WORKING DRAFT DOCUMENT

Global Harmonization Task Force

Title: Clinical Investigations

Authoring Group: Study Group 5

Date: –05 February 2007

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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.

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(PD)N1R7)

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 14155-1:2003)

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/protocol.

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 support compliance with the relevant Essential Principles; 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.

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*

GHTF documents proposed for public comment

SG1/N011R17 *Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)*

SG5(PD)/N1R7 *Clinical Evidence – Key definitions and Concepts*

SG5(PD)/N2R7 *Clinical Evaluation*

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: 2000 *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: **S**afety 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: A prospectively specified response variable chosen to assess device safety and/or performance within a clinical investigation.

5 General Principles When Considering the Need for a Clinical Investigation

When is it necessary to undertake a clinical investigation?

Clinical investigations provide clinical data that are unattainable through other methods, and are intended to provide objective evidence to support safety and/or performance through actual use in human subjects.

What is the justification for undertaking a clinical investigation?

A properly conducted risk analysis is essential in determining what clinical data are required for a particular device (see, for example, ISO 14971). A clinical investigation may be required 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 preclinical and clinical data (i.e. the currently available data are insufficient to demonstrate conformity with Essential Principles).

For long established technologies, clinical investigation data of a contemporary standard may not be available. The generation of additional clinical data via clinical investigation should not be necessary for such devices, as the available clinical data in the form of literature, reports of clinical experience, post-market reports and adverse event database data should, in principle, be adequate to establish the safety and performance of the device.

Where uncertainty exists as to whether current data are sufficient to demonstrate conformity with Essential Principles, discussion with Regulatory Authorities may be appropriate.

Note: In some jurisdictions, the regulatory framework may specifically require a clinical investigation for a particular medical device or particular circumstance.

6 General Principles of Clinical Investigation Design

The design of the clinical investigation 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;
- 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;

- 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.

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 14155-1:2003).

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; and
- care must be taken to ensure that the necessary data is obtained through a scientific and ethical investigational process that does not expose subjects to undue risks or discomfort.