PROPOSED DOCUMENT

International Medical Device Regulators Forum

Title: Clinical Evidence – Key Definitions and Concepts

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Preface

The document herein was produced by the International Medical Device Regulators Forum (IMDRF), a voluntary group of medical device regulators from around the world. The document has been subject to consultation throughout its development.

1.0 Introduction

It is anticipated that convergence of requirements for clinical evidence, including common data submissions, will lead to better understanding of medical device safety, clinical performance, and/or effectiveness by all stakeholders, more efficient use of resources of the clinical community, medical device regulators and industry, and increased transparency and confidence in the global regulatory model. Ultimately, there should be more efficient, predictable and timely access to safe and effective medical technology by patients and society worldwide.

Clinical evidence and the Essential Principles of safety and performance of medical devices

The IMDRF *Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices* (the Essential Principles) set out the requirements relating to the safety and performance of medical devices. Of these, Essential Principles 5.1.1, 5.1.6, 5.1.7 and 5.1.9 in particular require that a medical device achieve its intended performance during normal conditions of use and that the known, and foreseeable risks, and any undesirable side-effects, are minimised and acceptable when weighed against the benefits of the intended performance.

The diversity of medical devices and the technologies on which they are based pose special challenges for manufacturers, conformity assessment bodies and regulators alike when trying to identify what should constitute evidence sufficient to demonstrate compliance with the Essential Principles. Some technologies have been available for many years and are well characterised from a safety, clinical performance, and/or effectiveness viewpoint. On the other hand, many devices utilise new, state-of-the-art technology that has had little prior application in the treatment of humans.
Furthermore, their intended purpose and clinical application can vary widely with end results influenced by a wide range of different and differently experienced end-users.

Given the complexity of the medical devices milieu, the assessment of what is acceptable clinical evidence for the purpose of demonstrating compliance with the Essential Principles must be undertaken on a case-by-case basis. To this end, it is important to have an understanding of how medical devices are brought to market and of the role that clinical data and its evaluation plays in this process.

This document supersedes an earlier version produced under the Global Harmonization Task Force (GHTF) with the same title in May, 2007(GHTF/SG5/N1R8:2007).

2.0 Scope

This document is intended to:

- introduce the concepts of clinical evaluation and clinical evidence;
- examine the relationship between clinical investigation, clinical data, clinical evaluation and clinical evidence; and
- serve as guidance to all those involved in the generation, compilation and review of clinical evidence sufficient to support the marketing of medical devices (regulatory authorities, conformity assessment bodies, manufacturers of medical devices and their associated industry groups).

The definitions and concepts contained within this document are intended to apply to the establishment and maintenance of conformity with the relevant Essential Principles for medical devices generally. Specific guidance will be developed in other documents in relation to *in vitro* diagnostic devices. Similarly, guidance about how to generate, compile and present clinical evidence for the purpose of demonstrating compliance with the Essential Principles for safety and performance of a medical device will be addressed in future documents.

3.0 References

IMDRF/GHTF final documents

IMDRF GRRP WG/N47 FINAL: 2018 *Essential Principles of Safety and Performance of Medical Devices and IVD Medical Device*

GHTF SG1/ N78:2012 *Principles of Conformity Assessment for Medical Devices*

International standards

ISO 14155-2011 *Clinical investigation of medical devices for human subjects — Good clinical practice*

4.0 Definitions and Concepts

4.1 Clinical investigation

Definition: Any systematic investigation or study in or on one or more human subjects,

undertaken to assess the safety, clinical performance, and/or effectiveness of a medical device.

Explanation: This term is synonymous with 'clinical trial' and 'clinical study'.

An effective medical device has the ability to provide clinically significant results in a significant portion of the target population; effectiveness is established using documented scientific evidence that a medical device is effective.

Clinical investigations include feasibility studies and those conducted for the purpose of gaining market approval, as well as investigations conducted following marketing approval.

4.2 Clinical data

Definition: Safety, clinical performance, and/or effectiveness information that is generated from the clinical use of a medical device.

Explanation: Sources of clinical data may include:

(i) results of pre- and post-market clinical investigation(s) of the device concerned
(ii) results of pre- and post-market clinical investigation(s) or other studies reported in the scientific literature of a justifiably comparable device
(iii) published and/or unpublished reports on clinical experience of either the device in question or a justifiably comparable device
(iv) other sources of clinical experience such as registries and adverse event databases

4.3 Clinical evaluation

Definition: A set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety, clinical performance, and/or effectiveness of the device when used as intended by the manufacturer.

Explanation: This is a process undertaken by manufacturers of medical devices to help establish compliance with the relevant Essential Principles for safety and performance. The result of this process is a report that can be reviewed by conformity assessment bodies and regulators and which details the extent of available data and its quality and demonstrates how the compliance with the Essential Principles is satisfied by the clinical data. Clinical evaluation is an ongoing process - information about safety and clinical performance, and/or effectiveness (e.g. adverse event reports, results from any further clinical investigations, published literature etc.) should be monitored routinely by the manufacturer once the device is available on the market and the benefits and risks reassessed in light of this additional information.

Effectiveness is established using documented scientific evidence that a medical

device is effective.

The inputs for clinical evaluation are primarily clinical data in the form of clinical investigation reports, literature reports/reviews and clinical experience. The data required to establish the initial evidence of compliance with the Essential Principles may vary according to the characteristics of the device, its intended use, the claims made by the manufacturer, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. A key goal of the clinical evaluation is to establish that any risks associated with the use of the device are acceptable when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety. The clinical evaluation will, therefore, also need to cross-reference risk management documents.

4.4 Clinical evidence

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

Explanation: Clinical evidence is an important component of the technical documentation of a medical device, which along with other design verification and validation documentation, device description, labelling, risk analysis and manufacturing information, is needed to allow a manufacturer to demonstrate conformity with the Essential Principles. It should be cross-referenced to other relevant parts of the technical documentation that impact on its interpretation.

In accordance with applicable local regulations, clinical evidence, in part or in total, may be submitted to and reviewed by conformity assessment bodies and regulatory authorities. The clinical evidence is used to support the marketing of the device, including any claims made about the safety, clinical performance, and/or effectiveness of the device, and the labelling of the device. Figure 1 shows how the need for clinical evidence drives the processes of data generation and clinical evaluation, which produce clinical data and clinical evidence, respectively.

Clinical evidence should be reviewed and updated throughout the product life cycle by the manufacturer as new information relating to safety, clinical performance, and/or effectiveness is obtained from clinical experience during marketing (e.g. adverse event reports, results from any further clinical investigations, formal post market surveillance studies) of the device in question and/or comparable devices.

Figure 1 Overview of process for data generation and clinical evaluation