Conducting Clinical Studies in **Italy**

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Medical device manufacturers conduct clinical studies in Italy for various reasons, including the size of the Italian market and the presence of leading health-technology centres. This article discusses the manner in which the European requirements for medical device clinical investigations are interpreted and enforced in Italy.

Italian market

According to data from Eucomed, the European medical technology industry association, five European Union (EU) countries account for almost 78% of the EU market. These are Germany with a share of 34.4%, France with 16.3%, Italy with 11.2%, the United Kingdom with 10.5% and Spain with 5.4%. Therefore, Italy is the third largest European market for medical devices and a desirable location for exposure of medical devices to the clinical community during the clinical study process. In addition, leading health-technology centres are located in Italy, which also makes it an attractive location for medical device clinical studies. However, important changes have occurred in Italy recently, including the procedures for interpreting and enforcing the European requirements for device clinical studies. Understanding these changes and how to comply with new national requirements related to these changes will prevent delays and difficulties in initiating and managing clinical studies conducted in Italy.

European framework

Many companies preparing to conduct clinical studies in Europe mistakenly refer only to the medical device Directives. However, the Directives are not directly enforced and have been transposed by each country implementing the Directives. In the case of clinical studies, some differences exist from country to country, which can significantly effect clinical study planning and budget considerations.

Medical Device Directive

For example, Article 15 of the Medical Device Directive (MDD) (93/42/EEC) states that in the case of devices in Class III and implantable and long-term invasive devices in Class IIa or Class IIb, the manufacturer may initiate the relevant clinical investigation at the end of a period of 60 days after notification. However, this cannot occur if the Competent Authorities have notified the manufacturer within that period of a decision to the contrary based on considerations of public health or public policy. Article 15 also allows Member States to authorise manufacturers to begin clinical investigations with these categories of devices before the end of the period of 60 days, providing the relevant ethics committee has issued a favourable opinion on the clinical study programme.

In addition, Article 15 stipulates that in the case of devices other than those specified above, Member States may authorise manufacturers to commence clinical investigations immediately after the date of notification, providing the ethics committee concerned has delivered a favourable opinion with regard to the investigational plan.

Unfortunately, some manufacturers believe that it is always possible to begin a study after receiving a favourable opinion from the ethics committee. However, under paragraph 4 of Article 15, authorisation to start the clinical investigation before the 60-day waiting period or immediately after the date of notification to the Competent Authority must be provided by the Competent Authority. Therefore, the ability to begin a study before the elapse of the 60-day waiting period depends entirely on the national transposition of the MDD in each Member State. Thus, a clinical study of devices in Class III and implantable and long-term invasive devices in Class IIa or Class IIb cannot be initiated before the 60-day waiting period unless this is allowed in the national transposition. The same applies to a clinical investigation involving devices in other classes and categories.

Active Implantable Medical Device Directive

No options regarding the 60-day waiting period are included in the Active Implantable Medical Device (AIMD) Directive (90/385/EEC). Under Article 10 of the AIMDD, a manufacturer, unless notified to the contrary, may begin a clinical investigation 60 days after notification of the clinical study to the Competent Authority in the territory →

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➔ where the study is to be conducted. The option of initiating the clinical study before the end of the 60-day waiting period is not provided by the AIMDD.

Clinical study notification in Italy

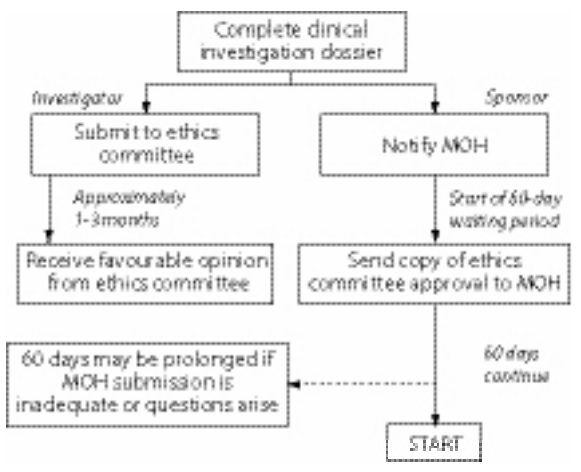
The Italian Law Decree of 24 February 1997[1] transposes the MDD. Under Article 14 of this Decree, the manufacturer or his authorised representative must transmit to the Ministry of Health (MOH) the information pertaining to the devices intended for clinical investigation listed in Annex VIII of the Decree. This Annex is the same as Annex VIII, Statement Concerning Devices for Special Purposes, of the MDD. The Decree states that the information must be in the Italian language and must be sent by registered mail.

To comply with Annex VIII, it is necessary to compile a statement containing the information listed in paragraph 2.2 of the Annex (see Table 1). Paragraph 3.3 lists the information and data, which is not required to be in the statement, that must be kept available for the Competent Authorities. The information listed in these two paragraphs in the Decree is the same as that listed in Annex VIII of the MDD. Some of the documents to be submitted are obvious such as the clinical investigation plan and opinion of the ethics committee. However, Annex VIII does not specify exactly which documents should be submitted to the MOH, nor has the MOH issued guidance regarding the documents to be submitted, but this should be available soon.

Table I: Information to be included in the statement specified in Annex VIII of the Italian Decree.

- Data allowing identification of the device in question.
- Investigation plan stating in particular the purpose, scientific, technical or medical grounds, scope and number of devices concerned.
- Opinion of the ethics committee concerned and details of the aspects covered by its opinion.
- Name of the medical practitioner or other authorised person and of the institution responsible for the investigations.
- Place, starting date and scheduled duration of the investigations.
- Statement that the device in question conforms to the essential requirements apart from the aspects covered by the investigations and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the patient.

Figure 1: Device clinical investigation submissions in Italy.



Until formal guidance is available, the MOH recommends that manufacturers submit the same information that is provided to the local ethics committee of the clinical sites involved in the study. At a minimum, this should include

- the clinical investigation plan or protocol
- the investigator's brochure
- device's instructions for use
- informed consent in the Italian language
- the insurance certificate.

In some cases, the MOH may accept some information in a language other than Italian. However, it is strongly advised that certain information be provided in the Italian language to help avoid questions and delays related to language-related uncertainties; this information should include

- a detailed synopsis of the clinical investigation plan
- a description of the investigational device and its mechanism of action, particularly if a new procedure, new mechanism of action, or method of use is involved.

In Italy, it is possible to simultaneously submit information on the clinical study to the ethics committee and the MOH (see Figure 1). However, it is often advisable to submit information to the ethics committee first; this helps ensure that the documents submitted to the MOH are final because they will already have been approved by the investigator and sponsor. In these cases, if an ethics committee requests that the MOH notification receipt is included in the clinical submission, it is generally possible to explain that it is acceptable in Italy to notify the MOH of the device clinical investigation after ethics committee submission. The ethics committee will evaluate the study and issue a "conditional approval," which becomes valid when the 60-day waiting period ends. It should also be mentioned that for some complex devices such as drug-device combination products, preliminary discussions with the MOH regarding device classification and the review pathway may need to take place so that the review process proceeds smoothly.

Italian review process

The MOH review process is a type of "silent assent" in that no formal approval is transmitted to the manufacturer or authorised representative. Under Article 14(2) of the Decree the clinical investigation with devices in Class III and implantable and long-term invasive devices in Class IIa or Class IIb can be initiated 60 days after the date of notification unless objections are received from the MOH based on considerations of public health or public policy. Some uncertainty regarding this 60-day waiting period has been caused by Article 14(3), which states that clinical investigations can begin before the end of the 60-day period if the ethics committee has expressed a favourable opinion on the clinical study programme. This appears to be an error in translation in that this provision should

have applied only to devices other than those in Class III and implantable and long-term invasive devices in Class IIa or Class IIb.

This is important because some companies may believe, based on Article 14(3), that a clinical investigation involving any type of device can be started in Italy before the end of the 60-day waiting period. However, in a letter of 4 March 2005 transmitted to all national ethics committees, the MOH has underlined the importance of allowing the full 60 days to elapse before beginning the clinical study to allow a response from the Italian authorities.

The Italian Law Decree of 14 December 1992[2] transposes the AIMDD. Article 7 specifies the requirements for conducting clinical investigations. The manufacturer or authorised representative must transmit the information specified in paragraph 2.2 of Annex VI to the MOH at least 60 days before the anticipated start of the investigation. The notification to the Competent Authority must contain the elements listed in Annex VI of the Decree. The 60-day waiting period is mandatory even if the ethics committee issues a favourable opinion before the 60-day period has elapsed.

Italian policy changes and forthcoming laws

On 23 June 2004, the Italian MOH issued a Decree that describes the reorganisation of the general offices for drugs and medical devices. The Decree states that the functions related to medical devices, which were previously managed by the general office for medical devices, are assigned to different offices. These include an office for marketed medical devices, one for in vitro diagnostic medical devices, one for medical monitoring and vigilance, and one for medical device clinical investigations.

The clinical investigation office is currently headed by Dr Mirella Colella and is responsible for the evaluation of clinical studies and compassionate use of devices and the institution of a national registry of clinical investigations. During its first year of operation, the office reviewed the clinical notifications received during previous years. Approximately 700 notifications had been received since 1997. No standardised review process was in place. Therefore, the MOH is implementing new procedures for the review and evaluation of clinical investigation notifications. Currently, the MOH receives seven to eight notifications each month. In depth reviews in accordance with the new procedures are now being conducted. In addition, the MOH is developing a programme to improve the overall process related to medical device clinical investigations. This will include education and training courses for ethics committees and other parties involved in the development, conduct and monitoring of clinical studies. For example, in a recent letter to all national ethics committees, the MOH emphasised the importance of ethics committee awareness of regulations regarding medical devices. Each letter indicated that selected standards related to clinical investigations had been purchased and were being included with the letter. In addition, the MOH suggested that the ethics committees access the United States (US) Food and Drug Administration's website to obtain useful information, including statistical guidance and other documents, on specific types of devices from the Center for Devices and Radiological Office of Device Evaluation.

Another recent change is the institution of a fee for the review of clinical investigation information. The review fee is €1859.25. Payment details may be found on the MOH website; however, they are in the Italian language only.

In the next few weeks, two new MOH Law Decrees are due to be adopted. A Decree on ethics committees is expected to include a requirement to expand the number of ethics committee members to encompass experts on medical devices, clinical engineering and tissue biocompatibility. Another Decree will include provisions on clinical investigation notifications such as more specific indications on the documentation to be submitted for a successful MOH notification. These Decrees will be available on the MOH website in Italian at www.ministerosalute.it/dispositivi/paginaMenu.jsp?menu=sperimentazione

Valuable results of the changes

Important changes have recently taken place within the Italian MOH concerning the regulatory management of the clinical investigation review process. These changes should not only contribute to a more effective implementation of the European requirements concerning the conduct of clinical investigations in Italy, but should also help to enhance the quality of the data obtained from Italian studies. This, in turn, will increase the acceptability of these data to support the CE-marking process and regulatory registrations and approvals outside Europe, including the US, thereby eliminating or reducing the need to duplicate studies already conducted in Europe.

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