Clinical Studies in Italy

Maria Donawa

The requirements for conducting medical device clinical studies in Europe are not identical in all Member States. That is, variations exist in the way that the requirements in the European Directives are interpreted and enforced. This article provides an overview of the requirements that currently apply in Italy.

Transposition of the revising Directive

New European medical device requirements, including those concerning the conduct of medical device clinical investigations, will come into force on 21 March 2010 as a result of changes introduced by the revising Directive 2007/47. At the time of writing, these changes, as they will be transposed into Italian law, have not been made publicly available by the Italian Ministry of Health (MOH). For this reason, this article will discuss only current requirements for conducting clinical studies in Italy; however, readers should check the new regulations as soon as they become available. In the meantime, it is hoped that this discussion will be beneficial to companies needing to meet current requirements until the new ones come into force. In addition, the differences between the Italian requirements and the European Directives provide an example of the differences that can occur as a result of national preferences. Readers should be aware that all the MOH documents referenced or referred to in this article are in the Italian language only. The article will not discuss performance evaluation studies of in vitro diagnostic medical devices.

Notification process


The requirements to notify the MOH of clinical investigations of AIMDs and medical devices subject to the MDD are virtually identical to the principal notification requirements in the AIMDD and MDD. That is, the manufacturer or his authorised representative must notify the Competent Authority (CA) of plans to conduct clinical investigations at least 60 days before the initiation of the investigations. The CA in Italy is the Italian MOH. The information that must be included in the notification is specified in Annex 6, Statement Concerning Devices Intended for Special Purposes, of the AIMD; and Annex VIII, Statement Concerning Devices for Special Purposes, of the MDD.

Companies wishing to conduct clinical studies in Italy must follow the procedures outlined in the Decree 2 Agosto 2005 (Decree of 2 August 2005), Modalitá di presentazione della documentazione per notifica di indagine clinica con dispositivi medici (Procedures for presenting documentation for the notification of medical device clinical investigations). The Decree, which can be obtained from the MOH’s website, includes requirements on the need to provide the notification in the Italian language; procedures for transmitting the notification to the MOH; fee to be paid; contents of the notification; declarations required from the manufacturer.
is included in a letter (circular) sent by the MOH to Italian
60 day period after notification has elapsed. This opinion
clinical studies should not be initiated until the entire
able opinion on the study(ies).
waiting period if the ethics committee has expressed a favour-
3 of Article 14 of the Italian transposition states that clinical
by the relevant ethics committee(s). For example, paragraph
ment for CA approval so that they can avoid initiating a
is important that manufacturers are aware of the require-
fee charged by the Italian MOH to review medi-
cal device clinical investigation notifications is €1859.25.
Instructions on how and when payments should be made
are included in the Decreto 2 Agosto 2005 and also in the
Circular del 5 Dicembre 2007 (Circular of 5 December
2007), which is discussed later. A receipt indicating that
the payment has been made must accompany the
notification.

Sixty-day waiting period
Paragraph 2 of Article 7 of the Italian transposition of
the AIMDD specifies that the active implantable medical
device cannot be used in the clinical study if, based on an
opinion of the Consiglio superiore di sanità (the Higher
Council of Health) (CSS), the MOH denies approval of
the study and informs the interested parties within 60
days. It also indicates that the European Commission
will be informed of the denial. Thus, this portion of the
requirement in the Italian transposition is similar to the
analogous requirement in the AIMDD, except for the
involvement of the CSS in the decision-making process.
The second subparagraph of Article 10 of the AIMDD
states that Member States may authorise manufacturers
to start the clinical investigations before the expiry of
the 60-day period, provided the relevant ethics commit-
tee has delivered a favourable opinion. The Italian MOH,
in its transposition of the AIMDD, has decided to require
CA approval in addition to ethics committee approval. It
is important that manufacturers are aware of the require-
ment for CA approval so that they can avoid initiating a
clinical investigation of an AIMDD before the expiration of
the 60-day period, even though they may have obtained a
favourable opinion from the ethics committee. An action
of this type would constitute a violation of Italian law.
The requirements in Article 14 of the Italian transposition
of the MDD are virtually identical with paragraphs 2 and 3 of
Article 15 of the MDD, which allow the possibility of initiat-
ing a clinical study before the expiration of the 60-day wait-
ing period, provided a favourable opinion has been issued
by the relevant ethics committee(s). For example, paragraph
3 of Article 14 of the Italian transposition states that clinical
investigations may begin before the expiration of the 60-day wait-
ing period if the ethics committee has expressed a favour-
able opinion on the study(ies).

Nevertheless, the MOH has expressed an opinion that
clinical studies should not be initiated until the entire
60 day period after notification has elapsed. This opinion
is included in a letter (circular) sent by the MOH to Italian
ethics committees.6 This opinion is not legally binding,
but it means that manufacturers are advised to wait until
60 days have elapsed before initiating a clinical study.
Otherwise, if the MOH identifies problems within the
60 day period, there is a danger that an ongoing study
would have to be stopped, which is likely to have signifi-
cant negative effects on study time and costs. It is hoped
that this type of difference will be avoided in coming
revisions of the Italian transposition of the MDD and any
associated nonbinding policy documents.

Clinical site requirements
Paragraph 4 of Article 7 of the Italian transposition of the
AIMDD states that medical device clinical studies can be
conducted only in public hospitals and institutions in
accordance with procedures and methods established by
MOH decree, taking into consideration opinions expressed
by the CSS. No other details are provided in paragraph 4.
The relevant decree to take note of, however, is the Decreto
Legislativo 30 Dicembre 1992, N. 502 (Legislative Decree
30 December 1992, N. 502), Riordino della disciplina in
materia sanitaria, a norma dell’articolo 1 della L. 23 otto-
bre 1992, N. 421 (Reorganisation of healthcare operations
in accordance with Article 1 of Law 23 October 1992,
No. 421), which is discussed below. This Decree outlines
the requirements that public hospitals must meet if they
are to be considered "Aziende ospedaliere“ and "Presidi
ospedalieri." There is no satisfactory English translation of
these terms, which approximate to hospital corporations
and hospital facilities.

Paragraph 4 of Article 14 of the Italian transposition of
the MDD states that clinical investigations must be
conducted in the Unità Sanitarie Locali (Local Health
Units) and hospital corporations or facilities that
meet the requirements in Article 4 of the Legislative
Decree of 30 December 1992, N. 502 and subsequent
amendments. The “Unità Sanitarie Locali” are now
called “Aziende Sanitarie Locali” or Local Health
Corporations. Furthermore, this paragraph states that the
conduct of clinical investigations in other public and
private health institutions must be approved in advance
by the MOH. In addition, the Circular of 26 February
2007, which is discussed below, states that the approval
process should be completed within 90 days; however,
written approval is required from the MOH before the
study can begin.

Manufacturers unaware of the clinical site require-
ments, which are not included in the AIMDD or the
MDD, may spend considerable time and resources nego-
tiating with clinical sites that will need prior approval
by the MOH before a medical device clinical investiga-
tion can be conducted at the site. Therefore, it is impor-
tant that manufacturers determine early in the process
of identifying prospective clinical sites in Italy whether
or not these will need to be approved by the MOH
before the clinical investigations can be conducted at
the site.
**Clinical studies with CE-marked devices**

The requirements for conducting clinical studies with CE-marked medical devices are in paragraph 7 of the Italian transposition of the MDD. This paragraph states that paragraphs 1, 2 and 3 do not apply if the clinical investigation is conducted with a device affixed with the CE mark, unless the investigation involves an intended use of the device that differs from the one covered by the CE mark. Paragraphs 1, 2 and 3 concern the need to notify the study and the 60-day waiting period. However, the requirements of Allegato X (Annex X), Valutazione Clinica (Clinical Evaluation) still apply. Although the AIMDD and the Italian transposition of the AIMDD do not specify requirements related to clinical studies with CE-marked devices, the MOH applies the requirements in paragraph 7 to clinical studies with AIMDs and devices covered by the MDD.

It is essential that manufacturers recognise that paragraph 4 of Article 14 of the Italian transposition of the MDD is not excluded by paragraph 7 of the transposition. This means that clinical studies with CE-marked devices used for their intended purpose, for example, for post-marketing clinical studies, must be conducted in public hospitals and institutions that meet the requirements set out in the Legislative Decree 30 December 1992, N. 502; or the clinical sites must be approved in advance by the MOH. This is further explained in the Circolare del 26 febbraio 2007 (Circular of 26 February 2007), which outlines the requirements and administrative procedures for conducting clinical studies with CE-marked medical devices. Additional clarification on this issue is provided in the Circolare del 5 Dicembre 2007 (Circular of 4 December 2007), which includes more information on the documentation needed to notify the MOH of a medical device clinical study. The Circulars can be obtained from the MOH website. A detailed discussion on the contents of these two important Circulars is beyond the scope of this article; however, manufacturers are urged to become informed of the procedures that the Circulars describe. Similar requirements are not in the AIMDD or the MDD.

**Significant changes**

This article has discussed some of the more important existing requirements for conducting clinical studies in Italy. It must be remembered, however, that the Italian MOH and other Member States are in the process of developing and publishing updated medical device requirements that will implement the revisions included in the revising Directive 2007/47. It is expected that significant changes related to the entire set of requirements for conducting medical device clinical studies in Italy will be introduced during this process to eliminate certain differences between Italian law and the European Directives and to introduce overall improvements to the current system. This will be welcomed by all parties involved in conducting medical device clinical studies in Italy.

**References**

2. The document can be downloaded in Italian: www.ministerosalute.it/imgs/C_17_normativa_516_allegato.pdf
3. The document can be downloaded from www.normativasanitaria.it/normsan-pdf/0000/18917_1.pdf
4. www.ministerosalute.it/dispositivi/paginaMenu.jsp?menu=sperimentazione
5. www.normativasanitaria.it/jsp/dettaglio.jsp?id=1954

Maria E. Donawa
Donawa Lifescience Consulting, Piazza Albania 10, I-00153 Rome, Italy, tel. +39 06 578 2665, e-mail: medonawa@donawa.com
www.donawa.com

*First published in Medical Device Technology, 20, 7 (November/December 2009).*