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Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745

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MDCG 2020-10/1 Rev.1 changes	
Section 3	new definitions
Section 4, intro	clarification on filling in the reporting table
Section 5, table	updated
Section 5.1	clarification on reporting duties
Section 5.2.2	internal reference
Section 9.4	clarification
Section 10.2.1	coding
Sections 10.2.15-17	new
Section 10.2.19-20	clarification

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1 Introduction

Safety reporting in clinical investigations of medical devices shall be performed in line with the requirements of the Regulation (EU) 2017/745 – Medical Device Regulation (MDR) Article 80(2):

The sponsor shall report, without delay to all Member States in which the clinical investigation is being conducted, all of the following by means of the electronic system referred to in MDR Article 73:

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).

The period for reporting shall take account of the severity of the event. Where necessary to ensure timely reporting, the sponsor may submit an initial report that is incomplete followed up by a complete report.

Upon request by any Member State in which the clinical investigation is being conducted, the sponsor shall provide all information referred to in paragraph 1.

For post-market clinical follow up (PMCF) investigations of CE-marked devices[1] used within the intended use covered by the CE-marking, reporting requirements of MDR Article 80(5) and (6) apply. This means that the vigilance provisions laid down in Articles 87 to 90 and in the acts adopted pursuant to Article 91 shall apply for PMCF clinical investigations. However, this guidance document is still relevant for PMCF clinical investigations as the reporting of serious adverse events where a causal relationship to the preceding investigational procedure has been established shall follow the reporting procedures of clinical investigations as outlined in Article 80.

1.1 Safety reporting in the absence of Eudamed

Since the electronic system referred to in Article 73 (Eudamed) will not be available and fully functional at the Date of application of the MDR this guidance outlines the procedures for safety reporting in clinical investigations in the absence of Eudamed.

This document defines Serious Adverse Event (SAE) reporting modalities and includes a summary tabulation reporting format.

[1] The PMCF investigations referred to in MDR Article 74(1).

2 Scope

2.1 Clinical investigations of medical devices

The reporting modalities and format set out in this guidance apply to:

- **Pre-market clinical investigations** covered by Articles 62 and 74(2) of the MDR conducted with:
  a) Non-CE marked devices,
  b) CE marked devices used outside the intended use(s) covered by the CE-marking.
  c) The term pre-market clinical investigation may also include some studies covered by MDR Article 82.

  As MDR Article 82 allows member states to define national requirements for such clinical investigations, sponsors are encouraged to check with the applicable NCA[2] whether this guidance or other reporting procedures should be applied.
  In situations where a clinical investigation has started using a non-CE marked device, and the right to bear the CE marking has been obtained before the end of the clinical investigation, the SAE reporting continues until completion of the investigation, according to the clinical investigation plan and these guidelines apply throughout the SAE reporting period.

  For pre-market clinical investigations involving CE marked comparator devices used within their intended purpose, SAEs occurring in or to subjects that are in the comparator arm of an investigation shall also be reported in accordance with these guidelines.

  Note: SAEs concerning CE marked devices which meet the vigilance reporting criteria also need to be handled under the post-market surveillance/vigilance system.

- Those **Post-Market Clinical Follow Up (PMCF) investigations** that involve procedures additional to those performed under the normal conditions of use of the device, and where those additional procedures imposed by the clinical investigation plan are invasive or burdensome, covered by MDR Article 74(1). For these clinical investigations the safety reporting for events pertaining to MDR Article 80(6) follow the Serious Adverse Event reporting process only, and are outlined in this guidance. Events pertaining to MDR Article 80(5) are reported following the vigilance process only and are outside the scope of this guidance.

- Note that other post-market clinical investigations may be subject to safety reporting requirements in line with this guidance due to national requirements following MDR Article 82, but there is no such general requirement. Sponsors are encouraged to check with the applicable NCA whether this guidance or other reporting procedures should be applied.

- Due to the transitional provisions in MDR Article 120(11) this guidance also covers clinical investigations which have started to be conducted in accordance with Article 10 of Directive 90/385/EEC (AIMDD) or Article 15 of Directive 93/42/EEC (MDD) prior to 26 May 2021. These investigations may continue to be conducted after date of application of the MDR, but the reporting of serious adverse events and device deficiencies shall be carried out in accordance with the MDR requirements from 26 May 2021 and onwards.

2.2 Medical devices used in clinical trials of medicinal products (drug trials)

- A CE-marked device which is used outside its intended purpose, or a non-CE marked device in a clinical drug trial would implicitly have to be assessed for safety and performance and the study shall follow both MDR (Chapter VI) and the applicable legislation for clinical drug trials. This guidance document is then relevant for compliance with the MDR regarding safety reporting.

[2] For the purpose of this guidance," NCAs" encompasses the National Competent Authorities of the EEA, Switzerland and Turkey.

- If a drug-device study (or a drug trial) is not undertaken to assess the safety or performance of a device used in the study, the reporting requirements of MDR Article 80 do not apply, as long as the device is CE marked and used within its intended purpose. This guidance is not applicable, but the vigilance reporting provisions of MDR apply in those situations, as for any commercially available device. Sponsors should make sure that the device manufacturer is notified about any incidents related to the device and the legal manufacturer of the device is responsible for the subsequent vigilance reporting.

3 Definitions

3.1 Investigational device

A device that is assessed in a clinical investigation
(MDR Article 2(46))

Note: An investigational device can be a non-CE marked device or a CE marked device. The definition in MDR Article 2(46) does not differentiate between different regulatory statuses of devices. However, the reporting requirements are different depending on whether the clinical investigation is done for purposes described in Article 62, 74 or 82. The definition is understood to cover also the devices investigated in PMCF investigations, even if they are not subject to notification per Art 74.1.

3.2 Adverse Event (AE)

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, whether or not related to the investigational device.
(MDR Article 2(57))

Note:

a. This definition includes events that are anticipated as well as unanticipated events
b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures[3] involved.

3.3 Adverse device effect (ADE)

Any adverse event related to the use of an investigational medical device or a comparator.

3.4 Anticipated serious adverse device effect (ASADE)

Any serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the last risk assessment document upon serious adverse device effect occurred.

3.5 Device deficiency (DD)

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.
(MDR Article 2(59))

3.6 Incident

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.
(MDR Article 2(64))

[3] For the purpose of safety reporting all activities related to the use of a medical device may be considered procedures

3.7 New Finding

New information discovered as the result of an inquiry/investigation/test based on the occurrence of the event. Follow-up from the event.

3.8 Serious Adverse Event (SAE)

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

(MDR Article 2(58))

3.9 Serious adverse device effect (SADE)

Any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

3.10 Serious incident

Any incident that directly or indirectly led, might have led or might lead to any of the following:

a) the death of a patient, user or other person,
b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health,
c) a serious public health threat.

(MDR Article 2(65))

3.11 Unanticipated serious adverse device effect (USADE)

Any serious adverse device effect, the nature, severity or outcome of which is not consistent with the reference safety information.

4 Reporting method

A new template for the Summary Reporting Form should be used for all studies from 26 May 2021. The tabular format featured in the Appendix needs to be filled in/updated for each reportable event or for new findings/updates to already reported events. It shall be transmitted to all NCAs where the clinical investigation is being performed. For a new finding or update, the line of the SAE needs to be updated and the first column set to “m”. Write the new findings in the free description of event column and highlight the additions. When applicable, update the others columns as well.

For more details on how to complete the form refer to section *10. Reporting form*.

4.1 Transition to reporting via Eudamed

Once Eudamed is available and fully functional the obligations and requirements that relate to performing safety reporting via Eudamed shall apply from the date corresponding to six months after the date of publication of the notice referred to in Article 34(3) of the MDR.

4.1.1 Ongoing events at time of transition to Eudamed

It is acknowledged that at the time of transition to reporting via Eudamed, there will be ongoing events for which initial reports have been made according to the procedures described in this document. For these reportable events follow-up and final reports will be submitted to the NCAs by the same procedure, but all new reportable events shall be entered in Eudamed.

Whether retrospective uploading of previous event reports to Eudamed will be possible is not clear at the time this guidance is issued.

4.2 Overview of formats to be used by sponsors when reporting to NCAs

Under directives legislation	
Until May 25th, 2021:	The tabular format from MEDDEV 2.7/3 Appendix I should be used
Transition period	
From May 26th, 2021 and until Eudamed is available	The Tabular format of this guidance (Appendix- Summary Reporting Form) should be used.
When Eudamed is available but not yet mandatory and until the timepoint when Eudamed becomes mandatory	Either the Tabular format of this guidance (Appendix- Summary Reporting Form) or the Eudamed web form can be used. Note: Once the shift to Eudamed reporting has been made for a specific clinical investigation, Eudamed should continue to be used for reporting all new events and updates to those events throughout the remainder of the clinical investigation.
From the timepoint when Eudamed is mandatory*	
*From the date corresponding to six months after the date of publication of the notice referred to in Article 34(3) of the MDR.	Web form via Eudamed shall be used for all new events, and updates to those events.
	The Tabular format of this guidance (Appendix- Summary Reporting Form) can be used only to transmit follow-up reports/final reports to the NCAs on events which were initially reported in this format.

4.3 Collecting reports from investigators

The format in which sponsors wish to receive single event reports from investigators will be up to the sponsor to design and they may be adapted to an individual clinical investigation. When sponsors design such reporting forms, they should consult this guidance document to ensure all relevant details are captured in the reports from the investigator, so that the sponsors can fulfil their reporting obligations.

5 Reportable events

For the purpose of this guidance and based on the definitions above, the following events are considered reportable events in accordance with MDR Art. 80(2):

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).

Serious adverse events related to a CE marked device which is part of the investigation procedure (for example a CE-marked implanting tool used in combination with a non-CE marked investigational device) are reportable per MDR Article 80(2) if there is a causal, (or reasonably possible) relationship to the device, the comparator or the investigation procedure. The reporting procedures described in this guide should then be followed in addition to the normal vigilance reporting procedures for CE marked devices.

All causality assessments should be made using the guidance in section 9. Only causality level 1 (i.e. “not related”) is excluded from reporting. If either the sponsor or the investigator has assigned a higher causality level than "not related", the event should be reported.

Type of Clinical Investigation	**Applicable legislation**	**MDR regulation**
Clinical investigation may be used for conformity procedure for investigational device cf. article 62	MDR	MDR art. 80 §2-3
PMCF investigation with additional burdensome and/or invasive procedures	MDR	• MDR art. 80 §5 => MDR chapter VII **AND** • MDR art. 80 §6 Notwithstanding §5, this Article shall apply where a “**causal relationship”** (per section 9 of this guide) between the serious adverse event and the **preceding investigational procedure** has been established. For more information see 5.1 Exceptions for PMCF investigations according to MDR Article 74.1
PMCF investigation without additional burdensome and/or invasive procedures	MDR	MDR chapter VII
Other clinical investigation cf. article 82 or other national legislation	National legislation	No provisions in MDR. Safety reporting may be regulated in national legislations in the country where the investigation is conducted.

5.1 Exceptions for PMCF investigations falling under MDR Article 74.1

Following Article 74.1 the SAE reporting for these PMCF clinical investigations is governed by Articles 80(5) and 80(6). Thus the provisions of vigilance laid down in Articles 87-90 and acts adopted pursuant to Article 91 shall apply. However, the SAEs where a causal relationship between the serious adverse event and the preceding investigational procedure has been established shall follow the reporting procedures of clinical investigations as outlined in Article 80.

This means that:

- **For the purpose of this guidance** (safety reporting in clinical investigations) reportable events in PMCF clinical investigations are those serious adverse events where a causal relationship between the serious adverse event and a preceding investigational procedure has been established. The other relationship categories i.e. not related, possible and probable do not need to be reported **in the context of the clinical investigation** under Article 80.
- **In the context of vigilance**, articles 87-90 need to be taken into account and this concerns the Serious Incidents where a relationship between the incident and the device or a procedure stated in the IFU is at least reasonably possible. Also not related, possible and probable events need to be reported in the context of vigilance (Art. 87-90).

It is thus possible that events occurring in such clinical investigations need to be reported to both the competent authorities in charge of SAE in clinical investigations AND to the competent authorities in charge of vigilance, as outlined above, including a relationship to a procedure stated in the IFU.

"Preceding investigational procedure" shall be understood as a procedure which is imposed by the Clinical Investigation Plan and which has taken place before (or coincided in time) with the serious adverse event. This includes both the investigational device application procedure and any additional burdensome or invasive procedure(s) which defines whether the study is subject to notification requirements following MDR article 74(1).

5.2 Reportable events occurring in other Member States / Third Countries

5.2.1 Reportable events occurring in other MS

The sponsor shall report the reportable SAEs per clinical investigation (CI). If several CIs are conducted with the same device, only those SAEs that happen in CIs that have the same clinical investigation plan (CIP) code should be reported for those CIs, and only to those MS where a CI with that specific CIP code is being conducted.

It is acknowledged that the same CI can be conducted under different versions of the same clinical investigation plan (same CIP code) in different Member States, e.g. with country specific adaptations, and in those cases the SAE reporting can normally be combined for all the versions of the CIP for the same clinical investigation.

5.2.2 Reportable events occurring in Third Countries

Reportable events occurring in Third Countries[4] in which a clinical investigation is performed under the same clinical investigation plan (see 5.2.1 Reportable events occurring in other MS for what is meant with same CIP) have to be reported in accordance with this guidance to the NCA(s) of the European countries in which the clinical investigation is being conducted.

- The NCA shall start receiving the reportable events occurring in Third Countries as soon as the clinical investigation is authorised to start in that Member State.
- Events occurring in Third Countries after the participating European sites have closed shall continue to be reported.

5.3 Transition period for reportable events in pre-market clinical investigations initiated under directives legislation

It is acknowledged that the MDR implies changes to the reporting requirements compared to the directives' requirements where all SAEs should be reported regardless of relatedness. Under MDR sponsors are no longer obliged to report SAEs that are "not related" to the clinical investigation procedures or the investigational device. At the date of application for MDR there will be ongoing events for clinical investigations initiated under directives legislation. As from the 26th of May 2021 sponsors are no longer expected to submit follow-up reports to NCAs for events that have been deemed "not related" (see section 9 of this document for guidance on causality assessment). For ongoing events that have a causality assessment other than "not related" follow up reports will still have to be provided.

To facilitate the transition and give time for sponsors to update Clinical Investigation Plans and study procedures in clinical investigations a sponsor may continue to report all SAEs to NCAs until Eudamed reporting is mandatory (see section 4.1 Transition to reporting via Eudamed). This applies only to studies which have started to be conducted[5] in accordance with Article 10 of Directive 90/385/EEC or Article 15 of Directive 93/42/EEC prior to 26 May 2021.

5.4 Transition for reportable events in PMCF clinical investigations initiated under directives legislation

In case of PMCF studies which required SAE reporting according to the Pre-MDR national legislations, MDR article 80 (5) and 80(6) shall apply from May 26th, 2021.

[4] Countries other than Switzerland, Turkey and those belonging to the EEA.

[5] For the purpose of safety reporting this is defined as "Authorised to start in the individual Member State in line with applicable directives legislation, regardless of whether any subjects have been recruited in the Member State or not."

6 Report by whom

Reportable events have to be reported by the sponsor of the clinical investigation, which could be the manufacturer, the legal representative or another person[6] or entity.

7 Report to whom

Reportable events must be reported at the same time to all NCAs where the clinical investigation has commenced using the summary tabulation featured in the Appendix.

A list of clinical investigation contact points within the NCAs is published at the Commission's homepage.

For the purpose of this guidance, an investigation is considered to have commenced in an individual Member State:

- For investigations under the directives: When the sponsor is authorized to start the investigation in accordance with the notification procedures in that Member State.
- For investigations started under the MDR: When the sponsor is authorized to start the investigation in that Member State in accordance with the provisions laid out in the MDR.

Member States may also require separate reporting to the Ethics Committee(s).

8 Reporting timelines

8.1 Report by sponsor to NCAs.

The sponsor must report to all NCAs where the clinical investigation is authorised to start:

- For all reportable events as described in section 5 which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: **Immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.**
  This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals.
  These concerns may be identified by either the NCA or the manufacturer.

- Any other reportable events as described in section 5 or a new finding/update to it: **Immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.**

In some cases, a different periodicity or different modalities may be agreed between the participating NCAs and the sponsor according to the investigation's design and to the pathology under clinical investigation. This would allow implementation of adequate provision for clinical investigations in which SAE frequency is expected to be high due to the natural progression of the disease (e.g. palliative oncology).

[6] Contact person established by the sponsor in line with Article 62(2) if accepted by Member State.

8.2 Report by the investigator to the sponsor

The sponsor shall implement and maintain a system to ensure that the reporting of the reportable events as defined under chapter 5 will be provided by the investigator to the sponsor immediately, but not later than 3 calendar days after investigation site study personnel's awareness of the event.

9 Causality assessment

The relationship between the use of the medical device[7] (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.

During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Investigation Plan or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there[8]. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

The above considerations apply also to the serious adverse events occurring in the comparison group.

For the purpose of harmonizing reports, each SAE will be classified according to four different levels of causality:

1. Not related
2. Possible
3. Probable
4. Causal relationship

The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational device, the comparator or the investigation procedure.

1. Not related: Relationship to the device, comparator or procedures can be excluded when:
   - the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
   - the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
   - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
   - the event involves a body-site or an organ that cannot be affected by the device or procedure;
   - the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
   - the event does not depend on a false result given by the investigational device used for diagnosis[9], when applicable;

   In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

[7] Intended as both investigational device and comparator.
[8] For a comparator device, the Operator's Manual could be a relevant document.
[9] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer) or might not be diagnosed with the correct disease or condition.

2. Possible: The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

3. Probable: The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship: the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
   - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has a temporal relationship with investigational device use/application or procedures;
   - the event involves a body-site or organ that
     - the investigational device or procedures are applied to;
     - the investigational device or procedures have an effect on;
   - the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
   - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
   - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
   - harm to the subject is due to error in use;
   - the event depends on a false result given by the investigational device used for diagnosis[10], when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

The relationship between a serious adverse event and the procedure or the device, needs to be assessed separately. This does however not mean that they are mutually exclusive, a serious adverse event can be related to both the procedure and the device, or it can be related only to the procedure or only to the device. When it is unclear whether an event is related to the device or to the procedure, the investigator should:

- set the Relationship to device to possible (or higher)

AND

- set the Relationship to procedure to possible (or higher)

[10] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

Since it is the healthcare provider who performs the procedures and manages/handles the medical device(s), the causality assessment of this healthcare provider should prevail.

In some particular cases the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator assessment is not available and/or the sponsor remains uncertain about classifying the serious adverse event, the sponsor should not exclude the relatedness; the event should be classified as “possible” and the reporting not be delayed.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse events. The occurrence of unanticipated events related could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

10 Reporting form

The reporting form template for the summary SAE tabulation is given in the Appendix of this document.

The reporting form is study specific and covers only a given clinical investigation, defined by a distinct clinical investigation plan. English is the recommended language for the reporting form. The report form can be modified in any applicable software (not only Microsoft Excel) but the file needs to be compatible with Microsoft Excel when sent to the participating NCAs.

The template form contains inserted filters and functionality to facilitate use of preferred terminology in the reporting. These are important for the analysis and should be maintained.

Sponsors who generate the excel report file by automated processes may implement other technical features in their systems for excel file generation to ensure the preferred terms listed in metadata are used.

The table gives a cumulative overview of the reportable events per clinical investigation and will be updated and transmitted to participating NCAs each time a new reportable event or a new finding to an already reported event is to be reported. More detailed information has to be provided on request of an NCA, if so requested by using the individual study specific reporting form (see further section *4.3 Collecting reports from investigators*).

10.1 Completion guidelines: Form header

10.1.1 EUDAMED/CIV-ID

The union-wide Single Identification Number mentioned in MDR Article 70(1) will not be possible to generate until Eudamed for MDR is fully functional. For the transition period, clinical investigations will get tracking numbers (CIV-ID) upon registration in the Eudamed2 database which is performed by the NCA upon receipt of an application. This CIV ID is provided to the sponsor during the NCA’s handling of the initial application for the clinical investigation and should be entered on the safety reporting form.

The CIV ID should already be available for a clinical investigation started under the directives’ legislation, where it should be indicated on the MEDDEV 2.7/3 reporting form etc. Sponsors who are not aware of the CIV ID of their clinical investigations are invited to contact the concerned NCA to get this information.

10.1.2 Title of Clinical Investigation

The identifying title of the Clinical Investigation. The title indicated here should be consistent with other title entries (such as in clinical investigation application form, clinical investigation plan cover page etc).

10.1.3 CIP number/code

The unique identification code or short name assigned to the specific clinical investigation plan by the Sponsor (numeric, alphanumeric or acronym) should be indicated.

10.1.4 Contact person

Name, address, e-mail and telephone number should be provided for the person who is sponsor's point of contact in case NCA have follow up questions regarding submitted safety report forms.

10.1.5 MS+NCA Reference numbers

For each participating Member State indicate the country code[11] and the NCA's national reference number for the clinical investigation.

Example:
SE 5.1-20YY-XXXXXX
DK 20YYXXXXXX

10.1.6 No. of subjects enrolled to date total

Indicate the total number of subjects who have been enrolled (per date of report) in the clinical investigation globally.

10.1.7 No. of subjects enrolled to date per country

List all countries where the clinical investigation has been authorised by date of report and indicate the number of subjects who have been enrolled in the clinical investigation (per date of report) in each country.

10.1.8 Device type

Indicate the type of device(s) assessed in the clinical investigation (e.g. pacemaker, coronary stent, hip implant).

10.1.9 Reference Member State

Indicate the name of the Member State which drew the unique EUDAMED/CIV ID (normally the first Member State receiving an application for the clinical investigation). Once the coordinated assessment procedure (per MDR Article 78) is up and running, the coordinating Member State should be indicated here.

10.1.10 No. of investigational devices used to date total

Indicate the total number of investigational devices which have been used (per date of report) in the clinical investigation globally.

10.1.11 No. of investigational devices used to date per country

List all countries where the clinical investigation has been authorised by date of report and indicate the number of investigational devices which have been used in the clinical investigation (per date of report) in each country.

10.1.12 Date of report

Indicate the date when the report is compiled for transmission to NCAs. Format DD/MM/YYYY.

10.2 Completion guidelines: Event details

Each unique reportable event is presented in a separate line. Updates to a previously reported event should be made by changing the information in the same line, and clearly identified according to the principles described below.

Any new information added in the form should be highlighted in bold and/or colour. This includes any new lines added and any changes made to the information in an already existing line.

[11] Use ISO-3166-1 alpha-2 codes, i.e.two-letter country codes as defined in ISO 3166-1

In the initial report, in any given line, no fields shall be left intentionally blank. To meet this requirement, preliminary information should be filled in, despite the need of further updating.

10.2.1 Status

The sponsor shall identify the new/updated information in the status column as:

A = added = new reportable event;

D = deleted = already reported event that has been deleted due to downgrading to non-serious, due to integration in another event, or … Add the reason for deletion in the corresponding cell in column “Description of event”.

M = modified = new finding/update to an already reported event;

U = unchanged.

Do not add other options.

10.2.2 Date Sponsor received report of SAE/DD

Indicate the date when the sponsor was first notified by the investigation site about the event. This date is checked for compliance with reporting timelines as outlined in section *8 Reporting timelines*.

Format DD/MM/YYYY.

10.2.3 Country code

Indicate the country code[11] for the country in which the subject associated with the event has been enrolled.

10.2.4 Investigation site

Name identifying institution or site where the clinical investigation is carried out.

10.2.5 Subject ID code

The study specific subject ID code, i.e. the link between study data and the actual subject identity (which is not to be provided in this form).

10.2.6 SAE ID code

The investigator, sponsor or manufacturer should assign a unique ID to each SAE that has occurred, This number shall remain unchanged throughout all other alterations of the particular SAE-reporting due to ongoing assessment.

10.2.7 Date of procedure/First use

Indicate the date of the relevant procedure or the date when the subject was exposed to the device for first use. Format DD/MM/YYYY.

10.2.8 Date of event onset

The date when the first signs of an event were noticed may be different (earlier) than the date when the event fulfilled the seriousness criteria (see further the definition in section 3.3 Serious Adverse Event (SAE)). The date when the event became an SAE should be reported as Date of event onset. In case of Device Deficiencies which did not lead to an SAE, the date the DD was discovered should be indicated.

Format DD/MM/YYYY.

10.2.9 SAE or DD

Choose one option from SAE(Serious Adverse Event) or DD (Device Deficiency).

Do not add other options.

10.2.10 Age

The subject's age at date of event onset should be indicated.

In cases where exact date of birth is not available as a basis for age calculation, it is acknowledged that an approximate age at date of event onset could be calculated based on the age at enrollment.

Normally the Age should be indicated in Years, although for paediatric/neonatal populations it may be more relevant to indicated age in months, weeks or days. When a different unit than years is used, the unit should be indicated as appropriate.

10.2.11 Patient gender

Choose one option from the following list (do not add other options):

- Female
- Male
- Other
- Unknown

10.2.12 Location of device

For this field, it is the location of the device at the time the report is submitted to NCA is of interest (i.e not at the time of investigator or sponsor awareness of the event). Changed location of the device is in itself not a reason to provide an updated report. However, whenever an update/final report is provided for other reasons, it is relevant to update this field if the device for example has reached the sponsor by then.

Choose one option from the following list (do not add other options):

- Investigational/study site
- Sponsor
- Subject
- Manufacturer
- Remains implanted
- Discarded
- Unknown
- Other

10.2.13 Classification of event

Choose one option from the following list of consequence characteristics (do not add other options):

- Death
- Life-threatening illness or injury
- Permanent impairment/ Chronic disease
- Hospitalization
- Medical or surgical intervention
- Foetal distress, fœtal death or congenital physical or mental or birth defect
- Not applicable (Note that this option is only to be selected in case of reportable Device deficiencies that did not lead to an SAE)

It is acknowledged that for a specific event two or more options may be equally applicable, e.g." Hospitalization" and "medical intervention". The highest-ranking classification should be indicated, using the following ranking order: 1) Death, 2) life threatening, 3) foetal distress, 4) permanent impairment, 5) Medical or surgical intervention 6) hospitalization.

10.2.14 Free description of event

Provide a description of the event in free text. Below is a non-exhaustive list of items that could be relevant to cover:

- Nature of the observed symptoms
- Duration and severity of the symptoms
- Date of onset of first signs of the event (before it became a SAE)
- Medical background of the patient
- Medical care of the patient
- Comments on the event in relation to already known safety data

Use of standardised terminology corresponding to relevant IMDRF codesis encouraged.

10.2.15 Device issue (if applicable)

In the worksheet "Device issue", the IMDRF codes applicable to device issues can be found. You can use this worksheet to look up the appropriate codes. Please report all the appropriate codes applicable for the SAE or DD reported. Please separate each code by ";".

10.2.16 Clinical signs/symptoms

In the worksheet "Device issue", the IMDRF codes applicable to clinical signs/symptoms can be found. You can use this worksheet to look up the appropriate codes. Please report all the appropriate codes applicable for the SAE or DD reported. Please separate each code by ";".

10.2.17 Clinical impact

In the worksheet "Device issue", the IMDRF codes applicable to clinical impact of the SAE or DD can be found. You can use this worksheet to look up the appropriate codes. Please report all the appropriate codes applicable for the SAE or DD reported. Please separate each code by ";".

10.2.18 Action/treatment /outcome

Provide information in free text on actions taken, treatment(s) administered and the outcome.

10.2.19 Relationship to procedure

Choose one option from the following list of causality levels (for explanatory texts see section 9 Causality assessment) (do not add other options):

- Not related
- Possible
- Probable
- Causal

Please report the assessments by sponsor and investigator in the respective columns.

10.2.20 Relationship to device

Choose one option from the following list of causality levels (for explanatory texts see section 9 Causality assessment) (do not add other options):

- Not related
- Possible
- Probable
- Causal

Please report the assessments by sponsor and investigator in the respective columns.

10.2.21 Unanticipated SADE

Choose option Yes or No

An Unanticipated Serious Adverse Device Effect[12] is an effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. Procedures associated with the use of a device should be addressed in the risk assessment, which makes it possible to determine whether the procedure related SAEs are Unanticipated Serious Adverse Device Effect or not. SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device should not be considered Serious Adverse Device Effects.

10.2.22 Investigation arm

Choose one option from the following list:

- Test group
- Comparison group
- Blinded
- Not applicable

Note: For some study designs it might be more relevant to add name of device; i.e. in a clinical investigation with several test groups it might be useful to differentiate which investigational device that the subject has been exposed to.

10.2.23 Event status

Choose one option from the following list (do not add other options):

- Resolved
- Resolved with Sequelae
- Ongoing
- Death

10.2.24 Date of event resolution

Add date in format DD/MM/YYYY. If event status is “Ongoing” enter Not Applicable.

11 References

1. Regulation (EU) 2017/745 of the European Parliament and of the council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.
2. Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices, last amended by Directive 2007/47/EC.
3. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, last amended by Directive 2007/47/EC.
4. Codes for the representation of names of countries and their subdivisions – Part 1: Country codes (ISO 3166-1) published by International Organisation for Standardization (ISO).

12 **Appendix** – Clinical Investigation Summary Safety Reporting Form

[12] An adverse device effect is an adverse event related to the use of an investigational device. A serious adverse device effect is an adverse device effect that has resulted in any of the consequence characteristics of a serious adverse event.