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GUIDELINES ON MEDICAL DEVICES

GUIDELINES ON CLINICAL INVESTIGATION: A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES

Note

The present Guidelines are part of a set of Guidelines relating to questions of application of EC-Directives on medical Devices. They are legally not binding. The Guidelines have been carefully drafted through a process of intensive consultation of the various interest parties (competent authorities, Commission services, industries, other interested parties) during which intermediate drafts where circulated and comments were taken up in the document. Therefore, this document reflects positions taken by representatives of interest parties in the medical devices sector.

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1 Introduction

These guidelines are based on the guidance document SG5/N3:2010 of the Global Harmonization Task Force. They are adapted to the requirements on clinical investigations laid out in annex 7 of directive 90/385/EEC and in annex X of directive 93/42/EEC as amended by directive 2007/47/EC. The clinical investigations shall be performed as described in these annexes.

They reflect the consensus view of the various interested parties with regard to clinical investigations under the above-mentioned medical devices directives.

What is a clinical investigation?

A clinical investigation is defined as “any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device.” (SG5/N1:2007).

The undertaking of a clinical investigation is a scientific process that represents one method of generating clinical data.

What is the objective of a clinical investigation?

The objective of a clinical investigation is to assess the safety and clinical performance of the device in question and evaluate whether the device is suitable for the purpose(s) and the population(s) for which it is intended (EN ISO 14155-1:2009).

How is a clinical investigation conducted?

EN ISO 14155-1:2009 *Clinical Investigation of Medical Devices for Human Subjects - General Requirements* details the general requirements for the conduct of clinical investigations and EN ISO 14155-2:2009 *Clinical Investigation of Medical Devices for Human Subjects - Clinical Investigation Plan* contains detailed information about the procedure and contents of a clinical investigation plan. Clinical investigations must take into account scientific principles underlying the collection of clinical data along with accepted ethical standards surrounding the use of human subjects. The clinical investigation objectives and design should be documented in a clinical investigation plan.

2 Scope

The primary purpose of this document is to provide guidance in relation to:

- when a clinical investigation should be undertaken for a medical device to demonstrate compliance with the relevant *Essential Requirements*; and

- the general principles of clinical investigations involving medical devices.

Given the wide diversity of medical devices and their associated risks, this document is not intended to provide comprehensive guidance for clinical investigations of specific medical devices.

The guidance contained within this document is intended to apply to medical devices generally and to combination products regulated as medical devices. It is not intended to cover in vitro diagnostic medical devices. Additionally, this document was drafted primarily to address the use of Clinical Investigations to support clinical evaluation and a conformity assessment procedure. Some aspects of this document may apply to studies conducted following commercial release of a device. A separate guidance document specifically addresses post-market clinical follow-up (MEDDEV 2.12/2: *Clinical Evaluation - Post Market Clinical Follow-up*).

3 References

Directive 90/385/EEC, as amended by Directive 2007/47/EC
Directive 93/42/EEC, as amended by Directive 2007/47/EC

Interpretative Documents

MEDDEV 2.7.1 Rev. 3; December 2009
Clinical Evaluation: A Guide for Manufacturers and Notified Bodies

MEDDEV 2.7.1, Appendix 1; December 2008
Evaluation of Clinical Data – A Guide for Manufacturers and Notified Bodies – Appendix 1: Clinical Evaluation of Coronary Stents

MEDDEV 2.7.2; December 2008
Guide for Competent Authorities in Making an Assessment of Clinical Investigations Notification

MEDDEV 2.12/2; May 2004
Clinical Evaluation - Post Market Clinical Follow-up

GHTF final documents

SG5/N1:2007 *Clinical Evidence – Key definitions and Concepts*

SG5/N2:2007 *Clinical Evaluation*

Harmonized/International standards

EN ISO 14155-1: 2009
Clinical investigation of medical devices for human subjects – Part 1 General requirements

EN ISO 14155-2: 2009
Clinical investigation of medical devices for human subjects – Part 2 Clinical investigation plans

EN ISO 14971: 2009
Application of risk management to medical devices

Other References
World Medical Association – Declaration of Helsinki - Ethical principles for medical research involving human subjects

4 Definitions

Clinical Data:
The safety and/or performance information that is generated from the use of a device. Clinical data are sourced from:
— clinical investigation(s) of the device concerned; or
— clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated; or
— published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated.

Clinical Evaluation:
The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer.

Clinical Evidence:
The clinical data and the clinical evaluation report pertaining to a medical device.

Clinical Investigation:
Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device.

Clinical Investigation Plan:
Document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation.

Clinical Performance:
The ability of a medical device to achieve its intended purpose as claimed by the manufacturer.

Clinical Safety:
The absence of unacceptable clinical risks, when using the device according to the manufacturer's Instructions for Use.

Conformity Assessment:

The systematic examination of evidence generated and procedures undertaken by the manufacturer, according to Article 9 of directive 90/385/EEC and Article 11 of directive 93/42/EEC, to determine that a medical device is safe and performs as intended by the manufacturer and, therefore, conforms to the *Essential Requirements* according to Annex 1 of directive 90/385/EEC and Annex I of directive 93/42/EEC.

Device intended for Clinical Investigation:

any device intended for use by a duly qualified medical practitioner when conducting investigations as referred to in Sections 2.1 of Annex 7 of directive 90/385/EEC and section 2.1 of Annex X of directive 93/42/EEC in an adequate human clinical environment.

Endpoint: Indicators measured or determined to assess the objectives of a clinical investigation, prospectively specified in the clinical investigation plan. (EN ISO 14155_2:2009, modified)

Residual Risk: Risk remaining after risk control measures has been taken (EN ISO 14971:2009).

Risk Management:

The systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk (EN ISO 14971:2009).

5 General Principles When Considering the Need for a Clinical Investigation

Clinical Evaluation

According to Annex 1.I.5a of directive 90/385/EEC and Annex I.I.6a of directive 93/42/EEC demonstration of conformity with the **essential requirements** must include a clinical evaluation in accordance with Annex 7/Annex X of the respective directive.

As a general rule, confirmation of conformity with the requirements concerning the characteristics and performances referred to in sections I.1 and I.3 of annex I of directive 90/385/EEC and in sections I.1 and I.2 of annex I of directive 93/42/EEC under the normal conditions of use of the device, and the evaluation of the side-effects and of the acceptability of the benefit/risk ratio referred to in Section I.5/I.6 of Annex I of directives 90/385/EEC and 93/42/EEC respectively, must be based on **clinical data**.

The kind and amount of clinical data needed will primarily depend on the specifics of the clinical claims with regard to clinical performance, considerations of clinical safety, including determination of undesirable side-effects and on risk management output, namely determination of residual risks and favorable benefit/risk ratio. Some factors that may typically influence the specificity/extent of clinical data

requirements are listed in section 6 of this guidance. Different clinical claims/intended purposes of a device may often necessitate different clinical data. For example, in the case of the closure of the heart defect patent foramen ovale, clinical performance/safety data and benefit/risk-considerations may vary in different intended purposes such as stroke prevention or migraine crisis prevention.

Conducting a proper **clinical evaluation** will demonstrate which clinical data are necessary, which clinical data can be adequately supplemented by other methods, such as literature search, prior clinical investigations, clinical experience or by using suitable clinical data from equivalent[1] devices, and which clinical data remain to be delivered by clinical investigations (see MEDDEV 2.7.1 Rev.3: "Clinical Evaluation: A Guide for Manufacturers and Notified Bodies").

The clinical evaluation and its documentation must be actively updated with data obtained from the post-market surveillance. New such data as well as considerations for new or changed intended purposes need updating of the clinical evaluation and may indicate necessity of additional clinical investigations.

When must/should a clinical investigation be undertaken?

The Conformity Assessment process for active implantable medical devices as well as for class III and implantable medical devices requires that a clinical investigation is undertaken unless it is duly justified to rely on existing data (section 1.2 of Annex 7 of directive 90/385/EEC and section I.1a of Annex X of directive 93/42/EEC). Any such justification will have to be based on a proper clinical evaluation.

Depending on clinical claims, risk management outcome and on the results of the clinical evaluation, clinical investigations may also have to be performed for non-implantable medical devices of classes I, IIa and IIb.

Additional clinical investigations may be feasible to corroborate the existing clinical evidence with regard to aspects of clinical performance, safety, benefit/risk-ratio or to determine relative effectiveness and safety with suitable comparators.

6 General Principles of Clinical Investigation Design

Any clinical investigation must:

- be part of the clinical evaluation process;
- follow a proper risk management procedure to avoid undue risks;
- be compliant with all relevant legal and regulatory requirements;
- be appropriately designed (see below);
- follow appropriate ethical principles (see Section 7).

[1] The concept of equivalency encompasses technical, biological and clinical equivalency.

Basic legal and administrative provisions given in directives 90/385/EEC and 93/42/EEC

Art. 4 of the two directives require that Member States shall not create any obstacle to devices intended for clinical investigation being made available to medical practitioners or authorized persons for that purpose if they meet the conditions laid down in Article 10/15 and in Annex 6/VIII of the respective directives. These devices shall not bear the CE marking.

Art. 10/15 of the directives contain the administrative provisions for clinical investigations, Annex 6/VIII respectively the contents and provisions for the statement and documentation required.

Annexes 7/X, sections 2.2 relate to ethical provisions, sections 2.3 specify basic methodological aspects of clinical investigations.

Further legal and regulatory/administrative requirements may be valid at national/regional level.

Factors to Influence Clinical Data Requirements

The design of the clinical investigation, including the study objectives and statistical considerations, should provide the clinical data necessary to address relevant aspects of clinical performance, safety, including undesirable side-effects as well as the residual risks identified in the risk management process. Some factors that may influence the extent of clinical data requirements include, but are not limited to, the following:

- type of device and/or regulatory classification;
- novel technology/relevant previous experience;
- clinical application/indications;
- nature of exposure to the product, e.g.: surface contact, implantation, ingestion;
- risks inherent in the use of the product, e.g.: risk associated with the procedure;
- performance claims made in the device labeling (including instructions for use);
- component materials and substances;
- disease process (including severity) and patient population being treated;
- demographic, geographic and cultural considerations (e.g.: age, race, gender, etc.);
- potential impact of device failure;
- period of exposure to the device;

- expected lifetime of the device;
- availability of alternative treatments and current standard of care; and
- ethical considerations.

Considerations for Device Study Designs

Some of the factors that need to be considered in the study design include, for example:

- clear statement of objectives
- appropriate subject population(s)
- minimization of bias (e.g., randomization, blinding)
- identification of confounding factors (e.g., concurrent medications, co-morbidities)
- choice of appropriate controls (e.g., cohort, sham, historical), where necessary
- design configuration (e.g., parallel, crossover, factorial)
- type of comparison (e.g., superiority, non-inferiority, equivalence)

Investigations should be planned in such a way as to maximize the clinical relevance of the data while minimizing confounding factors. Possible study designs include:

- **randomized controlled trials**
- **cohort studies**
- **case-control studies**
- **case series**

These are further explained in Appendix C of the document MEDDEV 2.7.1 Rev. 3 on Clinical Evaluation.

In designing the study, statistical considerations should be prospectively specified and should be based on sound scientific principles and methodology. Care must be taken in developing a statistical plan that includes consideration of, for example, the following:

- endpoints that are clinically relevant, clearly defined and assessed at a specified time point[2]
- a testable hypothesis
- statistical significance levels, power
- sample size justification

[2] See e.g. critical aspects of end point definition for regulatory trials [D.B. Kramer et al, American Journal of Therapeutics 17, 2-7 (2010)]

- analysis methodology (including sensitivity and poolability analysis)

The design should ensure that the statistical evaluation derived from the investigation reflects a meaningful, clinically significant outcome.

Discussion with a competent authority or a notified body may be appropriate when there is uncertainty as to whether the proposed clinical investigation plan is sufficient.

Conduct of Clinical Investigations

A properly conducted clinical investigation, including compliance to the clinical investigation plan and local laws and regulations, ensures the protection of subjects, the integrity of the data and that the data obtained is acceptable for the purpose of demonstrating conformity to the *Essential Requirements*. EN ISO 14155 outlines good clinical practice for clinical investigations of medical devices.

Final Study Report

The outcome of a clinical investigation has to be documented in a final study report (Annex 7/X, section 2.3.7 of directives 90/385/EEC and 93/42/EEC) This then forms part of the clinical data that is included in the clinical evaluation process and ultimately becomes integrated into the clinical evaluation report (see MEDDEV 2.7.1 Rev. 3) for the purposes of conformity assessment. The structure of a final study report is proposed in EN ISO 14155-1:2009.

7 Ethical Considerations for Clinical Investigations

In their sections 2.2 of Annex 7/Annex X, directives 90/385/EEC and 93/42/EEC require: “Clinical investigations must be carried out in accordance with the Helsinki Declaration adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the World Medical Assembly. It is mandatory that all measures relating to the protection of human subjects are carried out in the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results.”

As a general principle, “the rights, safety and wellbeing of clinical investigation subjects shall be protected consistent with the ethical principles laid down in the Declaration of Helsinki” (EN ISO 14155-1:2009).

It is ethically important in deciding to conduct a clinical investigation that it should generate new data and answer specific safety and/or performance questions that remain unanswered by the current body of knowledge. The desire to protect human subjects from unnecessary or inappropriate experimentation must be balanced with the need to protect public health through the use of clinical investigations where they are indicated. In all cases, however, care must be taken to ensure that the necessary data are obtained through a scientific and ethical investigational process that does not expose subjects to undue risks or discomfort. The rights, safety and well-being of subjects are paramount and appropriate trial design and conduct is essential to generate meaningful data.