



WORKING DRAFT DOCUMENT

Global Harmonization Task Force

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Preface

The document herein was produced by the Global Harmonization Task Force, a voluntary group of representatives from medical device regulatory agencies and the regulated industry. The document is intended to provide non-binding guidance for use in the regulation of medical devices, and has been subject to consultation throughout its development.

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1 Introduction

What is 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 evaluate whether the device is suitable for the purpose(s) and the population(s) for which it is intended.” (ISO 14155)

How are they conducted?

ISO 14155-1:2003 *Clinical Investigation of Medical Devices for Human Subjects - General Requirements* details the general requirements for the conduct of clinical investigations and ISO 14155-2:2003 *Clinical Investigation of Medical Devices for Human Subject - Clinical Investigation Plan* contains detailed information about the procedure and contents of a clinical investigation plan. In general, 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 Principles (see GHTF SG1/N041 – “*Essential Principles of Safety and Performance of Medical Devices*”); 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 the device component of combination products. 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 a marketing authorization application. Some aspects of this document may apply to studies conducted following commercial release of a device. Future GHTF documents will specifically address post-market follow-up studies.

3 References

GHTF final documents

- SG1/N029:2005 *Information Document Concerning the Definition of the Term "Medical Device"*
- SG1/N041:2005 *Essential Principles of Safety and Performance of Medical Devices*
- SG1/N040:2006 *Principles of Conformity Assessment for Medical Devices*
- SG1/N43:2005 *Labelling for Medical Devices*
- SG5/N1:2007 *Clinical Evidence – Key definitions and Concepts*
- SG5/N2:2007 *Clinical Evaluation*

GHTF documents proposed for public comment

- SG1/N011R20 *Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)*

International standards

- ISO 14155-1: 2003 *Clinical investigation of medical devices for human subjects – Part 1 General requirements*
- ISO 14155-2: 2003 *Clinical investigation of medical devices for human subjects – Part 2 Clinical investigation plans*
- ISO 14971: 2007 *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: Safety and/or performance information that are generated from the clinical use of a medical device.

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, under requirements established by the Regulatory Authority, to determine that a medical device is safe and performs as intended by the manufacturer and, therefore, conforms to the *Essential Principles of Safety and Performance for Medical Devices (SG1/N041:2005)*.

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

Residual Risk: Risk remaining after risk control measures have been taken (ISO 14971).

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

All definitions are developed by GHTF SG5 except where noted.

5 General Principles When Considering the Need for a Clinical Investigation

When is it necessary to undertake a clinical investigation?

Clinical investigations are necessary to provide the data not available through other sources (such as literature or preclinical testing) required to demonstrate compliance with the relevant Essential Principles (including safety, clinical performance and acceptability of risk/benefit ratio associated with its use). When a clinical investigation is conducted, the data obtained is used in the clinical evaluation process and is part of the clinical evidence for the device (see GHTF SG5/N2 – “*Clinical Evaluation*”).

What are the crucial steps in clarifying the need for clinical investigations?

1. Identifying relevant clinical **Essential Principles** (for example, specifics of safety, clinical performance, acceptability of risk/benefit-ratio) for the device and its intended use/purpose(s) and use(s) (see GHTF SG1/N041 – *Essential Principles of Safety and Performance of Medical Devices*);
2. Performing **risk management** (ISO 14971) activities will help in identifying the clinical data necessary to control residual risks and aspects of clinical performance not completely resolved by available information e.g. design solutions, preclinical and material/technical evaluation, conformity with relevant standards, labelling, etc.;
3. Conducting a proper **clinical evaluation** will demonstrate which clinical data are necessary and can be adequately contributed to by other methods, such as literature searching, prior clinical investigations or clinical experience, and which clinical data remain to be delivered by clinical investigation(s). Available clinical data for comparator devices should be carefully examined for comparability and adequacy (see SG5/N2:2007 *Clinical Evaluation*).

Note: This exercise is applicable for the introduction of a new device as well as for planned changes of a device, its intended use and/or claims.

What is the role of risk analysis?

A properly conducted risk analysis is essential in determining what clinical evidence may be needed for a particular device (see ISO 14971). A clinical investigation may be required when the currently available data from preclinical testing, and any prior clinical investigations or other forms of clinical data are insufficient to demonstrate conformity with the Essential Principles.

This would be the case when the manufacturer's risk analysis and the clinical evaluation of a medical device for a particular intended use, including new claims, shows that there are residual risks, including aspects of clinical performance, that have not been adequately addressed by the available data and cannot be addressed through other methods.

As described in ISO 14971, "residual risk" is the risk remaining after risk control measures have been taken. Risk control measures include inherent safety by design, protective measures in the medical device itself or in the manufacturing process, and information for safety. The decision to use a medical device in the context of a clinical procedure requires the residual risk to be balanced against the anticipated benefits of the procedure. A clinical investigation may be used to further elucidate the risk/benefit ratio in a defined patient population. For instance, risk can be measured through safety endpoints, and benefits may be measured through assessments of clinical performance. An example could be the introduction of a new aortic stent graft, where safety could be measured through incidence of endoleak, and benefits measured in terms of survival. Residual risks that could require the use of a clinical investigation might be an unknown rate of device failure.

For long established technologies, clinical investigation data that might be required for novel technologies may not be necessary. The available clinical data in the form of, for example, published literature, reports of clinical experience, post-market reports and adverse event data should, in principle, be adequate to establish the safety and performance of the device, provided that new risks have not been identified, and that the indications for use have not changed.

Where uncertainty exists as to whether current data are sufficient to demonstrate conformity with the Essential Principles, discussion with regulatory authorities or a conformity assessment body may be appropriate.

When is undertaking a clinical investigation justified?

In order to be justified and to avoid unnecessary experimentation on human subjects, the clinical investigation(s) must:

- be necessary (as assessed above)
- be designed properly (see Section 6)
- be ethical (see Section 7)
- follow a proper risk management procedure to avoid undue risks
- be compliant with all relevant legal and regulatory requirements

6 General Principles of Clinical Investigation Design

The design of the clinical investigation, including the study objectives and statistical considerations, should provide the clinical data necessary to address the residual risks, including

aspects of clinical performance. Some factors that may influence the extent of 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) and/or promotional materials;
- component materials;
- 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.

As a general rule, devices based on new or “unproven” technology and those that extend the intended purpose of an existing technology through a new clinical use are more likely to require supporting clinical investigation data.

Specific Considerations for Device Study Designs

Device technologies have introduced a variety of complex challenges influencing the design of clinical investigations. Some of the factors that need to be considered 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** – clinical investigations where subjects are randomized to receive either a test or reference device or intervention and outcomes and event rates are compared for the treatment groups
- **cohort studies** – data are obtained from groups who have and have not been exposed to the device (e.g. concurrent control) and outcomes compared
- **case-control studies** – patients with a defined outcome and controls without the outcome are selected and information is obtained about whether the subjects were exposed to the device
- **case series** – the device has been used in a series of patients and the results reported, with no control group for comparison

In designing the study, statistical considerations should be prospectively specified and 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:

- clinically relevant endpoints
- statistical significance levels, power
- sample size justification
- 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 regulatory authorities or a conformity assessment body may be appropriate when there is uncertainty as to whether the proposed clinical investigational 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 Principles. ISO 14155 outlines good clinical practice for clinical investigations of medical devices.

Final Study Report

The outcome of a clinical investigation should be documented in a final study report. The final study report 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 GHTF SG5/N2) for the purposes of conformity assessment.

7 Ethical Considerations for Clinical Investigations

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” (ISO 14155).

Specific considerations include that:

- clinical investigations should be used only when appropriate data cannot be obtained through any other method, as it is desirable to minimize experimentation on human subjects;
- the design of the investigation and its endpoints should be adequate to address the residual risks including aspects of clinical performance;
- 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; and
- ethics review and regulatory body oversight occurs in conformity to local laws or regulations.