



FINAL DOCUMENT

Title: Post-Market Clinical Follow-Up Studies

Authoring Group: Study Group 5

Endorsed by: The Global Harmonization Task Force

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A handwritten signature in black ink, appearing to read 'L Kelly', is positioned above the name of the chair.

Dr. Larry Kelly, GHTF Chair

The document herein was produced by the Global Harmonization Task Force, which is comprised 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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Preface

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1. INTRODUCTION

While clinical evidence is an essential element of the premarket conformity assessment process to demonstrate conformity to Essential Principles, it is important to recognise that there may be limitations in the clinical data available in the pre-market phase. Such limitations may be due to, for example, the duration of pre-market clinical investigations, the number of subjects involved in an investigation, the relative homogeneity of subjects and investigators and the control of variables in the setting of a clinical investigation versus use in the full range of conditions encountered in general medical practice.

It is appropriate to place a product on the market once conformity to the relevant Essential Principles, including a favourable risk/benefit ratio, has been demonstrated. Complete characterization of all risks may not always be possible or practicable in the pre-market phase. Therefore, there may be questions regarding residual risks that should be answered in the postmarket phase through the use of one or more systematic post-market clinical follow-up studies. Post-market clinical studies are not intended to replace the pre-market data necessary to make the decision as to approve the device.

Post-market clinical follow-up studies are one of several options available in a post-market surveillance programme (see GHTF SG2N47) and contribute to the risk management process.

2. SCOPE

This document is intended to provide guidance on post-market clinical follow-up studies developed specifically for issues of residual risk (including those mandated by regulation). However, the principles presented may be applicable to post-market clinical follow-up studies conducted for other purposes.

This document does not impose new regulatory requirements but is intended to provide guidance on the appropriate use and conduct of postmarket clinical follow-up studies.

This document provides guidance in relation to:

- i) the circumstances where a post-market clinical follow-up study is indicated;
- ii) the general principles of post-market clinical follow-up studies involving medical devices; and
- iii) the use of study information, including, for example, to provide information to update labelling.

This document does not apply to *in vitro* diagnostic devices.

3. REFERENCES

GHTF Final Documents:

SG1/N41:2005	<i>Essential Principles of Safety & Performance of Medical Devices</i>
SG1/N44:2008	<i>The Role of Standards in the Assessment of Medical Devices</i>
SG2/N47:2005	<i>Review of Current Requirements on Post-Market Surveillance</i>
SG5/N1:2007	<i>Clinical Evidence – Key Definitions and Concepts</i>
SG5/N2:2007	<i>Clinical Evaluation</i>
SG5/N3:2010	<i>Clinical Investigations</i>

GHTF Proposed Documents:

SG1(WD)N065	<i>Registration of Manufacturers and Other Parties and Listing of Medical Devices</i>
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International Standards:

ISO 14155-1: 2003	<i>Clinical investigation of medical devices for human subjects – Part 1 General requirements</i>
ISO 14155-2: 2003	<i>Clinical investigation of medical devices for human subjects – Part 2 Clinical investigation plans</i>

ISO 14971: 2007 [Application of risk management to medical devices](#)

Others:

Agency for Healthcare Research and Quality [Registries for Evaluating Patient Outcomes: A User's Guide](#)

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.

Device Registry: An organized system that uses observational study methods to collect defined clinical data under normal conditions of use relating to one or more devices to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves (a) predetermined scientific, clinical or policy purpose(s). (Agency for Healthcare Research and Quality, "Registries for Evaluating Patient Outcomes: A User's Guide", modified)

Note: The term "device registry" as used here should not be confused with the concept of device registration and listing. (See GHTF SG1N065)

Post-market clinical follow-up study: A study carried out following marketing approval intended to answer specific questions relating to clinical safety or performance (i.e. residual risks) of a device when used in accordance with its approved labelling. These may examine issues such as long-term performance, the appearance of clinical events (such as delayed hypersensitivity reactions or thrombosis), events specific to defined patient populations, or the performance of the device in a more representative population of providers and patients.

Residual Risk: Risk remaining after risk control measures have been taken (ISO 14971) (e.g. known or emerging risks, or potential risks due to statistical limitations).

5. Circumstances Where A Post-Market Clinical Follow-Up Study Is Indicated

The need for post-market clinical follow-up studies should be determined from the identification of residual risks that may impact the risk/benefit ratio.

Circumstances that may result in the need for post-market clinical follow-up studies include, for example:

- innovation, e.g., where the design of the device, the materials, the principles of operation, the technology or the medical indications are novel;
- a new indication or claim has been approved;
- significant changes to device design or labelling;
- higher risk classification;
- higher risk anatomical locations;
- severity of disease/treatment challenges;
- questions of ability to generalise clinical investigation results;
- unanswered questions of long-term safety and performance;
 - results of any previous clinical investigation including adverse events identified or from postmarket surveillance activities;

- identification of previously unstudied populations;
- discrepancy between the premarket follow-up time scales and the expected life of the product;
- risks identified from the literature or other data sources for similar marketed devices;
- sensitivity of target population;
- interaction with other medical products or treatments;
- training/learning curve issues;
- emergence of new information relating to safety or performance;

Post-market clinical follow-up studies may not be required in cases where the medium/long-term safety and clinical performance are already known from previous use of the device or where other appropriate post-market surveillance activities would provide sufficient data to address the risks.

6. Elements of A Post-Market Clinical Follow-Up Study

Postmarket clinical follow-up studies are performed on a device within its intended use/purpose(s) according to the instructions for use. It is important to note that post-market clinical follow-up studies must be conducted according to applicable laws and regulations, and should follow appropriate guidance and standards.

The elements of a post-market clinical follow-up study include:

- (a) clearly stated objective(s);
- a scientifically sound design with an appropriate rationale and statistical analysis plan;
- a study plan; and
- implementation of the study according to the plan, an analysis of the data and appropriate conclusion(s)

The objective(s) of post-market clinical follow-up studies

The objective(s) of the study should be stated clearly and should address the residual risk(s) identified and be formulated to address one or more specific questions relating to the clinical safety or performance of the device. A formal hypothesis should be clearly expressed.

The design of postmarket clinical follow-up studies

Postmarket clinical follow-up studies should be designed to address the objective(s) of the study. The design may vary based on the objective(s) and should be scientifically sound to allow for valid conclusions to be drawn.

The study design can take several forms, for example:

- the extended follow-up of patients enrolled in premarket investigations;
- a new clinical investigation;
- a review of data derived from a device registry; or
- a review of relevant retrospective data from patients previously exposed to the device.

The postmarket clinical follow-up study plan

All post-market clinical follow-up studies should have a plan appropriate for addressing the stated objectives. The study plan should justify, for example:

- the patient population;
- inclusion/exclusion criteria;
- controls/control groups (where relevant);
- the selection of sites and investigators;
- the endpoints and statistical considerations;
- the number of subjects involved;
- the duration of the study;
- the data to be collected;
- study endpoints;
- the analysis plan including any interim reporting; and
- procedures/criteria for early study termination.

Implementation of the post-market clinical follow-up study, analysis of data and conclusion(s)

The study should:

- be executed with adequate control measures to assure compliance with the plan;
- include data analysis with conclusions drawn according to the analysis plan by someone with appropriate expertise; and
- have a final report with conclusions relating back to original objective(s) and hypothesis/hypotheses.

7. The Use of Study Information

The data and conclusions derived from the post-market clinical follow-up study are used to provide clinical evidence to support the post-market surveillance program and input into the clinical evaluation process. This may result in the need to reassess whether the device continues to comply with the Essential Principles. Such assessment may result in corrective or preventive actions, for example, changes to the labelling/instructions for use, changes to manufacturing processes, changes to the device design, or public health notifications.