consent form according to the policies of the institution.

13. How many members serve on an EC?

According to the above mentioned Ministerial Decree regulating the functioning of the Ethics Committees, a minimum number of 12 members is required.

14. How many members constitute a quorum?

A majority of the appointed members (i.e. 50% + 1).

15. How are EC members appointed?

According to the section 2 of the above mentioned Ministerial Decree of May 12, 2006 the Ethics Committees members are appointed by the organ of administration of the health facilities or of the Regional Authorities, in case of Regional Ethics Committees.

16. How is the independence of members ensured?

The majority of the members and the Chairman must, by law, be independent by the institution, with no relationship or subordination to the organ of administration. In the case of Ethical Committee instituted to work for more than one public health structure, this percentage can be reduced but, in any case, it cannot be less than one third of the members.

17. How are conflicts of interest of EC members avoided?

If a member of the Ethics Committee is involved in a submitted trial, he or she cannot participate at that session in which the trial is evaluated. Both the members of the Ethics Committees and the single investigator are invited to sign a conflicts of interest form for each single trial.

18. What backgrounds and/or qualifications of members are actively sought?

The above mentioned Ministerial Decree of May 12, 2006 establishes that an Ethics Committee has to include two clinicians, a general practitioner and a paediatrician, a bioethicist, a statistician, a pharmacologist and an expert pharmacist of the health facility, a general director of hospital or a director of the regional health department, a lawyer or insurance expert or a legal medicine expert, and finally a representative of patients' organizations.

19. How do ECs obtain specialist expertise?

The Ethics Committee may require the presence of specialist experts only in case of the assessment of trials in specific fields not covered by the appointed members' expertise.

20. What are the training requirements for members of ECs?

None are laid down, but members must have a certified CV in their area of expertise.

21. What training programmes are available for EC members in Italy?

At the moment, no formal training programme has been defined, but many courses, seminars and meetings are organized both by governmental and private institutions.

22. What are the timelines for the assessment of single- and multi-site studies?

According to the Legislative Decree no. 211 of 24 June 2003, in the case of single site trials, the Ethics Committee has to notify its opinion to the sponsor, to the Italian Medicines Agency and to the competent Authority by 60 days from the receipt of the clinical trial application.

In the case of multi-sites trials, the single opinion has to be expressed by 30 days from the receipt of the application; the acceptance or refusal of it has to be notified by the Ethics Committees of the participating sites to the sponsor, to the other Ethics Committees, to the competent Authorities by 30 days from the receipt of the single opinion.

23. How are substantial amendments submitted during the review process dealt with?

The substantial amendments are submitted by the sponsor according to the same procedure followed to obtain the initial approval of the clinical trial. In the case of a single site trial the Ethics Committee releases its opinion by 35 days from the receipt of substantial amendments application.

In the case of a multi-centre trial the Ethics Committee of the coordinating site releases its opinion by 20 days from the receipt of the application and the Ethics

Committees of the collaborating sites may accept or refuse this opinion by 15 days form its receipt.

24. How does an EC assess the suitability of investigators and of sites?

Through an evaluation of the CVs of the investigators submitted with the application, and the assessment of the requirements which, according to the regulations the sites should possess, to participate in a clinical trial.

25. How are the requirements for (research) ethics committees to review the contractual or financial arrangements in clinical trials for both investigators and hospitals handled?

No requirements have been fixed by national laws and provisions to review the contractual or financial arrangements; the Ethics Committees have to review the financial aspects but the final decision is taken by the Director General of the health facility.

26. How are the requirements for ethics committees to review the compensation arrangements for study subjects handled?

In Italy compensation arrangements for the subjects participation in a clinical trial are not provided.

27. Is there an ongoing quality assurance process (e.g. audits, inspections, internal SOP) for (research) ethics committees in Italy?

Yes, Good Clinical Practice inspections by inspectors of the Italian Medicines Agency are conducted at Ethics Committees.

28. Is there an appeal mechanism?

No.

29. How do ECs deal with SUSAR reports and Annual Safety Reports?

The Ethics Committees receive SUSARs reports and Annual Safety Reports .

30. How are 'substantial amendments' defined?

According to the Detailed Guidance¹ for the request for authorisation of a clinical trial, issued by the European Commission, which in Italy is going to be implemented in a specific Ministerial Decree, substantial amendments are changes that are likely to have a significant impact on: the safety or physical or mental integrity of the patients;

¹ Detailed Guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial. October 2005.

the scientific value of the trial; the conduct or management of the trial; or the quality or safety of any IMP used in the trial.

31. What are the indemnity insurance requirements for research projects?

The insurance must cover any possible damages caused to the subjects following their participation in the trial.

A Ministerial decree providing indemnity/insurance requirements for clinical trials is going to be issued.

32. What are the indemnity insurance requirements for ethics committee members themselves?

The institution covers the Ethics Committee members' insurance.

33. How is informed consent obtained from vulnerable subjects who are potentially to be involved in a clinical trial?

The informed consent of vulnerable subjects to participate in a clinical trial may be obtained by the legal representative and must be the presumed expression of the will of the subject, provided that the subject has received information adequate to his/her capacity of comprehension; furthermore it may be withdrawn at any time.

On the basis of the communication of results which sponsors should make to the competent Authorities and Ethics Committees involved and to Italian Medicines Agency, even through the database of the National Monitoring Centre of Clinical Trials (OsSC).

34. How do ECs assess the progress and outcome of research projects that they have approved?

35. How does the EC ensure reception of the Annual Safety Report and the Summary of the Final Report of a research project that it has approved?

Not yet defined.

Further information

All Italian Regional Authorities have adopted the Ministerial Decree of May 12, 2006 within 180 days from its publication (July 22, 2006) and have transmitted the list and composition of Ethics Committees instituted within its region to the Italian Medicines Agency – AIFA for its registration into the Register of the National Monitoring Centre of Clinical Trials (OsSC).

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