Guidance on Reporting of Adverse Events in Clinical Investigations and Performance Studies

1. Introduction

The purpose of this document is to provide guidance to sponsors or legal representatives of clinical investigations and performance studies on the reporting of adverse events that may occur during the clinical investigations or performance studies. This guidance will assist sponsors to comply with obligations listed in the two EU Regulations (hereafter to be referred to as 'the Regulations') (EU) 2017/745 Medical Device Regulation (MDR) for medical devices and (EU) 2017/746 In vitro Diagnostic Medical Device Regulation (IVDR) for in-vitro diagnostic medical devices.

The mandatory use of the European databank platform will start when the entire EUDAMED modules have been declared fully functional, in accordance with Article 73 of the Medical Device Regulation.

2. Scope

This document has been prepared to guide sponsors on the reporting of adverse events which may occur during clinical investigations and performance studies, to ensure that the Medical Device Regulation and the In vitro Diagnostic Medical Device Regulation requirements and expectations are fulfilled.

3. Definitions and Abbreviations

Adverse event
An adverse event is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation or performance study, whether or not related to the investigational device. [Regulation (EU) 2017/745 Article 2(57) and Regulation (EU) 2017/746 Article 2(60)]

Clinical Investigation
A clinical investigation is defined as any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device. [Regulation (EU) 2017/745 Article 2(45)]

Device Deficiency
A device deficiency is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer. [Regulation (EU) 2017/745 Article 2(59) and Regulation (EU) 2017/746 Article 2(62)]

Ethics Committee
Ethics committee means an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of the Medical Devices Regulation, taking into account the views of laypersons, in particular patients or patients' organisations. [Regulation (EU) 2017/745 Article 2(56) and Regulation (EU) 2017/746 Article 2(59)]

Ethics Committee/s in Malta
Health Ethics Committee; Research Ethics Committee.

In vitro diagnostic medical device
An in vitro diagnostic medical device means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

(a) concerning a physiological or pathological process or state;
(b) concerning congenital physical or mental impairments;
(c) concerning the predisposition to a medical condition or a disease;
(d) to determine the safety and compatibility with potential recipients;
(e) to predict treatment response or reactions;
(f) to define or monitoring therapeutic measures.

Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices. [Regulation (EU) 2017/746 Article 2(2)]

Incident
Incident means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect. For in-vitro diagnostics it includes harm as a consequence of a medical decision, action taken or not taken on the basis of information or result(s) provided by the device. [Regulation (EU) 2017/745 Article 2(64) and Regulation (EU) 2017/746 Article 2(67)]

Intended purpose
Intended purpose means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the clinical evaluation. [Regulation (EU) 2017/745 Article 2(12) and Regulation (EU) 2017/746 Article 2(12)]

Investigator
Investigator is an individual responsible for the conduct of a clinical investigation at a clinical investigation site. [Regulation (EU) 2017/745 Article 2(54) and Regulation (EU) 2017/746 Article 2(48)]

Legal Representative
Where the sponsor of a clinical investigation is not established in the Union, that sponsor shall ensure that a natural or legal person is established in the Union as its legal representative. Such legal representative shall be responsible for ensuring compliance with the sponsor's obligations pursuant to the MDR and shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication with that legal representative shall be deemed to be a communication with the sponsor. [Regulation (EU) 2017/745 Article 62(2) and Regulation (EU) 2017/746 Article 58(4)]

Medical Device

Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means. [Regulation (EU) 2017/745 Article 2(1)]

Performance Study

A performance study means a study undertaken to establish or confirm the analytical or clinical performance of a device. [Regulation (EU) 2017/746 Article 2(42)]

Serious adverse event

Serious adverse event means any adverse event that led to any of the following:
(a) death,
(b) serious deterioration in the health of the subject, that resulted in any of the following:
(i) life-threatening illness or injury,
(ii) permanent impairment of a body structure or a body function,
(iii) hospitalisation or prolongation of patient hospitalisation,
(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
(v) chronic disease,
(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect. [Regulation (EU) 2017/745 Article 2(58) and Regulation (EU) 2017/746 Article 2(61)]

Serious public health threat

A serious public health treat is an event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time. [Regulation (EU) 2017/745 Article 2(66) and Regulation (EU) 2017/746 Article 2(69)]

Sponsor

Sponsor means any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation or the performance study. [Regulation (EU) 2017/745 Article 2(49) and Regulation (EU) 2017/746 Article 2(57)]

IVDR: In vitro Diagnostic Medical Device Regulation

MDR: Medical Device Regulation

MDCG: ` Medical Device Coordination Group

PMPF: Post-market clinical follow-up

PMCF: Post-market performance follow-up

4.1 Reporting obligations of the sponsor

Any untoward medical occurrences or clinical signs, unintended disease or injury occurring during the clinical investigation or performance study shall be documented according to good clinical practice. It is the legal obligation of the sponsor to report serious adverse events and certain device deficiencies to all regulatory agencies where the clinical investigation or the performance study is authorised to start, in line with Article 80 of the MDR and Article 76 of the IVDR. The sponsor must also submit the report to the Ethics Committee/s in Malta.

The legal requirements are further outlined in the guidance published by the MDCG 2020-10/1 *Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745.* In the absence of IVDR specific guidance, sponsors of performance studies should take into account the principles of this guidance.

In accordance with the above-mentioned articles of the Regulations, the following adverse events must be reported:
a) any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible
b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate
c) any new findings in relation to any event referred to in points a) and b).

These reporting procedures outlined in Article 80 of the MDR and Article 76 of the IVDR also apply to serious adverse events occurring during PMPF investigations and PMCF studies of CE-marked devices and in-vitro diagnostics which are used within the intended purpose, if a causal relationship between the serious adverse event and the preceding investigational procedure has been established. Reporting of other incidents having other relationship categories (not related, possible and probable) shall follow the same vigilance reporting procedure as that of CE marked devices in normal use, which are laid down in Articles 87-91 of the MDR and Articles 82 to 86 of the IVDR.

4.2. Reporting timelines

The sponsor shall implement a system to ensure that the investigator will inform the sponsor about the adverse events immediately, and not later than **three calendar days** after the study personnel's awareness of the event.

New reportable serious adverse events, or new information related to already reported events, must be reported immediately by the sponsor to the Malta Medicines Authority and not later than **seven calendar days** after the sponsor is informed by the investigator.

For cases which are alarming as a potential serious public health threat and when multiple deaths occur at short intervals, the sponsor must report these events, or new information in relation with such, already reported events, **within two calendar days** after the sponsor's awareness.

4.3 Reporting form

Clinical investigations for medical devices

The reporting form template for Serious Adverse Events is provided in the Appendix: Clinical investigation summary safety report form of the guidance document MDCG 2020-10/1 *Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745.* Reference should be made to this guidance document for instructions on the completion requirements of the reporting form.

Performance studies for in vitro diagnostic medical devices

In the absence of IVDR specific guidance by MDCG, until a template is published, the reporting template in the Appendix: Clinical investigation summary safety report form of the guidance document MDCG 2020-10/1 *Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745* may be used. Reference should be made to this guidance document for instructions on the completion requirements of the reporting form.

For both clinical investigations and performance studies, reportable events must be updated, and the form is to be sent to all participating National Competent Authorities each time a new reportable event or a new finding to an already reported event is to be reported.

4.4. Contact details for further information

All filled in forms should be submitted by email to mdforms.medicinesauthority@gov.mt.

5. References

Malta Medicines Authority - Medical Devices
https://medicinesauthority.gov.mt/medicaldevices?l=1

Cap 458 Act no VII of 2020, An Act to amend the Medicines Act
https://legislation.mt/eli/act/2020/7/eng

S.L. 458.59 Medical Devices and In-Vitro Diagnostic Medical Devices Provision On The Maltese Market Regulations https://legislation.mt/eli/sl/458.59/eng

EU legislations- Medical Devices and In-Vitro Diagnostic Medical Devices
https://health.ec.europa.eu/medical-devices-sector/new-regulations_en

MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 Guidance - MDCG endorsed documents and other guidance (europa.eu)

MDCG 2020-10/2 Appendix – Clinical Investigation Summary Safety Reporting Form Guidance - MDCG endorsed documents and other guidance (europa.eu)

Signatures on file