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Safety reporting in performance studies of *in vitro* diagnostic medical devices under Regulation (EU) 2017/746

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1 Introduction

Safety reporting in performance studies of *in vitro* diagnostic medical devices (IVDs) shall be performed in line with the requirements of Article 76(2) of Regulation (EU) 2017/746 – *In Vitro* Diagnostic Medical Device Regulation (IVDR):

The sponsor shall report without delay to all Member States in which a performance study is being conducted all of the following by means of the electronic system referred to in IVDR Article 69:

a) any serious adverse event that has a causal relationship with the device, the comparator or the study 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 performance study is being conducted, the sponsor shall provide all information referred to in paragraph 1 of IVDR Article 76(1).

For post-market performance follow-up (PMPF) studies of CE marked devices[1] used within the intended purpose covered by the CE marking, reporting requirements of IVDR Articles 76(5-6) apply. This means that the vigilance provisions laid down in IVDR Articles 82 to 85 and in the acts adopted pursuant to IVDR Article 86 apply to PMPF studies. However, this guidance document is still relevant for PMPF studies as the reporting of serious adverse events (SAEs) where a causal relationship to the preceding PMPF study has been established follow the reporting procedures of performance studies as outlined in IVDR Article 76.

Since the electronic system referred to in IVDR Article 69 (Eudamed and its module for clinical investigations and performance studies) is not yet available and fully functional from the date of application of the IVDR, this guidance outlines the procedures for safety reporting in performance studies in the absence of the Eudamed module or when Eudamed is not yet fully functional (see also sections 5.1 and 5.2 in this guidance).

This document defines SAE reporting modalities and includes a summary tabulation reporting format.

[1] The PMPF studies referred to in IVDR Article 70(1).

2 Scope

2.1 Performance studies of *in vitro* diagnostic medical devices

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

- Performance studies covered by IVDR Article 58(1):
  - in which surgically invasive sample-taking is done only for the purpose of the performance study;
  - that is an interventional clinical performance study as defined in IVDR Article 2(46);
  - where the conduct of the study involves additional invasive procedures or other risks for the subjects of the studies;
- performance studies covered by IVDR Article 58(2) involving companion diagnostics (except when only using left-over samples);
- PMPF studies covered by IVDR Article 70(1) that involve procedures additional to those performed under the normal conditions of use of the IVD and where those additional procedures are invasive or burdensome, in case a causal relationship between a SAE and the preceding performance study has been established;
- performance studies covered by IVDR Article 70(2) that are conducted to assess, outside the scope of its intended purpose, an IVD that already bears the CE marking.[2]
- combined studies of medicinal products and IVDs. When the study satisfies the definition of a performance study of an IVD, regardless of whether it is conducted in the context of a clinical trial of a medicinal product, the requirements of the IVDR and including its safety reporting obligations apply to the study. This guidance document is then relevant for compliance with the IVDR regarding safety reporting. MDCG 2022-10 provides further guidance on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and the IVDR.

3 Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
CDx	Companion diagnostic

[2] The performance study sponsor is responsible for reporting per IVDR Article 76. However, the device manufacturer remains responsible for postmarket surveillance and vigilance obligations for the CE Mark device per IVDR Articles 82-83.

DD	Device deficiency
IVD	*In Vitro* diagnostic medical device
IVDR	Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices
MDR	Regulation (EU) 2017/745 on medical devices
MS	Member State
NCA	national competent authority
PS	Performance study
PSP	Performance study plan
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
USADE	Unanticipated serious adverse device effect

4 Definitions

4.1 Adverse Device Effect (ADE)

Any adverse event related to the use of a device for performance study or a comparator[3]. See ISO 20916 section 3.1.

4.2 Adverse Event (AE)

Any untoward medical occurrence, inappropriate patient management decision, 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 performance study, whether or not related to the device for performance study. See IVDR Article 2(60).

4.3 Anticipated Serious Adverse Device Effect (ASADE)

Any serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk assessment. See ISO 20916 section 3.5.

4.4 Companion diagnostic (CDx)

A device which is essential for the safe and effective use of a corresponding medicinal product to:

(a) identify, before and/or during treatment, subjects who are most likely to benefit from the corresponding medicinal product; or

[3] A comparator might be: other CE-marked IVD, reference method, gold standard,…

(b) identify, before and/or during treatment, subjects likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product.

See IVDR Article 2(7).

4.5 Device for performance study

A device intended by the manufacturer to be used in a performance study. A device intended to be used for research purposes, without any medical objective, shall not be deemed to be a device for performance study. See IVDR Article 2(45).

4.6 Device deficiency (DD)

Any inadequacy in the identity, quality, durability, reliability, usability, safety or performance of a device for performance study, including malfunction, use errors or inadequacy in information supplied by the manufacturer. See IVDR Article 2(62).

4.7 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 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. See IVDR Article 2(67).

4.8 In-house IVD

An IVD manufactured and used within the same health institution as outlined in IVDR Article 5(5). Health institution is defined in IVDR Article 2(29).

4.9 Interventional clinical performance study

A clinical performance study where the test results may influence patient management decisions and/or may be used to guide treatment. See IVDR Article 2(46).

4.10 Investigator

An individual responsible for the conduct of a performance study at a performance study site. See IVDR Article 2(48).

4.11 Left-over sample

Unadulterated remainder of human derived samples collected as part of routine clinical practice and after all standard analysis has been performed. Such specimens/samples would be otherwise discarded as there is no remaining clinical need for them. This can include specimens collected for research or other purposes not connected to the clinical performance study in question. Left-over samples include “specimen or sample that are collected in the past and obtained from repositories (e.g. tissue banks, commercial vendor collections). See ISO 20916 section 3.25.

4.12 Malfunction

Any failure of an device for performance study to perform in accordance with its intended use when used in accordance with the instructions for use or performance study plan. See ISO 20916 section 3.27.

4.13 Manufacturer

A natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trade mark. See IVDR Article 2(23).

4.14 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. See MDCG 2020-10/1.

4.15 Performance study (PS)

A study undertaken to establish or confirm the analytical or clinical performance of a device. See IVDR Article 2(42).

4.16 Performance study plan (PSP)

A document that describes the rationale, objectives, design methodology, monitoring, statistical considerations, organisation and conduct of a PS. See IVDR Article 2(43).

4.17 Serious Adverse Device Effect (SADE)

Any ADE that has resulted in any of the consequences characteristic of a serious adverse event. See ISO 20916 section 3.43.

4.18 Serious Adverse Event (SAE)

Any AE that led to any of the following:

a) a patient management decision resulting in death or an imminent life-threatening situation for the individual being tested, or in the death of the individual's offspring,
b) death,
c) serious deterioration in the health of the individual being tested or the recipient of tested donations or materials, 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 subject 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,
d) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

See IVDR Article 2(61).

4.19 Specimen

Any discrete portion of a body fluid or tissue taken for examination, study, or analysis of one or more quantities or characteristics to determine the character of the whole body fluid or tissue. See ISO 20916 section 3.47.

4.20 Sponsor

Any individual, company, institution or organisation which takes responsibility for the initiation, for the management and setting up of the financing of the PS. See IVDR Article 2(57).

4.21 Study procedure

Any procedure foreseen in the PS (e.g. specimen collection) with the aim of investigating the device.

4.22 Subject

An individual who participates in a PS and whose specimen(s) undergo *in vitro* examination by a device for PS and/or by a device used for control purposes. See IVDR Article 2(47).

4.23 Unanticipated serious adverse device effect (USADE)

Any SADE, the nature, severity or outcome of which is not consistent with the reference safety information. See ISO 20916 section 3.52.

5 Reporting method

The template of the Summary Reporting Form[4] in the appendix should be used for all studies from 26 May 2022. The tabular form 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 national competent authorities (NCAs) where the PS 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, see section *11. Reporting form*.

5.1 Reportable events in pre-market PS initiated under directives legislation

Any SAE or DD that may (have) lead to a SAE occurring in a PS after 26 May 2022, regardless of when the PS started, should be reported in accordance with Article 76 of the IVDR.[5]

5.2 Transition to reporting via Eudamed

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

[4] National provisions can apply
[5] National requirements may apply to PS that commenced under the IVDD.

5.2.1 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.

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

From 26 May 2022 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 PS, Eudamed should continue to be used for reporting all new events and updates to those events throughout the remainder of the study.
When Eudamed is mandatory, i.e. from the date corresponding to six months after the date of publication of the notice referred to in MDR Article 34(3).	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.

5.4 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 PS. 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.

6 Reportable events

For the purpose of this guidance and based on the definitions above, the following events are considered reportable events in accordance with IVDR Article 76(2):

a) any SAE that has a causal relationship with the device[6], the comparator[7] or the study procedure or where such causal relationship is reasonably possible;

[6] Device= device for performance study.
[7] A comparator might be: other CE-marked IVD, reference method, gold standard,…

b) any DD that might have led to a SAE 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).

From the definition above, it also follows that SAEs related to a CE marked IVD which is part of a PS with an IVD for PS (for example a CE marked comparator IVD or a CE marked IVD that is used during the study procedure) are reportable if there is a causal (or reasonably possible) relationship to that IVD. The reporting procedures described in this guide should then be followed by the PS sponsor, in addition to the normal vigilance reporting for CE marked devices by the manufacturer (double reporting is certainly possible).

All causality assessments should be made using section 10 of this guidance. 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.

As not all safety provisions in the IVDR are applicable to all types of IVD PS, the following table depicts the safety provisions laid out in the IVDR that are applicable per type of IVD PS.

Type of PS	**IVDR safety reporting provisions**
PS referred to in IVDR Article 58(1-2): Any PS or any combined IVD study (a clinical study of a medicinal product, medical device, in which an IVD is also studied): a. in which surgically invasive sample-taking is done only for the purpose of the PS; b. that is an interventional clinical PS as defined in IVDR Article 2(46); c. where the conduct of the study involves additional invasive procedures or other risks for the subjects of the studies; d. involving CDx (except when only using left-over samples).	IVDR Article 76(2-3)
PMPF study referred to in IVDR Article 70(1) with additional burdensome and/or invasive procedures.	IVDR Article 76(5) **AND** IVDR Article 76(6) For more information, see section 6.1: Exceptions for PMPF studies falling under IVDR Article 70(1) and Section 10: causality Assessment.
PS referred to IVDR Article 70(2) conducted to assess, outside the scope of its intended purpose, a device which already bears the CE marking.	IVDR Article 76(2-3)

PS with an in-house IVD referred to in IVDR Article 5(5).	No provisions on safety reporting according to the IVDR. However, safety reporting may be regulated by national legislation.

6.1 Exceptions for PMPF studies falling under IVDR Article 70(1)

SAE reporting for PMPF studies falling under Article 70(1) is governed by Articles 76(5) and 76(6). This means that the provisions on vigilance apply and need to by the manufacturer of the CE marked device(s). However, when a causal relationship between the SAE and the preceding PS has been established, reporting procedures for PS should be followed by the PS sponsor.

This means that:

- **For the purpose of this guidance** (safety reporting in PS), reportable events in PMPF studies are those SAEs where a causal relationship between the SAE and the preceding PS has been established. The other relationship categories i.e. 'not related', 'possible' and 'probable' do not need to be reported.
- **In the context of vigilance**, IVDR Articles 82-85 need to be taken into account and this concerns the serious incidents where a relationship between the incident and the device is at least reasonably possible.

It is thus possible that events occurring in such PS need to be reported to both the competent authorities in charge of PS AND to the competent authorities in charge of vigilance.

6.2 Reportable events occurring in other MSs / Third Countries

6.2.1 Reportable events occurring in other MSs (MS)

The sponsor shall report the reportable SAEs per PS. If several PS are conducted (e.g. specimen collection in multiple sites) with the same device, only those SAEs that happen in PS that have the same PSP code should be reported for those PS, and only to those MS where a PS with that specific PSP code is being conducted[8].

It is acknowledged that the same PS can be conducted under different versions of the same PSP code in different MS, e.g. with country specific adaptations, and in those cases the SAE reporting can normally be combined for all the versions of the PSP for the same PS.

Reportable events occurring before the PS is authorised to start in a MS will be reported to this MS upon authorization in this MS.

[8] "Is being conducted" has to be interpreted as "has been approved or have been notified to the NCA".

6.2.2 Reportable events occurring in third countries

Reportable events occurring in third countries[9] in which a PS is conducted (e.g. specimen collection in that country) under the same PSP (see section 6.2.1 for what is meant with same PSP) have to be reported in accordance with this guidance to the NCA(s) of the European MS(s) in which the PS is being conducted.

- The NCA will start receiving the reportable events occurring in third countries as soon as the PS is authorised to start in that MS.
- Reportable events occurring in third countries after the participating European sites have closed, shall continue to be reported to the MSs in which the PS was conducted.

Reportable events occurring before the PS is authorized to start in a MS will be reported to this MS upon authorization in this MS.

7 Report by whom

Reportable events have to be reported by the sponsor of the PS (or the PS sponsor's delegate), which could be the manufacturer, the legal representative or another person[10] or entity.

8 Report to whom

Reportable events must be reported at the same time to all NCAs where the PS has commenced, using the summary table featured in the appendix.

A list of PS contact points within the NCAs is published at the European Commission's webpage.

For the purpose of this guidance, a PS is considered to have commenced in an individual MS when the sponsor is authorised to start the study in that MS in accordance with the provisions laid down in the IVDR.

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

9 Reporting timelines

9.1 Report by sponsor to NCAs.

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

- For all reportable events as described in section 6 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**

[9] Countries other than Switzerland, Turkey and those belonging to the EEA.
[10] Contact person established by the sponsor in line with IVDR Article 58(4) if accepted by MS.

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 sponsor.

- Any other reportable events as described in section 6 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 study's design and to the pathology studied in the PS. This would allow implementation of adequate provision for PS in which SAE frequency is expected to be high due to the natural progression of the disease (e.g. palliative oncology).

9.2 Report by the investigator to the sponsor

The sponsor must implement and maintain a system to ensure that the reporting of the reportable events as defined under section 6 will be provided by the investigator to the sponsor immediately, but not later than 3 calendar days after awareness of the event.

10 Causality assessment

The relationship between the use of the *in vitro* diagnostic medical device[11] (including the study procedure) and the occurrence of each SAE must be assessed and categorized.

During causality assessment activity, clinical judgement must be used and the relevant documents, such as the Investigator's Brochure, the PSP or the Risk Analysis Report must be consulted, as all the foreseeable SAEs and the potential risks are listed and assessed there[12]. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors must also be considered.

The above considerations also apply to the SAEs 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

[11] Intended as both device for PS and comparator.
[12] For a comparator device, the instructions for use could be a relevant document.

4. Causal relationship

The sponsor and the investigators will use the following definitions to assess the relationship of the SAE to the device for PS, the comparator or the study procedure.

1. Not related: the relationship to the device for PS, the comparator or to study procedures can be excluded when:
   - the event has no temporal relationship with the use of the device for PS, or the procedures related to use of the device for PS;
   - the relationship between the SAE and the device for PS is biologically implausible;
   - the discontinuation of device use 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 SAE;
   - the event involves a body-site or an organ that cannot be affected by the device for PS or procedure;
   - the SAE can clearly 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 SAE does not depend on a false result given by the device for PS ;

   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 SAE.

2. Possible: the relationship with the use of the device for PS or the comparator, or the relationship with study 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 device for PS or the comparator, or the relationship with study procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship: the SAE is associated with the device for PS, comparator or with study procedures beyond reasonable doubt when:
   - the product category the device for PS belongs to or similar IVDs and study procedures are known to have this event;
   - the event has a temporal relationship with the device for PS or study procedures;
   - 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 device for PS used for diagnosis[13], 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 SAE.

The sponsor and the investigators will distinguish between the SAEs related to the device for PS and those related to the procedures (any procedure specific to the PSP). Complications caused by concomitant treatments not imposed by the PSP are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to subjects regardless of the PSP. If routine procedures are not imposed by the PSP, complications caused by them are also considered not related.

The relationship between a SAE and the procedure or the device needs to be assessed separately. This does however not mean that they are mutually exclusive; a SAE 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)

When the healthcare provider performs the procedures and uses the device(s) for PS, the causality assessment of this healthcare provider should prevail. In case of self-tests, the assessment by the sponsor and the one by the user are equally weighted.

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 SAE, the sponsor should not exclude the relatedness; the event should be classified as “possible”, and the reporting is not to be delayed.

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

11 Reporting form

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

[13] If a device for performance study gives an incorrect diagnosis, the subject 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 subject 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.

The reporting form is study specific and covers only a given PS, defined by a distinct PSP. English is the recommended language for the reporting form. The reporting 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. 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 template form contains inserted filters and functionalities to facilitate the use of preferred terminology in the reporting. These are important for the analysis and should be maintained.

The table gives a cumulative overview of the reportable events per PS 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. If more detailed information has to be provided on request of an NCA, the individual study specific reporting form should be used.

11.1 Completion guidelines: Form header

11.1.1 EUDAMED/CIV-ID

It will not be possible to generate the Union-wide unique single identification number mentioned in IVDR Article 66 (1) before Eudamed is fully functional. Until Eudamed is fully functional, PS 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 PS and should be entered on the safety reporting form.

11.1.2 Title of PS

The identifying title of the PS. The title indicated here should be consistent with other title entries (such as in PS application form, PSP cover page etc).

11.1.3 PSP number/code

The unique identification code or short name assigned to the specific PSP by the sponsor (numeric, alphanumeric or acronym) should be indicated.

11.1.4 Contact person

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

11.1.5 MS+NCA Reference numbers

For each participating MS, indicate the country code[14] and the NCA's national reference number for the PS.

Example:
SE 5.1-20YY-XXXXXX

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

DK 20YYXXXXXX

11.1.6 No. of subjects enrolled to date total & No. of specimens tested with the IVD to date total

Indicate the total number of subjects who have been enrolled and number of specimens that have been tested with the IVD (per date of report) in the PS globally.

11.1.7 No. of subjects enrolled to date per country & No. of specimens collected to date per country

List all countries where the PS has been authorised by the report date and indicate the number of enrolled subjects and number of obtained specimens in the PS (per date of report) in each country.

11.1.8 Device type

Indicate the type of device(s) assessed in the PS according to EMDN categories (use the level as specialised as possible). The EMDN can be accessed and downloaded in pdf and excel format at webgate.ec.europa. eu/dyna2/emdn and the European Commission's website page for MDCG documents.

11.1.9 Reference MS

Indicate the name of the MS which drew the unique EUDAMED ID (normally the first MS receiving an application for the PS). Once the coordinated assessment procedure (per IVDR Article 74) is up and running, the coordinating MS should be indicated here.

11.1.10 No. of devices for PS used to date total

Indicate the total number of devices for PS (e.g. reagent kits) which have been used (per date of report) in the PS globally. The number of devices used could be indicative of a quality issue. Therefore, if not applicable to the device used, please provide justification and add another parameter to assess quality issues with the IVD.

11.1.11 No. of devices for PS used to date per country

List all countries where the PS has been authorised by the report date and indicate the number of devices for PS (e.g. reagent kits) which have been used in the PS (per date of report) in each country. The number of devices used could be indicative of a quality issue. Therefore, if not applicable to the device used, please provide justification and add another parameter to assess quality issues with the IVD.

11.1.12 Date of report

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

11.2 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.

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.

11.2.1 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 "Free description of event".

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

U = unchanged.

Do not add other options.

11.2.2 Date Sponsor received report of SAE/DD

Indicate the date when the sponsor was first notified by the study site about the event. This date is checked for compliance with reporting timelines as outlined in section *9 Reporting timelines*.

Format DD/MM/YYYY.

11.2.3 Country code

Indicate the country code[14] for the country in which the subject associated with the event has been enrolled. Choose from dropdown menu or enter manually if code is not available.

11.2.4 Study site

11.2.4.1 Specimen collection

Name identifying the institution or site where the specimen was collected.

11.2.4.2 Specimen analysis

Name identifying the institution or site where the specimen was analysed.

11.2.5 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).

11.2.6 SAE or DD ID code

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

11.2.7 Date of specimen collection

Indicate the date of the relevant collection of the specimen. Format DD/MM/YYYY.

11.2.8 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 4.15). The date when the event became an SAE should be reported as Date of event onset. In case of DDs which did not lead to an SAE, the date the DD was discovered should be indicated.

Format DD/MM/YYYY.

11.2.9 SAE or DD

Choose one option from SAE or DD. When a DD lead to a SAE, both need to be reported on separate lines. In the line of the DD/SAE, refer to the associated SAE/DD. Complete all possible information in both lines. This might mean double reporting of some information, but it is necessary that both the DD and the SAE have all information and can be analysed separately.

Do not add other options.

11.2.10 Subject gender

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

- Female
- Male
- Other
- Unknown

11.2.11 Classification of event

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

- Patient management decision resulting in death or an imminent life-threatening situation for the individual being tested or in the death of the individual's offspring
- Death
- Life-threatening illness or injury
- Permanent impairment of body structure or body function
- Hospitalization or prolongation of hospitalization
- Medical or surgical intervention
- Chronic disease
- Foetal distress, foetal death or congenital physical or mental or birth defect
- Not applicable (Note that this option is only to be selected in case of reportable DDs that did not lead to an SAE)

11.2.12 SAE connected to specimen collection or to specimen analysis

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

- Specimen collection
- Specimen analysis (including pre-analytical, analytical and post-analytical phase)

11.2.13 Free description of event

Provide a description of the event in free text.

Please provide other relevant information not already captured in this report.

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 subject
- Medical care of the subject
- Comments on the event in relation to already known safety data

11.2.14 Device issue (if applicable)

The IMDRF codes applicable to device issues can be found in annex A on the IMDRF webpage related to AE terminology. 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 only by ";". Please do not use the terminology, but only the codes.

11.2.15 Clinical signs/symptoms

The IMDRF codes applicable to clinical signs/symptoms can be found in annex E on the IMDRF webpage related to AE terminology. Please report all the appropriate codes applicable for the SAE or DD reported. Please separate each code only by ";". Please do not use the terminology, but only the codes.

11.2.16 Clinical impact

The IMDRF codes applicable to clinical impact of the SAE or DD can be found in annex F on the IMDRF webpage related to AE terminology. Please report all the appropriate codes applicable for the SAE or DD reported. Please separate each code only by ";". Please do not use the terminology, but only the codes.

11.2.17 Action / treatment / outcome

Provide information in free text on actions taken, treatment(s) administered and the outcome. "Outcome" is a broader term then "event status" and the value to be entered here is considered to be more specific than the options given for "event status" (see 11.4.13).

11.2.18 Relationship to procedure

Choose one option from the following list of causality levels (for explanatory texts see section 10 Causality assessment) (do not add other options):

- Not related

- Possible
- Probable
- Causal
- Not applicable (please justify)

Please report the assessments by sponsor and investigator in the respective columns. The investigator could mean the specimen collection site investigator or the specimen analysis site investigator.

11.2.19 Relationship to device

Choose one option from the following list of causality levels (for explanatory texts see section 10 Causality assessment) (do not add other options):

- Not related
- Possible
- Probable
- Causal
- Not applicable (please justify)

Please report the assessments by sponsor and investigator in the respective columns. The investigator could mean the specimen collection site investigator or the specimen analysis site investigator.

11.2.20 Study arm

Choose one option from the following list:

- Test group (described in the PSP)
- Comparison group (described in the PSP)
- Blinded
- Not applicable

Note: For some study designs it might be more relevant to add name of device; i.e. in a PS with several test groups it might be useful to differentiate which study device was used for testing the subject.

11.2.21 Event status (only applicable for SAE)

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

- Resolved
- Resolved with Sequelae
- Ongoing
- Death

Doesn’t need to be completed for DD.

11.2.22 Date of event resolution (only applicable for SAE)

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

12 References

1. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.
2. Council Directive 98/79/EC of 27 October 1998 on *in vitro* diagnostic medical devices.
3. Commission Decision 2010/227/EU of 19 April 2010 on the European Databank on Medical Devices (Eudamed).
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).
5. *In vitro* diagnostic medical devices — Clinical performance studies using specimens from human subjects — Good study practice (ISO 20916) published by International Organisation for Standardization (ISO).
6. Documents by the International Medical Device Regulators Forum (IMDRF) to support regulatory harmonization: https://www.imdrf.org/documents.
7. MDCG 2022-10: Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR).

13 **Appendix** – Performance Study Summary Safety Reporting Form