

COMBINE programme

Project 2: safety reporting in combined studies

Sponsors' guide

September 2026

This document has been endorsed by the Clinical Trial Coordination and Advisory Group (CTAG) and the Medical Device Coordination Group (MDCG). The CTAG and the MDCG are composed of representatives of all Member States and are chaired by a representative of the European Commission.

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1. Introduction

COMBINE Project 2 is part of the COMBINE programme and builds on the work done previously to analyse the challenges facing combined studies in Europe. Combined studies in the context of this sponsor guide are studies covered by more than one legal framework (Regulation (EU) No 536/2014 on clinical trials (CTR), and/or Regulation (EU) 2017/745 on medical devices (MDR), and/or Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR)).

Following the publication of the COMBINE analysis report¹, work was conducted to clarify different rules and criteria for the different regulations which apply to safety reporting. With the term ‘safety reporting’, this guidance refers to all communications in relation to safety events including (serious) adverse events [(S)AE], device deficiencies (DD) and human errors in the context of the applicable regulations. The requirements for documentation, reporting timelines and processes, as envisaged by the regulations, vary significantly between the CTR, IVDR and MDR. Conducting a combined study necessitates navigating all the requirements of each applicable regulation and reconciling the differences between them until a specific legislative framework for combined trials comes into force. Open issues that cannot be fully addressed within the current legal framework are being collected to create a reflection paper for optimised solutions via stakeholder consultation.

COMBINE Project 2 aims to clarify how to apply the CTR, MDR and IVDR requirements on safety reporting in combined studies. The initial focus of the work was on understanding the respective requirements, timelines, and existing practices for reporting of serious adverse events, with a view on how to align the understanding of the different definitions of seriousness criteria and to give guidance to sponsors on how to handle the reporting requirements based on the investigator’s causality assessment.

In addition, Project 2 provides a best practice guidance on the issues identified by stakeholders, including a diagram on information flow and communication across stakeholders.

¹ [Combined studies - European Commission](#)

2. Scope (including a “roadmap” and some key understandings important to the entire guidance)

This guidance clarifies how to practically manage safety events in combined studies in relation to recording and reporting requirements under the current legislations.

This guidance should not be seen as a stand-alone document and the current legislation and guidance documents need to be taken into account. This guidance does not replace the Medical Device Coordination Group (MDCG) guidance on adverse event reporting (MDCG 2020-10/1 rev.1 and MDCG 2024-4) nor the guidance for adverse event reporting under CTR ([bd165522-8acf-433a-9ab1-d7dceae58112_en](#)).

The only active deviation from those documents is the change of reporting timelines where these are defined in a guidance instead of the primary legislation. The rationale for this is simplification. For details, please refer to section 7.3.

This guidance was designed to guide the sponsor on safety reporting from study planning and forecasting of anticipated adverse events to the detection of events during the study conduct, the analysis of causality and seriousness, as well as communication of this information to the national competent authorities (NCAs). It is important to analyse and communicate the benefit risk impact safety relevant information may have on combined studies.

For this, there is an initial section where you will find the definitions in each legislation, and the requirement(s) in the planning of the study and the preparation of protocol(s) (Sections 3 and 4). Based on these protocols, investigation teams must be able to identify, record, and report, where required, all pertinent information from each safety report (Section 5). Investigators must also be able to assess the effects of adverse events and understand their seriousness; however, it is up to the sponsor to ensure that this assessment is adequate and that the impact has been properly measured (Section 6). The result of this assessment, which must take into account that it is a combined study, will determine what must be reported to the national competent authorities (NCAs) (Section 7). In the final section, specific cases are presented (Section 9).

It is up to the sponsor(s) to translate this guidance into the protocol(s) and other applicable study documents so that all investigators in a combined study are adequately informed and able to perform the investigator-tasks in a harmonised and consistent manner during study conduct.

Of note: Adequate communication between all parties involved (investigators from different sites and different types of sponsors) is necessary to ensure that reportable events and risk mitigation measures are reported to NCAs and investigators as quickly as possible and in line with their urgency, using the appropriate tools or communication channels. While figures might only show feedback loops on specific potential issues that can

be clarified and therefore only require a response to the investigator who raised a specific potential issue in section 6.4, verified issues which require risk mitigation measures have to be communicated to all investigators in a timely manner.

Throughout this document some terms and abbreviations are used that are uncommon or specific to a single legislative framework. These terms are expected to contribute to improving mutual understanding through harmonisation of terminology:

- **IMP** = Investigational Medicinal Product means a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial (CT)
- **CT** = Clinical Trial means a clinical study which fulfils any of the following conditions:
 - (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;
 - (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or
 - (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.
- **AxMP** = Auxiliary Medicinal Product means a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product
- **IMD** = Investigational Medical Device is a pseudonym of the term Investigational Device which is defined in the MDR as follows “‘investigational device’ means a device that is assessed in a clinical investigation;”.
- **CI** = Clinical Investigation means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device.
- **IIVD** = Investigational *In Vitro* Diagnostic Medical Device is not a defined term in IVDR, but in analogy, the term/abbreviation IIVD is used for an *in vitro* diagnostic medical device for which a performance study (PS) is undertaken.
- **PS** = Performance Study means a study undertaken to establish or confirm the analytical or clinical performance of an *in vitro* diagnostic medical device; An ‘interventional clinical performance study’ means a clinical performance study where the test results may influence patient management decisions and/or may be used to guide treatment

- **CDx** = Companion Diagnostic means a device which is essential for the safe and effective use of a corresponding medicinal product to:
 - (a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or
 - (b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product
- **AESI** = Adverse Event of Special Interest is an adverse event which is one of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted. The target group of this document is mainly the sponsor(s). The sponsor(s) should instruct the investigators by transferring the information regarding recording and reporting obligations to them via the protocol. In the scenario of multiple sponsors, it is up to them to define the responsibilities of the different sponsors.

In Annexes 1 and 2 to this document, you can find clarifications on national safety reporting routes and requirements. Involvement of ethics committees is out of scope of this document.

Reporting requirements for ethics committees differ significantly among the Member States and cannot be harmonized within this project.

3. Current legislation and EU-wide guidance documents on safety reporting

	Clinical Trials with medicinal products	Clinical Investigations with medical devices	Performance studies with IVDs
Legislation	CTR	MDR	IVDR
Guidance documents	• Q&As Reg (EU) 536/2014¹ • PM, Directive 2001/83/EC • GVP Module VI³ • ICH E2A, ICH E6, ICH E19⁴ • EudraLex Volume 10: Clinical trials guidelines: Auxiliary Medicinal Products in Clinical Trials¹	• Guidance MDCG 2020-10² • ISO 14155 • IMDRF/AE WG/N43⁵	• Guidance MDCG 2024-4² • ISO 20916 • 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 <i>in vitro</i> diagnostic medical devices (IVDR) ⁶
Local/national requirements	No	Yes (see Annex 1)	Yes (see Annex 2)

Links to websites where applicable documents can be found:

- 1: [EudraLex - Volume 10 - Public Health - European Commission](#)
- 2: [Guidance - MDCG endorsed documents and other guidance - Public Health](#)
- 3: [Good pharmacovigilance practices \(GVP\) | European Medicines Agency \(EMA\)](#)
- 4: [ICH Official web site](#)
- 5: [IMDRF: Terminologies For Categorized Adverse Event Reporting](#)
- 6: [MDCG 2022-10 - Q&A](#)

4. Requirements for protocol/CIP/CPSP content with regards to safety reporting

In CTR, MDR and IVDR different terms are used for the document describing the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of clinical trial (CT), clinical investigation (CI) or performance study (PS):

- 'Protocol' is the term used in the context of clinical trials
- 'Clinical investigation plan' (**CIP**) is term used in the context of clinical investigations
- 'Clinical performance study plan' (**CPSP**) is the term used in the context of performance studies

To improve readability in this guidance the term protocol(s) refers to protocol, CIP and CPSP.

For combined studies a single protocol approach is recommended, in which protocol and CIP or CPSP are integrated parts in one document.

Advantages of this recommended approach:

- Improved clarity on responsibilities of sponsors and reporting requirements for investigators and sponsor(s)
- Upload of only one document in Clinical Trials Information System (CTIS) during the application phase for trials following the single application approach (COMBINE 1 Pilot²)

Potential disadvantage:

- Protocol changes driven by aspects relevant for only one of the legal frameworks
→ might be outweighed by increased transparency of relevant changes to all parties involved

Submission of separate documents is also possible.

Protocol(s)/Plan(s) must clearly describe:

- Which SAEs and DDs have to be reported by investigators to which sponsor(s)
- Expected communication flow between CT-sponsor and CI/PS-sponsor
- Reporting obligations for:
 - IMP-related issues
 - Device-related issues / investigational/study procedure related issues
 - Combined issues

² [COMBINE Project 1 – pilot “all-in-one” coordinated assessment - Public Health](#)

It is up to the sponsor(s) to translate this guidance into the protocol(s) and other applicable study documents so that all investigators in a combined study are adequately informed and able to perform the investigator-tasks in a harmonised and consistent manner during study conduct.

- Protocol(s) should describe safety definitions considering the 3 regulations and this guidance.
- Protocol(s) should describe how investigators should record, assess and report relevant safety information to the sponsor(s).
- In multiple-sponsor studies, protocol(s) should define supervision responsibilities including communication plans (sponsor(s) CT, sponsor(s) CI, sponsor(s) PS), explaining how assessments (seriousness, causality, DD review) are coordinated and reported, where appropriate.

The protocol(s) must include the description of a process ensuring:

- Bidirectional communication between investigators and sponsors
- Exchange between CT-sponsor and CI/PS- sponsor
- That no reportable SAE or DD is missed in either clinical or laboratory settings
- Clinical trial protocols can describe derogation of recording and reporting obligations (see CTR, ICH E19 and AxMPs in CT guidance and CTR Q&A)

5. Definitions of safety information in a combined study

5.1 Overview of definitions in separate legislations

CTR, Reg. (EU) 536/2014	CTR Art 2(32). defines "Adverse event (AE)" as any untoward medical occurrence in a subject to whom a medicinal product is administered which does not necessarily have a causal relationship with this treatment. As further explained in question 7.1 of Q&As Reg (EU) 536/2014 Version 7.1 (date of publication 27 March 2025) an AE can be any unfavourable and <u>unintended sign</u> (including an abnormal laboratory finding), symptom or <u>disease temporally associated</u> with the use of a medicinal product, whether or not considered related to the medicinal product (see Section 2A1 of ICH E2A). Clinically significant abnormal laboratory findings are considered AEs, however abnormal laboratory findings may not be considered AEs if there is no change compared to baseline values (at randomisation). Art 2(33). Serious adverse event (SAE) means any untoward medical occurrence that at any dose requires
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	• inpatient hospitalisation³ or prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity, • results in a congenital anomaly or birth defect, • is life-threatening, • or results in death; Art 2(34) Unexpected serious adverse reaction means a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information. (Note: Abbreviation of suspected unexpected serious adverse reaction is “SUSAR”) Art. 53 lists other reporting obligations for all unexpected events (UE) which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 42.
MDR, Reg. (EU) 2017/745	MDR Regulation (EU) 2017/745 Art 2 (57) defines adverse event (AE) as any untoward medical occurrence, <u>unintended disease or injury or any untoward clinical signs</u>, including an abnormal laboratory finding, in <u>subjects, users or other persons</u>, in the context of a clinical investigation, whether or not related to the investigational device. Art 2(58) Serious Adverse Event (SAE) means any adverse event that led to any of the following: 1. death, 2. serious deterioration in the health of the subject, that resulted in any of the following: a. life-threatening illness or injury, b. permanent impairment of a body structure or a body function, c. hospitalisation or prolongation of patient hospitalisation, d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, e. chronic disease,

³ The latest version of the CTR Q&A should be taken into account for the correct definition of seriousness [bd165522-8acf-433a-9ab1-d7dceae58112_en](https://ec.europa.eu/health/medical_devices/clinical_trials/ctr_qa_en).

	3. foetal distress, foetal death or a congenital physical or mental impairment or birth defect Art2(59) Device Deficiency (DD) means 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. MDCG 2020-10/1 defines Adverse Device Effect (ADE) as any adverse event related to the use of an investigational medical device or a comparator. MDCG 2020-10/1 defines Serious Adverse Device Effect (SADE) as any ADE that has resulted in any of the consequences characteristic of a serious adverse event.
IVDR, Reg. (EU) 2017/746	IVDR Regulation (EU) 2017/746 Art 2 (60) defines Adverse Event (AE) in the same way as MDR Regulation (EU) 2017/745 Art 2 (57) with the important addition of <u>inappropriate patient management decision</u> in the context of a performance study, whether or not related to the device for performance study. Art 2 (61) Serious Adverse Event (SAE) means any adverse event that led to any of the following: 1. 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, 2. death, 3. 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: a. life-threatening illness or injury, b. permanent impairment of a body structure or a body function, c. hospitalisation or prolongation of patient hospitalisation, d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, e. chronic disease, 4. foetal distress, foetal death or a congenital physical or mental impairment or birth defect Art 2 (62) “device deficiency” (DD) means any inadequacy in the identity, quality, durability, reliability, safety or performance of a device for

	performance study, including malfunction, use errors or inadequacy in information supplied by the manufacturer. MDCG 2024-4 defines “Adverse Device Effect (ADE)” as any adverse event related to the use of a device for performance study or a comparator. MDCG 2024-4 defines “Serious Adverse Device Effect (SADE)” as any ADE that has resulted in any of the consequences characteristic of a serious adverse event.
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5.2 Definition of seriousness in a combined study

While the specific frameworks for medicinal products (CTR), medical devices (MDR), and *In Vitro* Diagnostics (IVDR) differ in scope, their definitions of an Adverse Event share a fundamental "common denominator".

An adverse event is any untoward medical occurrence. In most cases it is something negative that happens to a study participant during the conduct of the study (or a specific time thereafter) or to users or other persons, but it does not have to be causally related to the medicinal product, the medical device or the IVD investigated in the combined study. (Examples of adverse events, which are not explicitly negative, like euphoria or mood-related changes with psychedelics, are relevant to collected recorded regarding abuse potential.)

The definitions of adverse events in the three regulations need to be taken into account in a combined study, because adverse events of both medicinal product and/or the device/IVD as well as the investigational/study procedures need to be considered.

For clarity and to reduce complexity, in a combined study an adverse event is considered **serious** if it leads to, or could have led to, outcomes such as

- death,
- a life-threatening illness or injury,
- inpatient hospitalization or prolonged hospitalization,
- a persistent or significant disability or incapacity,
- or a congenital anomaly or birth defect.

Additional criteria that define a serious adverse event in at least one of the regulations include:

- A temporary but serious deterioration in health.

- Fetal distress or fetal death.
- Chronic disease. This term was introduced in the MDR and IVDR specifically to address the development of new chronic diseases when it comes to implantable devices (e.g. Pacemaker, Cobalt hip implant, Implantable intrauterine devices, drug eluting stents, etc.). Examples of newly developed or diagnosed chronic diseases are Kidney Disease, Osteomyelitis, COPD, Chronic Arrhythmia, Pacemaker-mediated tachycardia.
- Medical or surgical intervention necessary to prevent life-threatening outcomes or permanent impairment.
- 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.

It is acknowledged that MDR/IVDR requirements are not legally binding for CTR adverse events.

According to ICH E2A, important medical events⁴ that do not strictly meet these [common] criteria [see above] but could jeopardize the subject or require intervention to prevent the listed outcomes should also be considered serious based on medical judgment. So, applying medical judgement in the context of ICH E2A will, most of the time, lead to reporting of events described as additional seriousness criteria as per MDR/IVDR.

Planned hospitalization for a pre-existing condition or protocol-specified procedure is not usually considered a serious adverse event unless the individual's health seriously deteriorates.

6. Investigator responsibilities

This section guides investigators in assessing and reporting Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESIs), and Device Deficiencies (DDs) in combined studies involving Investigational Medicinal Products (IMP) and Investigational Medical Devices (IMD's) and/or Investigational In Vitro Diagnostic Medical Devices (IIVD's) This guidance applies to both:

⁴ The latest version of the CTR Q&A should be taken into account for the correct definition of seriousness [bd165522-8acf-433a-9ab1-d7dceae58112_en](https://www.ema.europa.eu/en/documents/clinical-trials/qa/clinical-trials-q-a).

- Specimen collection/treatment sites⁵, and
- Specimen testing/analysis sites⁶ (laboratories)

Note: Specimen collection/treatment sites and specimen testing/analysis sites do not necessarily need to be separate sites. Testing can take place on sites where the patients receive the IMP or where samples are taken (e.g. if a Point of Care device is used or if the clinical site also performs testing in the hospital lab).

The responsibilities can be summarized as follows:

- Record and document **all AEs and DDs**, unless the protocol specifies otherwise.

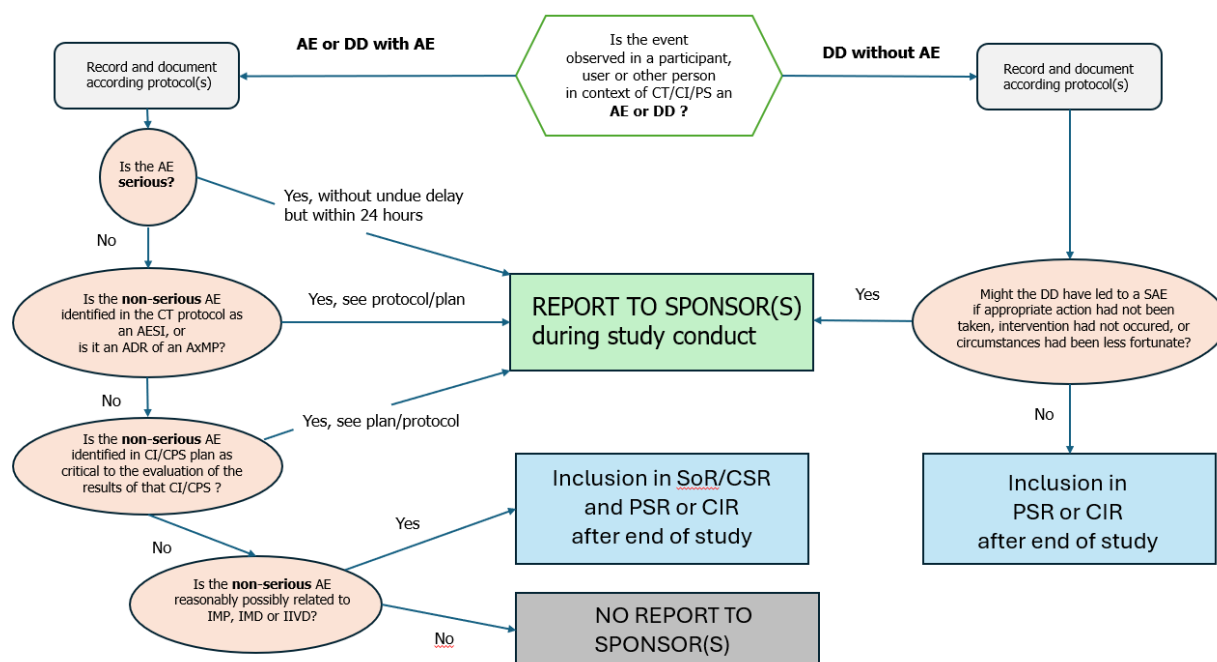
This includes any DD of the IMD/IIVD that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Note: Recording, documentation and reporting of AE/SAE/DD begins with signing of the Informed Consent Form (ICF) and consequently before the collection of samples.

- Assess **seriousness** (per criteria in section 5.2 of this document).
- Provide a **causality assessment** for:
 - IMP / IMD / IIVD
 - Comparator(s)
 - Study/investigational procedure
- Report events to the sponsor(s) according to protocol and within protocol-defined timelines.

⁵ For clarity throughout the document and within combined studies, the term specimen collection/treatment site refers to the site where the study participant is treated with the IMP/IMD or where the specimen for the IIVD is collected.

⁶ The (specimen) testing/analysis site is the institution or site where the collected specimens are tested/analysed.



Note: Specific (S)AEs can be excluded from recording and reporting requirements but only if specified in the protocol/plan. For ease of display this is not reflected in the figure above.

A single protocol approach is recommended for combined studies to improve clarity on reporting requirements for the investigators.

6.1 Investigator task: Assessing seriousness

Investigators must determine whether the event meets SAE criteria as described in section 5.2.

If the AE Is Serious

- Report all SAEs to the sponsor(s) **without undue delay**, and **within 24 hours** of becoming aware of the event, unless the protocol exempts certain SAE types (e.g. endpoints not requiring immediate reporting).
- Submit **follow-up information** as it becomes available.
- In multi-sponsor studies, follow the protocol instructions on **which sponsor(s)** receives which type of SAE.
- Provide seriousness and causality assessments for *each* investigational product and device in the combined study.

- Notify sponsor(s) of SAEs occurring **after trial end**, if causally related to the IMP, IMD or IIVD.

If the AE is Not Serious

- Document all non-serious AEs per CTR Article 41 unless the protocol specifies exemptions.
- Check with the CTR protocol if the AE is an Adverse Event of Special Interest (AESIs) or laboratory abnormality is designated as critical to safety evaluation.
- Check with the Clinical Investigation Plan (CIP) or the Clinical Performance Study Plan (CPSP), if the adverse event is identified as being critical to the evaluation of the results of that clinical investigation or performance study.

6.2 Investigator task: Assessing causality

The investigator must assess **suspected causality** with respect to:

- IMP / IMD / IIVD
- Any comparator (if applicable)
- The investigational/study procedure

This causality assessment:

- Must accompany the **initial SAE report**
- Must be performed **per product** in multi-product studies
- Must follow protocol-specific instructions for AxMPs (auxiliary medicinal products) if applicable

6.3 Investigator task: Reporting and Timelines

- **SAEs:** Report to sponsor(s) without undue delay but not later than within 24 hours unless protocol states otherwise
- **AESIs:** Report within protocol-defined timelines to responsible sponsor(s) when:
 - Defined in the CTR protocol as critical to evaluating the medicinal product
 - Defined in the CIP/CPSP as critical for evaluating the device
 - Required for AxMP-related events (Recording and reporting requirements in relation to AEs, which are reasonably possibly associated to an auxiliary medicinal product (AxMP), shall be detailed in the protocol.)

- Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same obligation to report as adverse reactions. (see CTR Annex III 2.1)
- **Post-trial SAEs with suspected causal link to IMP, IMD or IIVD:** report to sponsor(s) without undue delay (in accordance with CTR Article 41)
- **Device Deficiencies (DDs):** A **reportable device deficiency (DD)** is any deficiency that **might have led to an SAE** if:
 - Action had not been taken
 - Intervention had not occurred
 - Circumstances had been less fortunate

This applies to:

- IMDs
- IIVDs
- CE-marked devices used in the study

Investigator's task in context of DDs:

- Report device deficiencies to sponsor(s).
- Report DDs involving CE-marked devices to manufacturers.
- Follow national vigilance procedures (mandatory in many Member States).
- Provide preliminary seriousness and causality assessment of DDs even if no SAE occurred.

- **Serious incidents with CE-marked medical devices/IVDs:** report to manufacturer of device/IVD

MDR Art. 2 (64) defines 'incident' as 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.

IVDR Art 2. (67) defines 'incident' as 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.

MDR Art 2. (66) and IVDR Art 2 (69) define 'serious public health threat' as 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. MDR Art. 2 (65) and IVDR Art. 2 (68) define 'Serious incident' as 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

Recording and reporting requirements in relation to serious incidents with a CE-marked medical device/IVD which is used in a combined trial shall follow the national vigilance with a medical device/IVD rules.

It is highly recommended and in many MSs an obligation, that the investigator reports serious incidents, either directly to the manufacturer or via the contact point established within the investigator's institution. However, it is necessary to distinguish if the incident is with a CE marked MD/IVD which is used in combined study, or if it is being investigated in a combined study.

In the first case, a large list of MD/IVD are used during a CT and could lead to an incident or serious incident during their normal conditions use according to the instructions for use (IFU). In this case, the investigator team must act as usual according to the vigilance system of devices. Any person/ patient/ user/ economic operator etc should report by the routes of each healthcare institution/MS.

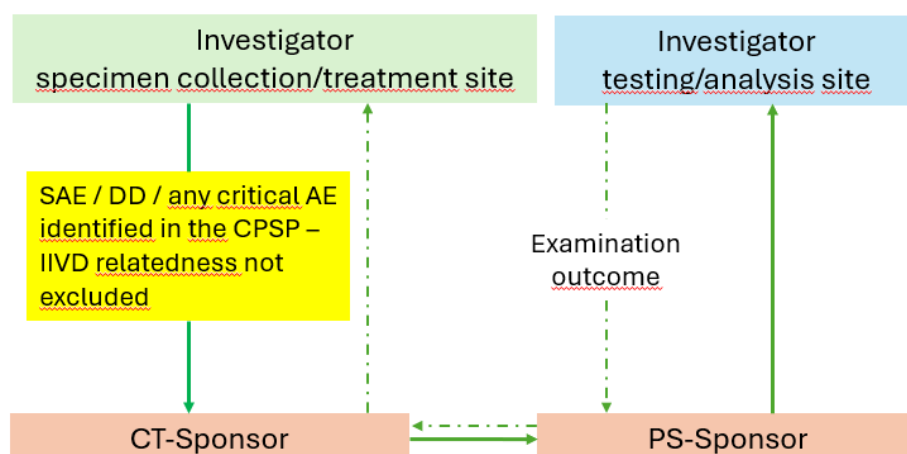
If the CE marked MD/IVD is the object of investigation in a combined study, (this is happening when MDs/IVDs are investigated outside the scope of their intended use), any incident should be evaluated by AE/SAE/DD definitions and follow the art 80 MDR/ art 76 IVDR. These definitions are intentionally broad and may overlap with vigilance incident definitions, meaning that a single event can fall under both safety reporting in a clinical investigation and the MDR/IVDR vigilance framework. For example, this could be the case of a death with causal relation to the device, and the investigator/sponsor concluded that the problem is related with the quality of the device and could occur with any patient that currently uses the device within the intended use. In this subcase, the death is simultaneously an incident and should also be treated by manufacturer and NCAs in the context of the vigilance system.

6.4 Communication requirements for a situation where impact assessment at a specimen collection/treatment site requires information from the specimen testing/analysis site and vice versa - Reporting pathways in dual sponsorship situation (as an example for multiple sponsorship)

Sponsors must communicate with each other to ensure no reportable events are missed and to investigators, where appropriate.

While the figures below might only show feedback loops on specific potential issues that can be clarified and therefore only require information back to the investigator who raised a specific potential, verified issues which require risk mitigation measures have to be communicated to all investigators in a timely manner.

Occurrence at the specimen collection/treatment site:



Solid line: initial information loop; **Dotted and dashed line:** feedback loop

The investigator at the specimen collection/treatment site has to report all SAEs to the clinical trial sponsor, including a preliminary causality assessment. The protocol should clarify which untoward occurrences might indicate an MD or IVD deficiency, which need to be reported within the timelines and format of an SAE.

If the investigator is unsure about a potential causal link to the IVD, the investigator can inform the sponsor accordingly. It is the sponsor's responsibility to decide on further actions.

In a dual/multi sponsorship scenario, it is recommended that the clinical trial sponsor contacts the PS sponsor who then contacts the (specimen) testing/analysis site for an

examination. This examination entails a causality assessment, but could also mean, for example, retesting of the original specimen, testing of a new specimen and/or performing an alternative test to the IVD.

This should serve as an example for managing communication. If a different approach ensuring appropriate information flow is preferred, this shall be described in the communication plan.

If the (specimen) testing/analysis site can prove the SAE is unrelated to the IVD, the original assessment of the specimen collection/treatment investigator can be updated to “not related to the IVD” by the sponsor in the sponsor’s assessment. More information on a causality assessment can be included in the column “Free description of the event” in the safety reporting form for the PS.

In a dual sponsorship scenario, the clinical trial sponsor then receives the report of the examination at the testing/analysis site from the PS sponsor.

In case the initial SAE report was identified to fulfil the requirements for suspected unexpected serious adverse reaction (SUSAR) reporting, the available outcome of the examination at the testing/analysis site should be integrated in a SUSAR follow-up report.

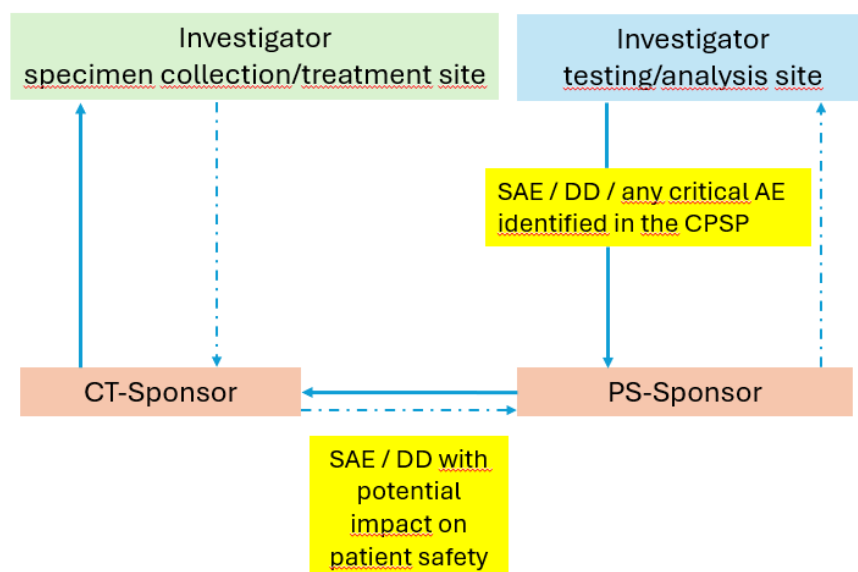
The protocol should describe these communication pathways.

It is recommended to communicate the outcome of the examination at the testing/analysis site to the appropriate investigator of the specimen collection/treatment site.

If the outcome of the investigation reveals information relevant for all investigators, this information shall be systematically shared to all investigators and not only the one raising the issue.

A similar problem might occur for the investigator at the testing/analysis site (e.g. if a negative effect of a DD on the study participant cannot be excluded) and a similar communication approach has to be taken.

Occurrence at the testing/analysis site:



Solid line: initial information loop; **Dotted and dashed line:** feedback loop

6.5 Double reporting

The challenge of double reporting of the same SAE will need to be dealt with as long as separate legislation exists. On guidance level, safety reporting for MDR and IVDR is intended to be revised. The issue of double reporting cannot be dealt with before the new safety reporting procedures for MDR and IVDR are implemented for single regulation studies. For example, see figures section 6.4 occurrence at the specimen collection/treatment site (relatedness to IIVD cannot be excluded) and information flow from testing/analysis site when impact on patient safety is suspected.

Although the same SAE might have to be reported twice, sponsors are allowed to hand over reporting duties to a 3rd party handling safety reporting for combined trials. While third-party delegation is operationally possible, it does not resolve the underlying double reporting burden that combined studies face.

Double reporting currently remains an unresolved issue that requires legislative harmonisation.

In case of multiple sponsorship, sponsors are allowed to transfer reporting duties to the other sponsor(s) if described in the respective safety section of the protocol or safety data handling agreement. Alternatively, in case of multi-sponsorship, these activities can be delegated to a single applicant, but each sponsor remains responsible for respective safety data handling and reporting duties.

The sponsor(s) can provide the investigator(s) with a single form for safety recording and reporting in relation to the IMP/IIVD/IMD. It is then the sponsor(s)'s obligation to direct the

information to the correct recipients (Eudravigilance, NCAs for PS/CI, ...).

7. Sponsor responsibilities

7.1 Sponsor task: Check causality assessment:

If the sponsor(s) receive(s) an SAE report, they need to take into account the preliminary causality assessment of the reporting investigator in their own causality assessment. The causality assessment of an investigator should never be changed by the sponsor(s) (see figures in section 6.4).

In case of disagreement between an investigator and a sponsor, the sponsor can explain the diverging opinion in the sponsor's SUSAR comments or in the column "Free description of the event" in the safety reporting form for the CI or PS.

7.2 Sponsor task: Reporting safety information in a combined study

Reporting obligations MDR/IVDR

The following events are considered reportable events in accordance with MDR Art. 80(2) and IVDR Art. 76(2):

- a) any **serious adverse event (SAE)** that has a causal relationship with the investigational device, the comparator or the investigation/study procedure or where such causal relationship is reasonably possible;
- b) any **device deficiency (DD)** 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/follow up report in relation to any event referred to in points a) and b).

It is the **CI/PS-sponsor's obligation** to evaluate the DD and forward reportable DDs to all Member States in which the combined study is being conducted without delay.

If the CI/PS-sponsor determines that DDs might affect the benefit-risk balance of a combined study even if the relevance for the benefit-risk effect is only detected based on cumulative data, this should be communicated to the CT-sponsor(s) to enable them to report this issue via CTIS as an **unexpected event notification**.

DDs where implications to some/all trial participants are suspected need to be reported as UE as this situation is a typical example of a DD affecting the benefit-risk balance of a combined study.

Not limited to such a scenario, there is the need for communication between the sponsors in case of multiple sponsors.

Reporting requirements in relation to **serious incidents** (for definition see MDR Art 2 (64) & (65) and IVDR Article 2 (67) & (68)) **with a CE-marked medical device/IVD** which is used in the combined trial shall follow the national vigilance procedures for a medical device/IVD.

In case the CI/PS-sponsor is also the distributor or importer of the device(s) of the combined trial, the safety reporting obligations of these actors also apply. The CI/PS-sponsor then has the legal obligation to transfer complaints or reports (i.e. not limited only to serious incidents) received by users, Health Care Professionals (HCPs) or study participants, to the manufacturer(s).

This reporting shall be done without undue delay. In case the CI/PS-sponsor is also the manufacturer, the CI/PS-sponsor shall follow the vigilance obligations applicable to manufacturers.

Obligation after the end of a combined study

According to MDR, a summary of serious adverse events, adverse device effects, device deficiencies and any relevant corrective actions need to be provided in a clinical investigation report. See MDR Annex XV Clinical Investigations chapter 3 point 7 and [MDCG 2024-15](#) "Guidance on the publication of the clinical investigation reports and their summaries in the absence of EUDAMED".

Reporting obligations CTR

For SAEs possibly related to an IMP (SARs), the CT-sponsor determines expectedness by consulting the Reference Safety Information of the IMP as defined in the CTR.

a) **SUSARs**: All suspected unexpected SARs (**SUSARs**) must be reported by the CT-sponsor to the CT module in the EudraVigilance (EVCTM) database.

Note: SARs of IMPs that are expected should be reported by the CT-sponsor as part of the annual safety report (ASR) in the "cumulative summary tabulation of serious adverse reactions".

b) **AxMP** related safety reporting

Specific guidance concerning AxMPs in clinical trials is available in Eudralex Volume 10, Clinical trials guidelines, Chapter III⁷.

- A) Unauthorised or authorised modified AxMPs follow the reporting requirements of IMPs.
- B) Where an adverse event is suspected to be related only to an authorised, unmodified AxMP and does not result from a possible interaction with the IMP, reporting should comply with pharmacovigilance rules for authorised medicinal products, irrespective of whether the authorised AxMPs are used in accordance with the terms of the marketing authorisations of those products. The suspected (S)AR should be reported to the EudraVigilance Postmarketing Module (EVPM) in line with the guidance provided in guideline on good pharmacovigilance practices (GVP) Module VI.

Different reporting routes are listed in GVP module VI. The parties responsible for reporting to EVPM and their specific responsibilities should be clarified in the protocol of the clinical trial to avoid double reporting. The EU clinical trial number and protocol code as well as information that the suspected medicinal product was not used as an IMP in the clinical trial, but as an AxMP, should be added in the narrative section of the Individual Case Safety Report (ICSR).

c) Annual Safety Reports (ASRs) in combined studies

The Annual Safety Report should summarize the relevance of information concerning SAEs and DDs that theoretically could lead to SAEs observed during the ASR reporting period in the “evaluation of risks” section or, where appropriate, in the section “benefit-risk considerations”.

If actions for safety reasons have been taken during the ASR reporting period due to SAEs related to IMD or IIVD, this should also be mentioned in the appropriate section.

To support the benefit-risk considerations or actions for safety reasons, information related to SAEs of the combined study occurring with the IIVD or the IMD can be reported in the ASR. In addition, it is recommended to include investigational/study procedure

⁷ Auxiliary Medicinal Products in Clinical Trials [1bf35e45-134c-4f2e-9c68-0e8537eef867_en](#)

related SAEs, but excluding SAEs related to procedures on study participants which are not defined in the CIP or CPSP, if relevant in this context. Serious incidents with a comparator MD with a CE-certificate do not need to be reported in the ASR.

There are 4 options how to present SAEs in an ASR:

1. If SAEs are possibly related to an IMD or IVD in a combined study, a Line Listing with IMDRF coding of the SAEs could be added as an appendix in DSURs. This would include SAEs for which relatedness is unknown according to MDR and IVDR. Only IMDRF codes A, E and F need to be included.

IMDRF codes:

- Annex A: medical device problem,
- Annex E: health effects - clinical signs and symptoms or conditions
- Annex F: health effects – health impact

When possible, a technical link from the IMDRF Line Listing could link to the respective case in the MedDRA Line Listing. An example which illustrates the difference in coding between IMDRF and MedDRA is provided in Annex 3.

2. SAEs could be integrated in the ASRs Cumulative Summary Tabulation with a comment or footnote, or
3. A dedicated table only displaying case reports for SAEs involving IMD/IVD could be added to the ASR.
4. If periodic safety reports for medical devices or IVDs are prepared to meet local reporting requirements for NCAs, it is also acceptable to include these reports as an annex to the ASR instead of the line listing options described above. Those reports do not necessarily have to exactly cover the ASR reporting period.

A separate ASR of the AxMPs is not required. However, any information relating to (authorised or unauthorised) AxMPs, which are relevant to the benefit-risk consideration of the IMP should be included in the ASR of the IMP.

NOTE: Marketing authorisation holders (MAHs), who are sponsors of ongoing combined studies with their authorized product as IMP, have the additional obligation to include information from these studies in their PBRER (respectively PSUR) for this product. GVP Module VII should be followed.

d) Obligations for notifications

SAEs reasonably possibly causally related to a medical device or IVD should be notified via CTIS if this SAE potentially impacts the benefit-risk balance of the combined study. Reporting in CTIS should be done via an UE notification.

e) Obligation after the end of combined study

According to CTR, all AEs should be included in the summary of results (SoR) of the clinical trial and, if applicable, the clinical study report (CSR).

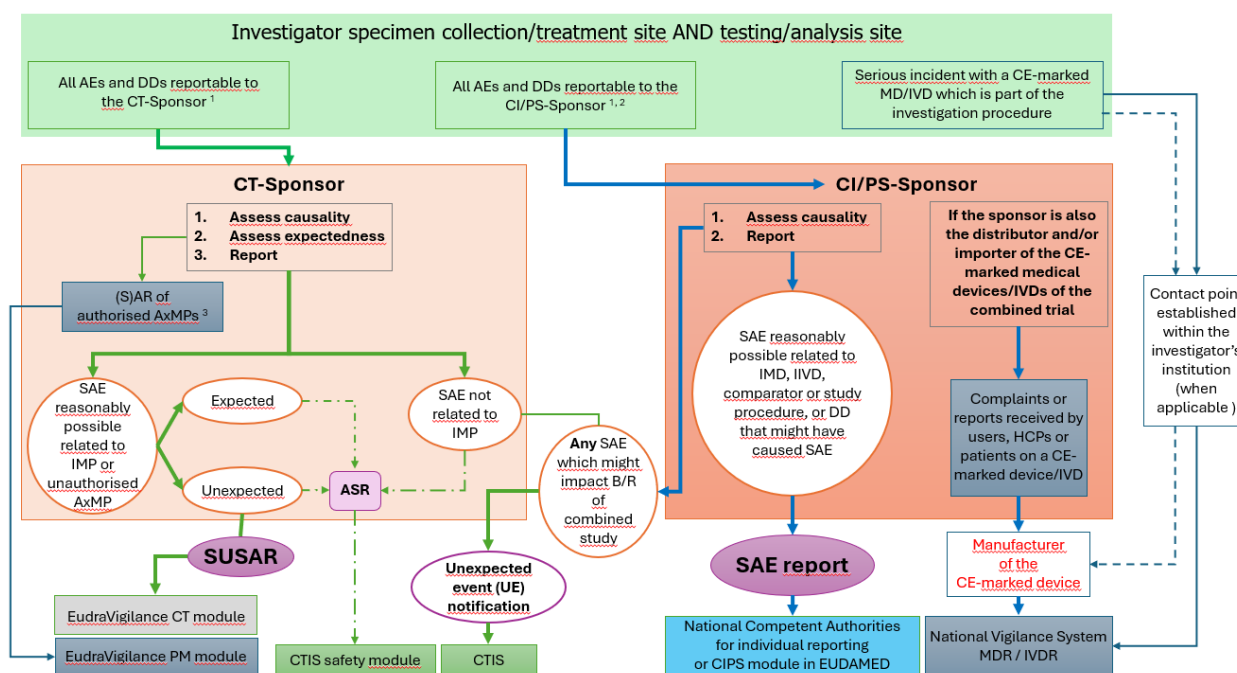
Other communication:

- Single sponsor: follow internal SOPs
- Multiple sponsors: have a communication/responsibility plan within the CT/CI/PS-application (e.g. in the protocol but it can be a separate document) in which the responsibilities and timelines (if applicable) per sponsor are described.

NOTE: If applicable, consider reporting obligations of site-specific plans such as the Safety Management Plan.

Flowcharts for illustration of sponsor reporting obligations in dual sponsorship situations (as an example for multiple sponsorship)

Example 1 - in case there are no separate sites for specimen collection/treatment and testing/analysis:



Notes:

¹ The sponsors can decide if the investigator of a specimen collection/treatment and testing/analysis site reports the reportable AEs and DDs to the separate sponsors or to 1 sponsor who then forwards a subset to the other sponsor. This has to be defined within the protocol.

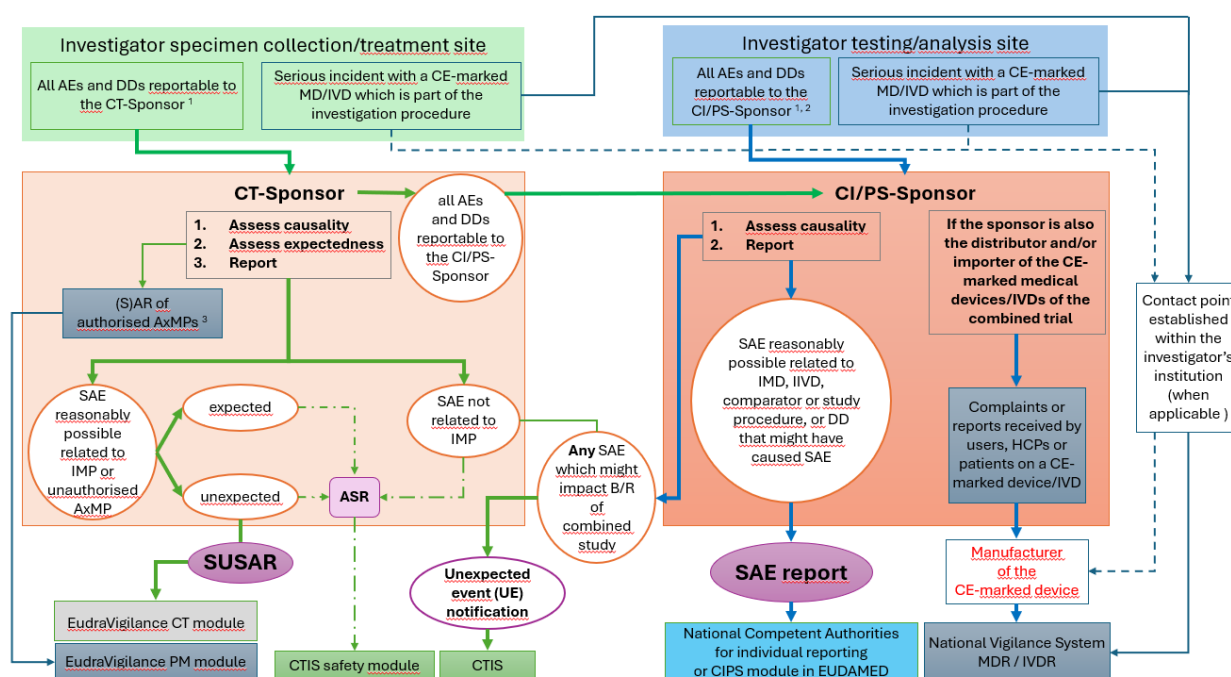
² This includes AEs and DDs related to a comparator or a CE-marked device which is part of the investigational/study procedure if there is a causal, (or reasonably possible causal) relationship to the device, the comparator or the investigational/study procedure.

³ Adverse Reactions (ARs) concerning concomitant medication should be reported in accordance with pharmacovigilance rules (GVP). The reporting obligations in relation to authorised AxMPs can deviate from this flowchart if described differently in the protocol.

Full blue line: obligatory process

Dashed blue line: encouraged process

Example 2 - in case there are separate sites for specimen collection/treatment and specimen testing/analysis:



Notes:

1: This includes AEs and DDs related to a comparator or a CE marked device which is part of the investigational/study procedure if there is a causal, (or reasonably possible causal) relationship to the device, the comparator or the investigational/study procedure.

2: Adverse Reactions (ARs) concerning concomitant medication should be reported in accordance with pharmacovigilance rules (GVP). The reporting obligations in relation to authorised AxMPs can deviate from this flowchart if described differently in the protocol.

³ Adverse Reactions (ARs) concerning concomitant medication should be reported in accordance with pharmacovigilance rules (GVP). The reporting obligations in relation to authorised AxMPs can deviate from this flowchart if described differently in the protocol.

Full blue line: obligatory process

Dashed blue line: encouraged process

7.3 Safety reporting timelines for a combined study

For practical reasons active decisions on reporting timelines were taken that deviate from current guidance in order to facilitate the safety reporting in combined trials. On all other aspects the guidance documents listed in section 3 remain valid and should be followed just as for non-combined studies.

Safety Reporting requirements/timelines for investigators

Type of event	Reporting obligations of investigators
AE unrelated to the IMP, IMD, IIVD, comparator or investigational/study procedure experienced by study participants	All need to be recorded, unless the protocol provides differently
AE reasonably possibly causally related to the IMP (=AR), IMD, IIVD, comparator or investigational/study procedure	All recorded unless the protocol provides differently, but reporting to the sponsor(s) only if specified in the protocol and according to timelines specified in the protocol
SAE stemming from the CT (including unauthorized or authorized modified AxMPs), the CI or the PS and DD regardless of causality	All recorded and reported to sponsor(s) without undue delay but not later than within 24 hours, unless the protocol provides differently . In case of a co-sponsor scenario the protocol(s) should clearly define which kind of SAE should be reported to which sponsor(s).
AR related to authorized unmodified AxMPs	All ARs have to be recorded and reported in line with GVP VI

Safety reporting timelines for the sponsor(s)

Type of event	Reporting obligations of sponsors	Reporting route
AE related to the IMP, IMD, IIVD, comparator or investigational/study procedure	All AEs recorded by investigators should be included in the Summary of Results (SoR) and if applicable the Clinical Study Report (CSR), the final Performance Study Report (PSR) and/or Clinical Investigation Report (CIR).	SoR/CSR → CTIS ----- Final PSR → NCA (in future EU-DAMED)

	Alternatively, a combined results document is possible. When separate SoRs/CSR/PSR/CIR are provided only AEs in relation to the specific legal framework should be included.	----- CIR → NCA (in future EUDAMED)
SAE reasonably possibly related to any MD, any IVD or CI/PS procedure, as well as reportable DDs	SAE reasonably possibly related to IMD, IIVD, comparator or investigational/study procedure, as well as reportable DDs, should be reported to all NCAs responsible for MDR/IVDR within 7 calendar days after awareness by sponsor(s). Although MDCG guidance suggests that events that 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 [the event], should be reported within 2 days, reporting timelines are harmonized in line with reporting timelines for fatal or life-threatening SUSARs as defined in the CTR. The MDCG 2020-10 and MDCG 2024-4 guidance and accompanying templates should be used for this reporting (see Annexes). Note: SAE stemming from the CT, the CI or the PS and DD regardless of causality, which potentially affect the B/R of the combined study should be notified <u>within 15 calendar days</u> after awareness by the sponsor(s) via	NCAs

	CTIS as an unexpected event (see below: Overview of timelines for safety notifications according to CTR).	
SUSAR (= suspected unexpected serious adverse reaction)	(a) Reporting in the case of fatal or life-threatening SUSAR, as soon as possible and not later than 7 days after the sponsor became aware of the reaction; (b) Reporting in the case of non-fatal or non-life-threatening SUSAR, not later than 15 days after the sponsor became aware of the reaction; (c) in the case of a SUSAR which was initially considered to be non-fatal or non-life threatening, but which turns out to be fatal or life-threatening, as soon as possible and not later than 7 days after the sponsor became aware of the reaction being fatal or life-threatening	EVCTM
SARs only related to unauthorized or modified authorised AxMPs	The sponsor responsible for IMP(s) or unauthorized or modified authorised AxMPs should submit fatal or life-threatening SUSARs as soon as possible and in any event not later than 7 calendar days after awareness. In case of non-fatal or non-life-threatening SUSARs submission is required not later than 15 days after the sponsor became aware of the reaction.	EVCTM

(S)ARs related to authorized unmodified AxMPs⁸	SARs are reported within 15 days after awareness by the sponsor (unless reporting responsibility has been defined differently in the protocol). Non-serious ARs are reported within 90 days after awareness by the sponsor. The sponsor should report these (S)ARs as solicited reports (report from studies, type 'others'). It is recommended to indicate the protocol code and EU CT number in the case narrative and to state that the medicinal product was not used as an IMP but as an AxMP or concomitant medication. The MAH of the relevant product can access reports related to their products via EVPM. See GVP VI and Q&A.	EVPM
ASR (DSUR)	ASRs should be submitted within 60 days after the ASR data lock point (DLP) . For more detailed information see section "How to approach an SAE in a combined	CTIS

⁸ Only events, which are suspected to be causally related exclusively to the AxMPs, must be reported by investigators. If there is a suspicion of an adverse event involving the IMP, or if an adverse event due to an interaction of AxMP with the IMP cannot be ruled out, the reporting rules for the IMP will apply. In the latter cases both the IMP and AxMP should be entered in the Individual Case Safety Report (ICSR) as suspect or interacting. Different reporting obligations apply for authorised and unauthorised AxMPs, which are explained in EudraLex Volume 10 -Clinical trials guidelines: Auxiliary Medicinal Products in Clinical Trials.

	study - the Sponsor(s)'s point of view" Note: The obligation to provide ASRs starts at the date of the sponsor's first authorisation to conduct the first clinical trial with the IMP in any country – world-wide, which is the development international birth date (DIBD). Submission of an ASR is only required if there also is a CT ongoing of that sponsor with that IMP in the EU/EEA. The DLP for an ASR reporting period is the last day of the yearly reporting period.	
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Overview of timelines for safety notifications according to CTR:

CTIS offers a functionality for sponsors to provide information outside of CT applications. Safety related information can be conveyed via the following notification types:

- UE notification:** The sponsor(s) shall notify the Member States concerned of a CT, through the CTIS, of all unexpected events which affect the benefit-risk balance of the clinical trial but are not SUSARs. This should be done without undue delay but **no later than 15 days** from the date the sponsor(s) became aware of this event.
- Urgent safety measure (USM) notification:** Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor(s) and the investigator shall take appropriate urgent safety measures to protect the study participants. The sponsor(s) shall notify the Member States concerned of a CT, through the CTIS, of the event and the measures taken without undue delay but **no later than 7 days** from the date the measures have been taken. More information can be found in chapter 8.
- TH notification:** Temporary halt (TH) of a clinical trial means an interruption of the conduct of a clinical trial by the sponsor(s), that is not provided for in the protocol, with the intention to resume the trial. This notification shall be made **within 15 days** from the temporary halt of the clinical trial in all Member States concerned and shall include the reasons for this action.

- **EarT notification:** Early termination (EarT) of a clinical trial means the premature end of a clinical trial for any reason before the conditions specified in the protocol are met. This notification shall be made without undue delay but **no later than 15 days** of the date of the early termination. The early termination should not be notified in CTIS before the last-patient-last-visit has occurred.
In the case of early termination of the clinical trial for reasons not affecting the benefit-risk balance, the sponsor(s) shall notify each Member State concerned of the CT via CTIS of the reasons for such action and, when appropriate, follow-up measures for the participants.

Reporting timelines in case of a co-sponsor scenario

In case of a combined study with more than one sponsor it is essential to clearly define reporting obligations for the different sponsors within the protocol in a communication plan.

8. Implementation of urgent safety measures

Implementation of an urgent safety measure outside a substantial modification is not foreseen in the MDR and IVDR (or the MDCG guidance) at this timepoint. The need for such a procedure is acknowledged. However, as this requires a change in the legislations, this has to be dealt with outside the COMBINE project.

NCAAs can take corrective measures via MDR Art. 76 / IVDR Art. 72, after a complete assessment.

9. How to handle safety reporting in specific cases?

9.1. Performance studies involving companion diagnostics using only left-over samples

As PSs involving CDx using only left-over samples only need to be notified to the NCA, it is up to each NCA to define the safety reporting requirements for these studies (=national competence).

It should be noted that there cannot be any adverse events (to patients) when leftover specimens are tested with the 'new' device. However, there could be some operator related adverse events for the individual performing the testing with the new device. These are the only types of AEs that could occur for CDx studies using only left-over specimens.

DDs could be detected and should be reported as per national requirements (see Annex).

The COMBINE project group 2 has performed a survey on national safety reporting requirements. The results of this survey are published in Annexes 1 and 2 of this guidance.

9.2. Clinical investigations, not performed pursuant to any of the purposes listed in MDR Article 62(1)

According to MDR Art. 82 (1), these CIs do not need to comply with MDR Art. 80, which is the article on safety reporting requirements. MDR Art. 82 (2) states that each MS shall define any additional requirements for such investigations, as appropriate for each Member State concerned. It is thus up to each MS to define safety reporting requirements for these studies (=national competence). The COMBINE project group 2 has performed a survey on national safety reporting requirements. The results of this survey are published together with this guidance.

10. Abbreviations

AE – Adverse Event

AR – Adverse Reaction

ADR – Adverse Drug Reaction

ASR (DSUR) – Annual Safety Report (Development Safety Update Report)

AxMP – auxiliary medicinal product

NCA – National Competent Authority

CDx – Companion Diagnostic

CI – Clinical Investigation

CIEPSE – MDCG Clinical Investigation and Evaluation, Performance Studies and Evaluation Working Group

CIP – Clinical Investigation Plan-~~protocol~~

CIR – Clinical Investigation Report

CPSP – Clinical Performance Study Plan

CSR – Clinical Study Report

CT – Clinical Trial

CTIS – Clinical Trials Information System

CTR – regulation (EU) 536/2014 on clinical trials on medicinal products for human use

DD – Device Deficiency

EarT – Early Termination

EVCTM – EudraVigilance Clinical Trial Module

EVPM – EudraVigilance Postmarketing Module

GVP – Guideline on good pharmacovigilance practices

HCP – Health Care Professional

ICF – Informed Consent Form

IFU – instructions for use

IIVD – Investigational IVD, see definition IVDR Art 2(45)

IMD – Investigational Medical Device, see MDR Art 2(46)

IME – Important Medical Event

IMP – Investigational Medicinal Product

IVD – *In Vitro* Diagnostic medical device

IVDR – regulation (EU) 2017/746 on *in vitro* diagnostic medical devices

MAH – Marketing authorisation holder

MDCG – Medical Device Coordination Group

MDR – regulation (EU) 2017/745 on medical devices

NCA – National Competent Authority

PBRER (PSUR)–Periodic Benefit-Risk Evaluation Report (Periodic Safety Update Rep.)

PI – Principal Investigator

PM – Post Marketing

PS – Performance Study

PSR – Final Performance Study Report

PSUR – Periodic Safety Update Report

SAE – Serious Adverse Event

SADE - Serious Adverse Device Effect

SADR – Serious Adverse Drug Reaction

SAR – Serious Adverse Reaction

SOPs - Standard Operating Procedures

SoR – Summary of Results (CTR)

SUSAR – Suspected Unexpected Serious Adverse Reaction

TH – Temporary Halt

UE – unexpected event

USM – Urgent safety measure

Annexes

Annex 1

National requirements MDR

Clinical investigations with a medical device: Guidance on safety reporting requirements and sub- mission routes in EU/EEA/EFTA-member states and Türkiye as an EU partner country

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Introduction

Since the module for safety reporting in a clinical investigation in the electronic system referred to in MDR Article 73 (Eudamed) is not yet available safety reporting in clinical investigations needs to be done directly to the competent authorities of the EU/EEA/EFTA member states and Türkiye where a clinical investigation is conducted. In COMBINE project 2, the stakeholders indicated through a survey and multiple workshops that the different reporting routes over the various member states (email, submission platform...) are unclear and would best be communicated in a clear and structured manner.

In addition, the stakeholders indicated that it is unclear to them what the safety reporting requirements across the various member states are. As some member states require more safety reporting, on the one hand by requesting other documents than only the MDCG 2020-10/2 excel, on the other hand by requesting reporting for clinical investigations for which the MDR doesn't require safety reporting.

Scope

This guidance provides the national safety reporting requirements and national safety reporting routes for clinical investigations with medical devices across various EU-Member states and some EU partner countries per type of clinical investigation. Reporting requirements on interruption of the trial and early termination are not included in this guidance as they are not exclusively safety related. For guidance on the reporting requirements for these notifications please consult the MDR, the MS-specific legislation and guidance, and contact the applicable competent authorities when necessary.

The countries that participated in this guidance are: Austria, Belgium, Bulgaria, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden and Türkiye.

Abbreviations

SAE: serious adverse event

MDR: medical device regulation (EU) 2017/745

DD: device deficiency

CA: competent authority

MS: member state

CI: clinical investigation with a medical device

NA: not applicable

Definitions

See MDR and MDCG endorsed documents and other guidance (mainly [MDCG-2020-10: Safety reporting in clinical investigations of medical devices under the MDR](#))

MDR links

[Regulation \(EU\) 2017/745 on medical devices \(MDR\)](#)

[Guidance - MDCG endorsed documents and other guidance - European Commission](#)

MDR legislation on safety reporting according to the type of clinical investigation

The MDR distinguishes different types of clinical investigations. Some clinical investigations “don’t fall under the MDR” but may be regulated in national legislations in the country where the investigation is conducted. Table 1 lists the different types of clinical investigations as identified in the MDR and provides reference to the applicable MDR articles on safety reporting for each type of clinical investigation. The next sections of this guidance provide national safety reporting routes and requirements per type of clinical investigation as identified in Table 1.

Table 1: Legislation and applicable guidance on safety reporting according to the type of clinical investigation

MDR	Type of clinical investigation	MDR on safety reporting and applicable guidance
Article 62(1)	Clinical investigations carried out as part of the clinical evaluation for conformity assessment purposes, for one or more of the following purposes: a) to establish and verify that, under normal conditions of use, a device is designed, manufactured and packaged in such a way that it is suitable for one or more of the specific purposes listed in point (1) of Article 2, and achieves the	Article 80(2-3) MDCG guidance 2020-10

	performance intended as specified by its manufacturer; b) to establish and verify the clinical benefits of a device as specified by its manufacturer; c) to establish and verify the clinical safety of the device and to determine any undesirable side-effects, under normal conditions of use of the device, and assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the device.	
Article 74(1)	Clinical investigations conducted to further assess, within the scope of its intended purpose, a device which already bears the CE marking in accordance with Article 20(1), ('PMCF investigation'), and where the investigation would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive or burdensome.	- Article 80(5) => MDR chapter VII: Post-market surveillance, vigilance and market surveillance AND - Article 80(6): Notwithstanding §5, this Article shall apply where a "causal relationship" between the serious adverse event and the preceding investigational procedure has been established. For more information see MDCG guidance 2020-10
Article 74(2)	Clinical investigations conducted to assess, outside the scope of its intended purpose, a device which already bears the CE marking in accordance with Article 20(1).	Article 80 (2-3) MDCG guidance 2020-10
Article 82	Clinical investigations not performed for any of the purposes listed in Article 62(1): each Member State shall define any additional requirements for such investigations, as appropriate for each Member State concerned.	No provisions in MDR. Safety reporting may be regulated in national legislations in the country where the investigation is conducted.
	PMCF investigation without additional burdensome and/or invasive procedures	MDR chapter VII: Post-market surveillance, vigilance and market surveillance

Reporting requirements per country per type of clinical investigation

1. Clinical investigations that follow MDR article 62(1) (CIs carried out as part of the clinical - evaluation for conformity assessment purposes) or MDR article 74(2) (CIs with a CE marked device used out of intended purpose)

1.1. Reporting according to the MDCG guidance 2020-10

All countries mentioned in the scope, follow the MDCG guidance 2020-10 and the use of the associated excel, for CIs that follow MDR article 62(1) or MDR article 74(2).

The excel may be submitted as a hard copy or electronically via e-mail, a submission platform or by regular mail or in person, depending on the country.

Table 2: Links to e-mail addresses, submission platforms and associated guidelines per country for reporting according to the MDCG guidance 2020-10 for CIs that follow MDR article 62(1) or MDR article 74(2)

Country	Via e-mail address	Guideline	Via submission platform	Via another route
Austria	clinicaltrials@basg.gv.at	Link to webpage on safety reporting on www.basg.gv.at	-	-
Belgium	ct.rd@fagg-afmps.be	Link to guideline on www.fagg-afmps.be	• CESP • Link to guideline on submission via CESP	-
Bulgaria	devices-CIPS@bda.bg	-	-	By regular mail (or in person): BULGARIAN DRUG AGENCY, 8 Damyan Gruev Str., Sofia 1303, BULGARIA
Cyprus	cymda@mphs.moh.gov.cy	-	-	-

Czechia	khzp@sukl.gov.cz	Link to webpage on safety reporting on sukl.gov.cz	Link to RZPRO platform and to its guideline	
Denmark	med-udstyr@dkma.dk	Link to webpage on safety reporting on laegemiddelstyrelsen.dk	-	-
Estonia	mso@ravimiamet.ee	-	-	-
Finland	laitetutkimus@fimea.fi cie@fimea.fi	Link to webpage on safety reporting on fimea.fi	-	-
France	ec.dm-cos@ansm.sante.fr	Link to webpage on safety reporting on ansm.sante.fr	-	-
Germany	mpsae@bfarm.de	Link to webpage on safety reporting on www.bfarm.de	-	-
Greece	protokollo@eof.gr	-	-	-
Iceland	ima@ima.is	Link to webpage on safety reporting on www.lyfjastofnun.is	-	-
Ireland	devices@hpra.ie	Link to guideline on hpra.ie	-	-
Italy	dqfdm@posta-cert.sanita.itacert	-	-	-
Latvia	info@zva.gov.lv	Link to webpage on safety reporting on www.zva.gov.lv	-	-
Lithuania	vaspvt@vaspvt.gov.lt	-	-	-
Luxembourg	meddevices.vigilance@ms.etat.lu	Link to webpage on safety reporting on santesecu.public.lu	-	-
Netherlands	-	-	• Research Portal	-

			• Link to guideline on ccmo.nl	
Norway	kki@noma.no	Link to webpage on safety reporting on www.dmp.no	-	-
Poland	incydenty@urpl.gov.pl	-	-	-
Portugal	-	-	Link to RNEC platform and to its guideline	-
Romania	dscdm@anm.ro	Link to webpage on safety reporting on www.anm.ro	-	-
Slovak Republic	clinical-investigation-md@sukl.sk	-	-	-
Slovenia	info@jazmp.si	Link to webpage on safety reporting on www.jazmp.si	-	-
Spain	psinvclinic@aemps.es	Link to webpage on safety reporting on www.aemps.gob.es	-	-
Sweden	-	-	• Link to submission platform • Link to webpage on safety reporting on www.lakemedelsverket.se	-
Türkiye	md.ci@titck.gov.tr	Link to webpage on safety reporting on www.titck.gov.tr	Link to submission platform	-

1.2. Periodic Safety report

The following table lists the countries that request a periodic safety report and provides more information on templates, guidelines and submission routes for CIs that follow MDR article 62(1) or MDR article 74(2).

Table 3: Periodicity and links to submission platforms and associated guidelines per country for periodic safety reporting for CIs that follow MDR article 62(1) or MDR article 74(2) in those countries that request this additional type of reporting.

Country	Periodicity	Template	Submission route (email address or platform)
Czechia	Fixed timepoint: not later than the 31st of January	No, see ISO 14155, annex D	khzp@sukl.gov.cz or Link to RZPRO platform and to its guideline
Denmark	Annual Please note that an annual safety report is solely required as a condition in the authorisation for class III / implants.	No	med-udstyr@dkma.dk
Germany	Quarterly	Link to webpage on safety reporting on www.bfarm.de	mpsae@bfarm.de
Italy	Upon request	No	dqfdm@postacert.sanita.it
Ireland	Upon request, risk based, when requested typically annual	No	devices@hpra.ie
Latvia	Annual	No	info@zva.gov.lv Link to guideline on www.zva.gov.lv
Luxembourg	Annual	• Link to template • Link to guideline	contact@cner.lu

Türkiye	Annual	Link to template	Link to submission platform
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1.3. Other type of safety reporting

The following table lists the countries that require **another, additional type** of safety reporting for CIs that follow MDR article 62(1) or MDR article 74(2).

Table 4: Periodicity and links to templates, submission platforms and associated guidelines per country for other type of safety reporting for CIs that follow MDR article 62(1) or MDR article 74(2) in those countries that request this additional type of reporting.

Country	Template	Periodicity	Email address	Guideline
Austria	Link to where template can be found	The requirement to notify the Austrian competent authority on safety related events, interruption of the trial and early termination.	clinicaltrials@basg.gv.at	-
Finland	No	Medical Devices Act (719/2021) includes safety reporting obligation for investigators: "The investigator shall inform the sponsor without delay of incidents and other adverse events referred to in Article 80(2) of the MD Regulation and in Article 76(2) of the IVD Regulation."	laitetutkimus@fimea.fi	-
Germany	Link to template	Immediately (within 24 hours) after the event occurs for a participating subject from Germany.	mpsae@bfarm.de	Link to guideline on www.bfarm.de
Netherlands	No	Requirement for line listings. The periodicity depends on the risks associated with the clinical investigation.	-	Link to guideline on ccmo.nl

Türkiye	Link to template	Without delay of incidents and other adverse events referred to in Article 80(2) of the MDR	md.ci@titck.gov.tr	- Link to guideline on www.titck.gov.tr
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2. Clinical investigations that follow MDR article 74(1) (PMCF investigations with additional invasive or burdensome procedures)

2.1. Reporting according to the MDCG guidance 2020-10

For post-market clinical follow up (PMCF) investigations of CE-marked devices 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, the MDCG guidance 2020-10 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.

Table 5: Links to e-mail addresses, submission platforms and associated guidelines per country for reporting according to the MDCG guidance 2020-10 for CIs that follow MDR article 74(1).

Country	Via e-mail address	Guideline	Via submission platform	Via another route
Austria	clinicaltrials@basg.gv.at	Link to webpage on safety reporting on www.basg.gv.at	-	-
Belgium	ct.rd@fagg-afmps.be	Link to guideline on www.fagg-afmps.be	• CESP • Link to guideline on submission via CESP	For reporting according to Articles 87 to 92: vigilance.meddev@fagg-afmps.be
Bulgaria	medical@bda.bg	-	-	-
Cyprus	cymda@mphs.moh.gov.cy	-	-	-

Czechia	khzp@sukl.gov.cz	Link to webpage on safety reporting on sukl.gov.cz	Link to RZPRO platform and to its guideline	
Denmark	med-udstyr@dkma.dk	Link to webpage on safety reporting in PMCF investigations on laege-middelstyrelsen.dk	-	-
Estonia	mso@ravimiamet.ee	-	-	-
Finland	laitetutkimus@fimea.fi cie@fimea.fi	Link to webpage on safety reporting on fimea.fi	-	-
France	ec.dm-cos@ansm.sante.fr if established causality between SAE and the additional invasive/burdensome procedures	Link to webpage on safety reporting on ansm.sante.fr	-	For reporting according to Articles 87 to 90: materiovigilance
Germany	mpsae@bfarm.de	Link to webpage on safety reporting on www.bfarm.de	-	-
Greece	protokollo@eof.gr	-	-	-
Iceland	ima@ima.is	Link to webpage on safety reporting on www.lyfjastofnun.is	-	-
Ireland	devices@hpra.ie	Link to guideline on hpra.ie	-	SAE or MIR as per MDCG 2020-10
Italy	dqfdm@posta-cert.sanita.itacert	-	-	-

Latvia	info@zva.gov.lv	Link to webpage on safety reporting on www.zva.gov.lv	-	-
Lithuania	vaspvt@vaspvt.gov.lt	-	-	-
Luxembourg	meddevices.vigilance@ms.etat.lu	Link to webpage on safety reporting on santesecu.public.lu	-	-
Netherlands	-	-	• Research Portal • Link to guideline on ccmo.nl	-
Norway	kki@noma.no	Link to webpage on safety reporting on www.dmp.no	-	-
Poland	incydenty@urpl.gov.pl	-	-	-
Portugal	-	-	Link to RNEC platform and to its guideline	-
Romania	dscdm@anm.ro mdevice@anm.ro	Link to webpage on safety reporting on www.anm.ro	-	Link to webpage on safety reporting under vigilance on www.anm.ro
Slovak Republic	clinical-investigation-md@sukl.sk	-	-	-
Slovenia	info@jazmp.si	Link to webpage on safety reporting on www.jazmp.si	-	-
Spain	psinvclinic@aemps.es	Link to webpage on safety reporting on www.aemps.gob.es	-	-

Sweden	-	Link to webpage on safety reporting on <u>www.lakemedelsverket.se</u>	Link to submission platform	• Link to webpage on reporting of incidents on <u>www.lakemedelsverket.se</u> • https://www.lakemedelsverket.se/sv/medicinteknik/folj-upp-anvandning/rapportering-av-allvarliga-tillbud#hmain-body6 • https://www.lakemedelsverket.se/en/permission-application-proval-and-control/clinical-trials/medical-devices/clinical-investigation-of-medical-device/safety-reporting
Türkiye	md.ci@titck.gov.tr	Link to webpage on safety reporting on <u>www.titck.gov.tr</u>	Link to submission platform	-

2.2. Periodic Safety report

The following table lists the countries that request a periodic safety report and provides more information on templates, guidelines and submission routes for CIs that follow MDR article 74(1).

Table 6: Periodicity and links to submission platforms and associated guidelines per country for periodic safety reporting for CIs that follow MDR article 74(1) in those countries that request this additional type of reporting.

Country	Periodicity	Template	Submission route (email address or platform)
Ireland	Upon request, risk based, when requested typically annual	No	devices@hpra.ie
Luxembourg	Annual	Link to template Link to guideline	contact@cner.lu
Türkiye	Annual	Link to webpage on safety reporting on www.titck.gov.tr	Link to submission platform

2.3. Other type of safety reporting

The following table lists the countries that require an additional type of safety reporting for CIs that follow MDR article 74(1).

Table 7: Links to e-mail addresses, submission platforms and associated guidelines per country

Country	Template	Periodicity	Email address	Guideline
Türkiye	Link to template	Without delay of incidents and other adverse events referred to in Article 80(2) of the MDR	md.ci@titck.gov.tr	Link to guideline on www.titck.gov.tr

3. Clinical investigations that follow MDR article 82 (National legislation might apply)

No provisions for safety reporting are listed in the MDR and according to the MDCG guidelines for CIs that follow MDR article 82. Safety reporting may be regulated in **national legislations** in the country where the investigation is conducted.

3.1. Reporting according to the MDCG guidance 2020-10

Table 8: Links to e-mail addresses, submission platforms and associated guidelines per country for reporting according to the MDCG guidance 2020-10 for CIs that follow MDR article 82

Country	Via e-mail address	Guideline	Via submission platform	Via another route or comment
Austria	clinicaltrials@basg.gv.at	Link to webpage on safety reporting on www.basg.gv.at	-	-
Belgium	ct.rd@fagg-afmps.be	Link to guideline on www.fagg-afmps.be	• CESP • Link to guideline on submission via CESP	For reporting according to Articles 87 to 92: vigilance.meddev@fagg-afmps.be
Bulgaria	devices-CIPS@bda.bg medical@bda.bg	-	-	By regular mail (or in person): BULGARIAN DRUG AGENCY, 8 Damyan Gruev Str., Sofia 1303, BULGARIA
Cyprus	cymda@mphs.moh.gov.cy	-	-	-
Czechia	khzp@sukl.gov.cz	Link to ISZP platform and to its guideline		
Denmark	Serious incidents for CE marked medical	Link to webpage on incident reporting on	-	-

	devices are to be reported to med-udstyr@dkma.dk using usual vigilance reporting	laegemiddelstyrelsen.dk		
Estonia	mso@ravimiamet.ee	-	-	-
Finland	laitetutkimus@fimea.fi cie@fimea.fi	Link to webpage on safety reporting on fimea.fi	-	-
France	ec.dm-cos@ansm.sante.fr	Link to webpage on safety reporting on ansm.sante.fr	-	For reporting according to Articles 87 to 90: materiovigilance
Germany	mpsae@bfarm.de	Link to webpage on safety reporting on www.bfarm.de	-	-
Greece	protokollo@eof.gr	-	-	-
Iceland	ima@ima.is	Link to webpage on safety reporting on www.lyfjastofnun.is	-	-
Ireland	devices@hpra.ie	Link to guideline on hpra.ie	-	-
Italy	-	-	-	-
Latvia	-	-	-	-
Lithuania	vaspvt@vaspvt.gov.lt	-	-	-
Luxembourg	meddevices.vigilance@ms.etat.lu	Link to webpage on safety reporting on santesecu.public.lu	-	-
Netherlands	-	-	• Research Portal • Link to guideline on ccmo.nl	Timelines: <7 days fatal or life threatening and <15 other SAE.

Norway	kki@noma.no	Link to webpage on safety reporting on <u>www.dmp.no</u>	-	-
Poland	incydenty@urpl.gov.pl	-	-	-
Portugal	-	-	Link to RNEC platform and to its guideline	-
Romania	dscdm@anm.ro mdevice@anm.ro	Link to webpage on safety reporting on <u>www.anm.ro</u>	-	Link to webpage on safety reporting under vigilance on <u>www.anm.ro</u>
Slovak Republic	-	-	-	-
Slovenia	info@jazmp.si	Link to webpage on safety reporting on <u>www.jazmp.si</u>	-	-
Spain	-	-	-	-
Sweden	-	Link to webpage on safety reporting on <u>www.lakemedelsverket.se</u>	Link to submission platform	• Link to webpage on reporting of incidents on <u>www.lakemedelsverket.se</u> • https://www.lakemedelsverket.se/sv/medicinteknik/folj-upp-anvandning/rapportering-av-all-varliga-tillbud#hmain-body6 • https://www.lakemedelsverket.se/en/permission-

				approval-and-control/clinical-trials/medical-devices/clinical-investigation-of-medical-device/safety-reporting
Türkiye	md.ci@titck.gov.tr	Link to webpage on safety reporting on www.titck.gov.tr	Link to submission platform	-

3.2. Periodic Safety report

Table 9: Periodicity and links to submission platforms and associated guidelines per country for periodic safety reporting for CIs that follow MDR article 82 in those countries that request this additional type of reporting.

Country	Periodicity	Clarification	Email address	Submission platform and comment
Czechia	Fixed timepoints (for example 30/06)	not later than the 31st of January	khzp@sukl.gov.cz	Link to ISZP platform and to its guideline. See also ISO 14155, Annex D
Ireland	Other	Upon request, risk based, typically when requested it is annual	devices@hpra.ie	-
Türkiye	Annual	Link to guideline on www.titck.gov.tr	md.ci@titck.gov.tr	• Link to submission platform

3.3. Other type of safety reporting

The following table lists the countries that require **another, additional type** of safety reporting for CIs that follow MDR article 82.

Table 10: Periodicity and links to templates, submission platforms and associated guidelines per country for other typen of safety reporting for CIs that follow MDR article 82 in those countries that request this additional type of reporting.

Country	Clarification	Guideline
Netherlands	We do often require line listings. The periodicity depends on the risks associated with the clinical investigation.	Link to guideline on ccmo.nl
Finland	For CI conducted under Article 82, Medical Devices Act, Section 16 states "If a clinical investigation is also carried out outside the European Union or the European Economic Area, the sponsor shall submit, without delay, information to the Finnish Medicines Agency on the death of a subject or on a serious injury to a subject in connection with the investigation and, every three months, a summary of incidents under Article 80(2) which have occurred outside the European Union or the European Economic Area."	-
Türkiye	Without delay of incidents and other adverse events referred to in Article 80(2) of the MDR	Link to guideline on www.titck.gov.tr

4. National legislation rules for safety reporting in types of clinical investigations that are not mentioned in the MDR, or do you have other national guidelines or requirements for safety reporting for clinical investigations

No other national legislation rules or requirements for safety reporting were reported by the countries that participated in this survey.

Annex 2

National requirements IVDR

Performance studies with an *in vitro* diagnostic device: Guidance on safety reporting requirements and submission routes in EU/EEA/EFTA-member states and Türkiye as an EU partner country

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Introduction

Since the module for safety reporting in a performance study in the electronic system referred to in IVDR Article 69 (Eudamed) is not yet available, safety reporting in performance studies needs to be done directly to the competent authorities of the EU/EEA/EFTA member states and Türkiye where a performance study is conducted. In COMBINE project 2, the stakeholders indicated through a survey and multiple workshops that the different reporting routes over the various member states (email, submission platform...) are unclear and would best be communicated in a clear and structured manner.

In addition, the stakeholders indicated that it is unclear to them what the safety reporting requirements across the various member states are. As some member states require more safety reporting, on the one hand by requesting other documents than only the MDCG 2024-4/appendix excel, on the other hand by requesting reporting for performance studies for which the IVDR doesn't require safety reporting.

Scope

This guidance provides the national safety reporting requirements and national safety reporting routes for performance studies with IVD devices across various EU-Member states and some EU partner countries per type of performance study. Reporting requirements on interruption of the study and early termination are not included in this guidance as they are not exclusively safety related. For guidance on the reporting requirements for these notifications please consult the IVDR, the MS-specific legislation and guidance, and contact the applicable competent authorities when necessary.

The countries that participated in this guidance are: Austria, Belgium, Bulgaria, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden and Türkiye.

Abbreviations

SAE: serious adverse event

IVDR: *in vitro* diagnostic regulation (EU) 2017/746

DD: device deficiency

CA: competent authority

MS: member state

PS: performance study with an IVD

NA: not applicable

Definitions

See IVDR and MDCG endorsed documents and other guidance (mainly [MDCG-2024-4: Safety reporting in performance studies of *in vitro* diagnostic medical devices under the IVDR](#))

IVDR links

[Regulation \(EU\) 2017/746 on IVD medical devices \(IVDR\)](#)

[Guidance - MDCG endorsed documents and other guidance - European Commission](#)

IVDR legislation on safety reporting according to the type of performance study

The IVDR distinguishes different types of performance studies. Some performance studies “don’t fall under the IVDR” but may be regulated in national legislations in the country where the study is conducted. Table 1 lists the different types of performance studies as identified in the IVDR and provides reference to the applicable IVDR articles on safety reporting for each type of performance study. The next sections of this guidance provide national safety reporting routes and requirements per type of performance study as identified in **Table 11**.

Table 11: Legislation and applicable guidance on safety reporting according to the type of performance study

IVDR	Type of performance study	IVDR on safety reporting and applicable guidance
Article 58(1)	Performance study a) in which surgically invasive sample-taking is done only for the purpose of the performance study; b) that is an interventional clinical performance study as defined in point (46) of Article 2; or c) where the conduct of the study involves additional invasive procedures or other risks for the subjects of the studies	Article 76(2-3) MDCG guidance 2024-4
Article 58(2)	Performance study involving companion diagnostics.	Article 76(2-3) MDCG guidance 2024-4

Article 70(1)	Performance study conducted to further assess, within the scope of its intended purpose, a device which already bears the CE marking in accordance with Article 18(1) (' PMPF study '), and where the performance study would involve submitting subjects to procedures additional to those performed under the normal conditions of use of the device and those additional procedures are invasive or burdensome .	- Article 76(5) => IVDR chapter VII: Post-market surveillance, vigilance and market surveillance AND - Article 76(6): Notwithstanding paragraph 5, this Article shall apply where a causal relationship between the serious adverse event and the preceding performance study has been established. For more information see MDCG guidance 2024-4
Article 70(2)	Performance study conducted to assess, outside the scope of its intended purpose , a device which already bears the CE marking in accordance with Article 18(1).	Article 76(2-3) MDCG guidance 2024-4
	Performance study involving companion diagnostics using only left-over samples.	No provisions on safety reporting in the PS according to the IVDR. However, safety reporting may be regulated by national legislation in the country where the study is conducted.
	PMPF study without additional burdensome and/or invasive procedures	No provisions on safety reporting in the PS according to the IVDR. However, safety reporting may be regulated by national legislation in the country where the study is conducted. IVDR chapter VII: Post-market surveillance, vigilance and market surveillance.
	Performance study with an in-house IVD referred to in IVDR Article 5(5).	Provided that the device complies with IVDR Article 5(5) and that the study is conducted to further assess the device <u>within the scope</u> of its intended purpose (Cf. Q9 in MDCG 2025-5 (Q&A on PS)), there are no provisions on safety reporting in the PS according to the IVDR. However, safety reporting may be regulated

		by national legislation in the country where the study is conducted. Otherwise, the study could be subject to application or notification according to art. 58 or 70, and if so, the provisions on safety reporting would apply.
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Reporting requirements per country per type of performance study

5. Performance studies that follow

* IVDR article 58(1) or

* IVDR article 58(2) (PSs involving CDx not using only left-over samples)

5.1. Reporting according to the MDCG guidance 2024-4

All countries mentioned in the scope follow the MDCG guidance 2024-4 and the use of the associated excel, for PSs that follow IVDR article 58(1) or IVDR article 58(2).

The excel may be submitted as a hard copy or electronically via e-mail, a submission platform or by regular mail or in person, depending on the country.

Table 12: Links to e-mail addresses, submission platforms and associated guidelines per country for reporting according to the MDCG guidance 2024-4 for PSs that follow IVDR article 58(1) or IVDR article 58(2)

Country	Via e-mail address	Guideline	Via submission platform	Via another route
Austria	clinicaltrials@basg.gv.at	Link to webpage on safety reporting on www.basg.gv.at	-	-
Belgium	ct.rd@fagg-afmps.be	Link to guideline on www.fagg-afmps.be	• CESP • Link to guideline on submission via CESP	-
Bulgaria	devices-CIPS@bda.bg	-	-	By regular mail (or in person): BULGARIAN DRUG AGENCY,

				8 Damyan Gruev Str., Sofia 1303, BULGARIA
Cyprus	cymda@mphs.moh.gov.cy	-	-	-
Czechia	khzp@sukl.gov.cz	Link to webpage on safety reporting on sukl.gov.cz	Link to RZPRO platform and to its guideline	
Denmark	med-udstyr@dkma.dk	Link to webpage on safety reporting on laegemiddelstyrelsen.dk	-	-
Estonia	mso@ravimiamet.ee	-	-	-
Finland	laitetutkimus@fimea.fi cie@fimea.fi	Link to webpage on safety reporting on fimea.fi	-	-
France	ec.dm-cos@ansm.sante.fr	Link to webpage on safety reporting on ansm.sante.fr	-	-
Germany	mpsae@bfarm.de	Link to webpage on safety reporting on www.bfarm.de	-	-
Greece	protokollo@eof.gr	-	-	-
Iceland	ima@ima.is	Link to webpage on safety reporting on www.lyfjastofnun.is	-	-
Ireland	devices@hpra.ie	Link to guideline on hpra.ie	-	-
Italy	dqfdm@posta-cert.sanita.itacert	-	-	-
Latvia	info@zva.gov.lv	Link to webpage on safety reporting on www.zva.gov.lv	-	-

Lithuania	vaspvt@vaspvt.gov.lt	-	-	-
Luxembourg	meddevices.vigilance@ms.etat.lu	Link to webpage on safety reporting on santesecu.public.lu	-	-
Netherlands	-	-	• Research Portal • Link to guideline on ccmo.nl	-
Norway	kki@noma.no	Link to webpage on safety reporting on www.dmp.no	-	-
Poland	incydenty@urpl.gov.pl	-	-	-
Portugal	-	-	Link to RNEC platform and to its guideline	-
Romania	dscdm@anm.ro	Link to webpage on safety reporting on www.anm.ro	-	-
Slovak Republic	clinical-investigation-md@sukl.sk	-	-	-
Slovenia	info@jazmp.si	Link to webpage on safety reporting on www.jazmp.si	-	-
Spain	psinvclinic@aemps.es	Link to webpage on safety reporting on www.aemps.gob.es	-	-
Sweden	-	-	• Link to submission platform • Link to webpage on safety reporting on www.lakemedelsverket.se	-
Türkiye	md.ci@titck.gov.tr	Link to webpage on safety reporting on www.titck.gov.tr	Link to submission platform	-

5.2. Periodic Safety report

The following table lists the countries that request a periodic safety report and provides more information on templates, guidelines and submission routes for PSs that follow IVDR article 58(1) or IVDR article 58(2).

Table 13: Periodicity and links to submission platforms and associated guidelines per country for periodic safety reporting for PSs that follow IVDR article 58(1) or IVDR article 58(2) in those countries that request this additional type of reporting.

Country	Periodicity	Template	Submission route (email address or platform)
Czechia	Fixed timepoint: not later than the 31st of January	No	khzp@sukl.gov.cz or Link to RZPRO platform and to its guideline
Germany	Quarterly	Link to webpage on safety reporting on www.bfarm.de	mpsae@bfarm.de
Ireland	Upon request, risk based, when requested typically annual	No	devices@hpra.ie
Latvia	Annual	No	info@zva.gov.lv Link to guideline on www.zva.gov.lv
Luxembourg	Annual	Link to template Link to guideline	contact@cner.lu
Türkiye	Annual	Link to template	Link to submission platform

5.3. Other type of safety reporting

The following table lists the countries that require **another, additional type** of safety reporting for PSs that follow IVDR article 58(1) or IVDR article 58(2).

Table 14: Periodicity and links to templates, submission platforms and associated guidelines per country for other type of safety reporting for PSs that follow IVDR article 58(1) or IVDR article 58(2) in those countries that request this additional type of reporting.

Country	Template	Periodicity	Email address	Guideline
Austria	Link to where template can be found	The requirement to notify the Austrian competent authority on safety related events, interruption of the trial and early termination.	clinicaltrials@basq.gv.at	-
Germany	Link to template	Immediately (within 24 hours) after the event occurs for a participating subject from German trial sites.	mpsae@bfarm.de	Link to guideline on www.bfarm.de
Netherlands	No	Requirement for line listings. The periodicity depends on the risks associated with the performance study.	-	Link to guideline on ccmo.nl
Türkiye	Link to template	Without delay of incidents and other adverse events referred to in Article 76(2) of the IVDR	md.ci@titck.gov.tr	Link to guideline on www.titck.gov.tr

6. Performance studies that follow IVDR article 70(2) (Performance study conducted to assess, outside the scope of its intended purpose, a device which already bears the CE marking)

IVDR Art 70(2): Where a performance study is to be conducted to assess, outside the scope of its intended purpose, a device which already bears the CE marking in accordance with Article 18(1), Articles 58 to 77 shall apply.

6.1. Reporting according to the MDCG guidance 2024-4

Table 15: Links to e-mail addresses, submission platforms and associated guidelines per country for reporting according to the MDCG guidance 2024-4 for PSs that follow IVDR article 70(2).

Country	Via e-mail address	Guideline	Via submission platform	Via another route
Austria	clinicaltrials@basg.gv.at	Link to webpage on safety reporting on www.basg.gv.at	-	-
Belgium	ct.rd@fagg-afmps.be	Link to guideline on www.fagg-afmps.be	• CESP • Link to guideline on submission via CESP	-
Bulgaria	devices-CIPS@bda.bg	-	-	By regular mail (or in person): BULGARIAN DRUG AGENCY, 8 Damyan Gruev Str., Sofia 1303, BULGARIA
Cyprus	cymda@mphs.moh.gov.cy	-	-	-
Czechia	khzp@sukl.gov.cz	Link to webpage on safety reporting on sukl.gov.cz	Link to RZPRO platform and to its guideline	-
Denmark	med-udstyr@dkma.dk	-	-	-
Estonia	mso@ravim-iamet.ee	-	-	-
Finland	laitetutkimus@fimea.fi cie@fimea.fi	-	-	-

France	ec.dm-cos@ansm.sante.fr	Link to webpage on safety reporting on ansm.sante.fr	-	-
Germany	mpsae@bfarm.de	Link to webpage on safety reporting on www.bfarm.de	-	-
Greece	protokollo@eof.gr	-	-	-
Iceland	ima@ima.is	Link to webpage on safety reporting on www.lyfjastofnun.is	-	-
Ireland	devices@hpra.ie	Link to guideline on hpra.ie	-	-
Italy	dgfdm@posta-cert.sanita.it	-	-	-
Latvia	info@zva.gov.lv	Link to webpage on safety reporting on www.zva.gov.lv	-	-
Lithuania	vaspvt@vaspvt.gov.lt	-	-	-
Luxembourg	meddevices.vigilance@ms.etat.lu	Link to webpage on safety reporting on santesecu.public.lu	-	-
Netherlands	-	-	• Link to guideline on ccmo.nl • Link to the Research Portal	-
Norway	kki@noma.no	Link to webpage on safety reporting on www.dmp.no	-	-
Poland	incydenty@urpl.gov.pl	-	-	-
Portugal	clinicalstudies.devices@infarmed.pt	-	-	-
Romania	dscdm@anm.ro	Link to webpage on safety reporting on www.anm.ro	-	-

Slovak Republic	clinical-investigation-md@sukl.sk	-	-	-
Slovenia	info@jazmp.si	Link to webpage on safety reporting on www.jazmp.si	-	-
Spain	psinvclinic@aemps.es	-	-	-
Sweden	-	-	• Link to submission platform • Link to webpage on safety reporting on www.lakemedelsverket.se	-
Türkiye	md.ci@titck.gov.tr	Link to webpage on safety reporting on www.titck.gov.tr	Link to submission platform	-

6.2. Periodic Safety report

The following table lists the countries that request a periodic safety report and provides more information on templates, guidelines and submission routes for PSs that follow IVDR article 70(2).

Table 16: Periodicity and links to submission platforms and associated guidelines per country for periodic safety reporting for PSs that follow IVDR article 70(2) in those countries that request this additional type of reporting.

Country	Periodicity	Template	Submission route (email address or platform)
Czechia	Fixed timepoint: not later than the 31st of January	No template	khzp@sukl.gov.cz or Link to RZPRO platform and to its guideline
Germany	Quarterly	Link to webpage on safety reporting on www.bfarm.de	mpsae@bfarm.de

Iceland	-	-	ima@ima.is Link to webpage on safety reporting on www.lyfjastofnun.is
Ireland	Upon request, risk based, when requested typically annual	No template	devices@hpra.ie
Latvia	Annual	No template	info@zva.gov.lv Link to guideline on www.zva.gov.lv
Luxembourg	Annual	Link to template Link to guideline	contact@cner.lu
Türkiye	Annual	Link to guideline	Link to submission platform

6.3. Other type of safety reporting

The following table lists the countries that require **another, additional type** of safety reporting for PSs that follow IVDR article 70(2).

Table 7: Periodicity and links to templates, submission platforms and associated guidelines per country for other type of safety reporting for PSs that follow IVDR article 70(2) in those countries that request this additional type of reporting.

Country	Template	Periodicity	Email address	Guideline
Austria	Link to where template can be found	The requirement to notify the Austrian competent authority on safety related events, interruption of the trial and early termination.	clinicaltrials@basg.gv.at	-
Germany	Link to template	Immediately (within 24 hours) after the event occurs for a participating subject from German trial sites.	mpsae@bfarm.de	Link to guideline on www.bfarm.de
Netherlands	No template	Requirement for line listings. The periodicity depends on the risks	-	Link to guideline on ccmo.nl

		associated with the performance study.		
Türkiye	Link to template	Without delay of incidents and other adverse events referred to in Article 76(2) of the IVDR	md.ci@titck.gov.tr	Link to guideline on www.titck.gov.tr

7. Performance studies that follow IVDR article 70(1) (PMPF study involving additional invasive or burdensome procedures)

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 be reported 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 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.

7.1. Reporting according to the MDCG guidance 2024-4

Table 8: Links to e-mail addresses, submission platforms and associated guidelines per country for reporting according to the MDCG guidance 2024-4 for PSs that follow IVDR article 70(1).

Country	Via e-mail address	Guideline	Via submission platform	Via another route
Austria	clinicaltrials@basg.gv.at	Link to webpage on safety reporting on www.basg.gv.at	-	-

Belgium	ct.rd@fagg-afmps.be	Link to guideline on www.fagg-afmps.be	• CESP • Link to guideline on submission via CESP	For reporting according to Articles 82 to 86: vigilance.meddev@fagg-afmps.be
Bulgaria	devices-CIPS@bda.bg medical@bda.bg	-	-	By regular mail (or in person): BULGARIAN DRUG AGENCY, 8 Damyan Gruev Str., Sofia 1303, BULGARIA
Cyprus	cymda@mphs.moh.gov.cy	-	-	-
Czechia	khzp@sukl.gov.cz	Link to webpage on safety reporting on sukl.gov.cz	Link to RZPRO platform and to its guideline	-
Denmark	med-udstyr@dkma.dk	-	-	-
Estonia	mso@ravim-iamet.ee	-	-	-
Finland	laitetutkimus@fimea.fi cie@fimea.fi	-	-	-
France	ec.dm-cos@ansm.sante.fr	Link to webpage on safety reporting on ansm.sante.fr	-	-
Germany	mpsae@bfarm.de	Link to webpage on safety reporting on www.bfarm.de	-	-

Greece	protokollo@eof.gr	-	-	-
Iceland	ima@ima.is	Link to webpage on safety reporting on www.lyfjastofnun.is	-	-
Ireland	devices@hpra.ie	Link to guideline on hpra.ie	-	-
Italy	dgfdm@posta-cert.sanita.it	-	-	-
Latvia	info@zva.gov.lv	Link to webpage on safety reporting on www.zva.gov.lv	-	-
Lithuania	vaspvt@vaspvt.gov.lt	-	-	-
Luxembourg	meddevices.vigilance@ms.etat.lu	Link to webpage on safety reporting on santesecu.public.lu	-	-
Netherlands	-	-	• Link to guideline on ccmo.nl • Link to the Research Portal	-
Norway	kki@noma.no	Link to webpage on safety reporting on www.dmp.no	-	-
Poland	incydenty@urpl.gov.pl	-	-	-
Portugal	clinicalstudies.devices@infarmed.pt	-	-	-
Romania	dscdm@anm.ro	Link to webpage on safety reporting on www.anm.ro	-	-
Slovak Republic	clinical-investigation-md@sukl.sk	-	-	-
Slovenia	info@jazmp.si	Link to webpage on safety reporting on www.jazmp.si	-	-

Spain	psinvclinic@aemps.es	-	-	-
Sweden	-	-	• Link to submission platform • Link to webpage on safety reporting on www.lake-medelsverket.se	• Link to submission platform for serious incidents • Link to webpage on vigilance reporting on www.lake-medelsverket.se
Türkiye	md.ci@titck.gov.tr	Link to webpage on safety reporting on www.titck.gov.tr	Link to submission platform	-

7.2. Periodic Safety report

The following table lists the countries that request a periodic safety report and provides more information on templates, guidelines and submission routes for PSs that follow IVDR article 70(1).

Table 9: Periodicity and links to submission platforms and associated guidelines per country for periodic safety reporting for PSs that follow IVDR article 70(1) in those countries that request this additional type of reporting.

Country	Periodicity	Template	Submission route (email address or platform)
Czechia	Fixed timepoint: not later than the 31st of January	No template	khzp@sukl.gov.cz or Link to RZPRO platform and to its guideline
Germany	Quarterly	Link to webpage on safety reporting on www.bfarm.de	mpsae@bfarm.de
Iceland	-	-	• ima@ima.is

			• Link to webpage on safety reporting on www.lyfjastofnun.is
Ireland	Upon request, risk based, typically when requested it is annual.		devices@hpra.ie
Latvia	Annual	No template	info@zva.gov.lv Link to guideline on www.zva.gov.lv
Luxembourg	Annual	• Link to template • Link to guideline on template	contact@cner.lu
Türkiye	Annual	Link to guideline	-Link to submission platform

7.3. Other type of safety reporting

The following table lists the countries that require **another, additional type** of safety reporting for PSs that follow IVDR article 70(1).

Table 10: Periodicity and links to templates, submission platforms and associated guidelines per country for other type of safety reporting for PSs that follow IVDR article 70(1) in those countries that request this additional type of reporting.

Country	Template	Periodicity	Email address	Guideline
Austria	Link to where template can be found	The requirement to notify the Austrian competent authority on safety related events, interruption of the trial and early termination.	clinicaltrials@basg.gv.at	-
Germany	Link to template	Immediately (within 24 hours) after the event occurs for a participating subject from German trial sites.	mpsae@bfarm.de	Link to guideline on www.bfarm.de
Netherlands	No template	Requirement for line listings. The periodicity depends on the risks associated with the performance study.	-	Link to guideline on ccmo.nl

Türkiye	Link to template	Without delay of incidents and other adverse events referred to in Article 76(2) of the IVDR	md.ci@titck.gov.tr	Link to guideline on www.titck.gov.tr
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8. National legislation rules for safety reporting in performance studies with companion diagnostics using only leftover samples

8.1. Reporting according to the MDCG guidance 2024-4

Table 11: Links to e-mail addresses, submission platforms and associated guidelines per country for reporting according to the MDCG guidance 2024-4 for PSs with companion diagnostics using only leftover samples.

Country	Via e-mail address	Guideline	Via submission platform	Via another route or comment
Austria	clinicaltrials@basg.gv.at	Link to webpage on safety reporting on www.basg.gv.at	-	-
Belgium	ct.rd@fagg-afmps.be	Link to guideline on www.fagg-afmps.be	• CESP • Link to guideline on submission via CESP	-
Bulgaria	devices-CIPS@bda.bg	-	-	By regular mail (or in person): BULGARIAN DRUG AGENCY, 8 Damyan Gruev Str., Sofia 1303, BULGARIA
Cyprus	cymda@mphs.moh.gov.cy	-	-	-

Czechia	khzp@sukl.gov.cz	Link to webpage on safety reporting on sukl.gov.cz	Link to RZPRO platform and to its guideline	-
Denmark	No need to report to the nCA			
Estonia	mso@ravim-iamet.ee	-	-	-
Finland	No need to report to the nCA			
France	No need to report to the nCA			
Germany	mpsae@bfarm.de	Link to webpage on safety reporting on www.bfarm.de	-	-
Greece	protokollo@eof.gr	-	-	-
Iceland	ima@ima.is	Link to webpage on safety reporting on www.lyfjastofnun.is	-	-
Ireland	No need to report to the nCA			
Italy	No need to report to the nCA			
Latvia	info@zva.gov.lv	Link to webpage on safety reporting on www.zva.gov.lv	-	-
Lithuania	vaspvt@vaspvt.gov.lt	-	-	-
Luxembourg	meddevices.vigilance@ms.etat.lu	Link to webpage on safety reporting on santesecu.public.lu	-	-
Netherlands	No need to report to the nCA			
Norway	No need to report to the nCA			
Poland	incydenty@urpl.gov.pl	-	-	-
Portugal	clinicalstudies.devices@infarmed.pt	-	-	-
Romania	dscdm@anm.ro	Link to webpage on safety reporting on www.anm.ro	-	

Slovak Republic	clinical-investigation-md@sukl.sk	-	-	-
Slovenia	info@jazmp.si	Link to webpage on safety reporting on www.jazmp.si	-	-
Spain	psinvclinic@aemps.es	-	-	-
Sweden	-	-	• Link to submission platform • Link to webpage on safety reporting on www.lakemedelsverket.se	
Türkiye	md.ci@titck.gov.tr	Link to webpage on safety reporting on www.titck.gov.tr	Link to submission platform	-

8.2. Periodic Safety report

Table 12: Periodicity and links to submission platforms and associated guidelines per country for periodic safety reporting for PSs with companion diagnostics using only leftover samples in those countries that request this additional type of reporting.

Country	Periodicity	Clarification	Email address	Submission platform and comment
Czechia	Fixed timepoints (for example 30/06)	not later than the 31st of January	khzp@sukl.gov.cz	Link to ISZP platform and to its guideline. See also ISO 14155, Annex D
Ireland	Other	Upon request, risk based, typically when requested it is annual	devices@hpra.ie	
Türkiye	Annual	Link to guideline	md.ci@titck.gov.tr	Link to submission platform

8.3. Other type of safety reporting

The following table lists the countries that require **another, additional type** of safety reporting for PSs with companion diagnostics using only leftover samples.

Table 13: Periodicity and links to templates, submission platforms and associated guidelines per country for other typen of safety reporting for PSs with companion diagnostics using only leftover samples in those countries that request this additional type of reporting.

Country	Template	Periodicity	Email address	Guideline
Austria	Link to where template can be found	The requirement to notify the Austrian competent authority on safety related events, interruption of the trial and early termination.	clinicaltrials@basq.gv.at	-
Germany	Link to template	Immediately (within 24 hours) after the event occurs for a participating subject from German trial sites.	mpsae@bfarm.de	Link to guideline on www.bfarm.de

9. National legislation rules for safety reporting in types of performance studies for which no safety reporting requirements are mentioned in the IVDR or other national guidelines or requirements for safety reporting in performance studies

Country	Guideline
Luxembourg	Link to webpage on safety reporting on santesecu.public.lu
Türkiye	Link to webpage on safety reporting on www.titck.gov.tr

Annex 3

Example: Case description (common for both coding systems)

A patient in a clinical trial for the treatment of therapy-resistant hypertension receives an antihypertensive medicinal product and simultaneously an implantable medical device for the stimulation of baroreceptors (single arm). The patient reports dizziness and the device indicates a malfunction. The overstimulating device was surgically replaced and the patient recovered.

Explanation to IMDRF codes

MedDRA-based LL		IMDRF Based LL		
Case ID	2026-001	Case ID	2026-001	2026-001
Patient ID	P-0145	Patient ID	P-0145	P-0145
Age / Sex	62 / m	Age / Sex	62 / m	62 / m
Study ID	HTN-STUDY-03	Study ID	HTN-STUDY-03	HTN-STUDY-03
Reaction Term (MedDRA PT)	Dizziness	Date of procedure/First use	23-11-2025	23-11-2025
Seriousness	Yes (medical significant)	Onset Date	14-01-2026	14-01-2026
Outcome	Recovering	Stop Date	16-01-2026	Not applicable
Onset Date	14-01-2026	SAE or DD	SAE	DD
Stop Date	16-01-2026	Classification of event	Medical or surgical intervention	Not applicable
Relatedness (Investigator)	Possibly related	Device Problem (if applicable) (IMDRF Annex A)	A07, A0713, A071302	A07, A0713, A071302
Drug Suspect	Investigational Product A	Clinical signs/symptoms (IMDRF Annex E)	E0112	E0112
Dose	20 mg daily	Clinical impact (IMDRF Annex F)	F08, F15, F1905	F08, F15, F1905
Action Taken	Dose interrupted	Action/treatment/patient outcome	Component replaced	Component replaced
		Relatedness (Investigator) to device	Possible	Not applicable
		Relatedness (Investigator) to procedure	Not related	Not applicable
Relatedness (Sponsor)	Not related	Relatedness (Sponsor) to device	Causal	Not applicable
		Relatedness (Sponsor) to procedure	Not related	Not applicable

		Unanticipated SADE?	No	Not applicable
		Investigation arm	Not applicable	Not applicable
		Event status (resolved, resolved with sequelae, ongoing, death)	resolved	Not applicable
A07 (MedDRA:10083688:Device electrical/electronic failure) A0713 (MedDRA:10075322:Device inappropriate shock delivery) A071302 (Inappropriate/Inadequate Shock/Stimulation)				
E0112 (MedDRA:10013573:Dizziness)				
F08 (Hospitalization or Prolonged Hospitalization) F15 (Recognized Device or Procedural Complication) F1905 (Device Revision or Replacement)				