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The Danish Medicines Agency's guidance on risk-based recording and reporting of adverse events in clinical trials on medicinal products under Regulation (EU) no. 536/2014

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1. Introduction

The recording and reporting of adverse events is a critical process for safeguarding the safety of participants in a clinical trial and essential for ensuring the evidence and accuracy of a medicinal product's safety profile. However, it is acknowledged that the collection and reporting of adverse events can be resource-consuming for both the investigator and sponsor and therefore should be risk-adjusted based on the added value gained from collecting the adverse event data.

Detailed recording of adverse events is particularly important for medicinal products that are not yet authorised, and where the data on the medicinal product's safety profile are insufficient. In contrast, clinical trials involving well-established authorised medicinal products contribute less with new significant safety data.

Article 41(2) of the legislation on clinical trials with medicinal products, regulation (EU) No 536/2014 of 16 April 2014 (CTR)[1] allows adaptation of adverse event management[2] in relation to the individual protocol:

REGULATION (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use:

CHAPTER VII, Article 41(2):
"The investigator shall record and document all adverse events, unless the protocol provides differently. The investigator shall report to the sponsor all serious adverse events occurring to subjects treated by him or her in the clinical trial, unless the protocol provides differently.
The investigator shall report serious adverse events to the sponsor without undue delay but not later than within 24 hours of obtaining knowledge of the events, unless, for certain serious adverse events, the protocol provides that no immediate reporting is required. Where relevant, the investigator shall send a follow-up report to the sponsor to allow the sponsor to assess whether the serious adverse event has an impact on the benefit-risk balance of the clinical trial."

In practice, this means that the clinical trial adverse event management can be adapted based on the trial's specific design and purpose. Risk adaptation of adverse event management must be solid justified within the protocol with patient safety and the integrity of trial data remaining as the top priorities.

This guidance describes the requirements and processes needed for implementing risk-adapted adverse event management.

In the case of clinical trials serving a regulatory purpose (e.g. an indication extension or marketing authorisation), reference is also made to the *ICH guideline E19 on a selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials*[3].

[1] More information about the clinical trials regulation is provided on the website of the Danish Medicines Agency.
[2] The term 'adverse event management' will be used in this guidance document as a collective term for recording and reporting of adverse events.
[3] ICH guideline E19 on a selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials is available on the European Medicines Agency's website.

For general considerations on the risk assessment of clinical trials, please refer to the *Risk proportionate approaches in clinical trials - Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (25 April 2017)*[4].

2. Requirements in relation to risk adaptation in adverse event management

Sponsors intending to apply any risk adaptation in adverse event management in clinical trials should pay attention to the following:

1. Any risk-adapted adverse event management must be justified in relation to the specific trial's purpose, design and risk assessment. The protocol must include a clear justification along with a detailed description of the risk-based approaches, including a description of the processes in place for adverse event management. Guidance on these areas is given in the following sections:
   - Process for assessing adverse events in a clinical trial (section 3)
   - Risk assessment of a clinical trial (section 4)
   - Risk-adapted adverse event management in a clinical trial (section 5)

2. The sponsor must establish whether the medicinal products included in a clinical trial are subject to stricter national reporting requirements and/or additional monitoring in the EU. Risk adaptation is usually not possible for authorised medicinal products subject to stricter reporting requirements or additional monitoring. In case of risk-adapted adverse event management, the sponsor must confirm in the protocol that the medicinal products in a clinical trial are not subject to stricter national reporting requirements in the concerned Member States involved in the clinical trial or additional monitoring in the EU. The medicinal products subject to stricter reporting requirements in Denmark is available in the list published by the Danish Medicines Agency. The list of medicines under additional monitoring in the EU is available on the European Medicines Agency's website.

3. Risk-adapted adverse event management may only be implemented in relation to the recording and reporting of adverse events and adverse reactions from investigator to sponsor. For information about the sponsor's reporting obligations, reference is made to the requirements of the CTR[5].

4. Clinical trials investigating diseases with high morbidity or mortality may have primary or secondary efficacy endpoints that fall under the definition of a suspected unexpected serious adverse reaction (SUSAR). In such trials, according to CTR Annex III, section 2.5 point (21), it may be justified to designate specific serious events as disease-related and exempt them from SUSAR obligations. This in order to avoid systematic unblinding and to maintain the integrity of the trial data. In such cases, a Data Safety Monitoring Board (DSMB) should be established to monitor unblinded data. If a DSMB is not established, it must be justified how continuous safety monitoring is ensured in some other way. It may also be justified to exempt the same serious events from immediate reporting by the investigator to the sponsor. However, this requires an alternative procedure to ensure that the DSMB has continuous access to complete safety data.

[4] Risk proportionate approaches in clinical trials - Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (25 April 2017) is available at EudraLex - Volume 10 - Clinical trials guidelines.

[5] The sponsor's obligations in relation to reporting to the authorities are provided in articles 42 and 43 of CTR 536/2014.

5. The annual safety report (ASR) must describe the risk-adapted approaches under which the ASR has been prepared. The sponsor is obligated to include all serious adverse reactions (SARs) and all suspected unexpected serious adverse reactions (SUSARs) in the ASR. If there are exemptions to immediate reporting of serious adverse events to the Sponsor, it is important to note that all registered serious adverse events must still be reported to the sponsor, in a timely manner, for the sponsor to include all the registered serious events in the ASR. The protocol must also state if a single safety report is submitted for all investigational medicinal products used in the clinical trial, see article 43(2) of the CTR.

6. Adverse events exempted from recording are not expected to be documented elsewhere. However, the investigator remains responsible for ensuring that the trial participants' medical records are continuously updated with clinically relevant information for healthcare professionals who are otherwise involved in the patients' present or future care and treatment. During GCP-inspections particular attention may be given to how medical records entries are handled.

The protocol template published by the Danish Medicines Agency can be used to prepare the protocol. The template describes the particulars to be included in the protocol for compliance with the CTR.

3. Process for assessing adverse events in a clinical trial

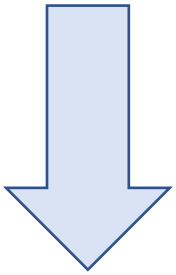
It is essential for the safety of trial participants and the data integrity, that the sponsor, investigator and other relevant staff understand and have received training in the processes for assessment, recording and reporting of adverse events. The processes for assessment of adverse events and the definitions of relevant terms must therefore be sufficiently described in the protocol.

The process for assessing whether it is a serious adverse event (SAE), a serious adverse reaction (SAR) or a suspected unexpected serious adverse reaction (SUSAR) is described below (Figure 1). You will find the full flow chart for assessment of all events in Appendix 1 and a description of relevant terms in Appendix 2.

These processes must be in place irrespective of whether risk-adapted recording and reporting of adverse events is implemented.

Figure 1. Assessment of serious adverse events and adverse reactions.

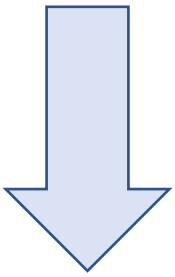
SAE (serious adverse event)	A serious adverse event (SAE) means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.



Causality assessment – is the serious adverse event related to the investigational medicinal product?
In determining whether an adverse event is an adverse reaction, consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the investigational medicinal product (IMP) based on an analysis of available evidence.

See the reference provided in Appendix 2 for guidance on the causality assessment

SAR (serious adverse reaction)	A serious adverse reaction (SAR) is an SAE that is assessed to be related to the IMP, i.e. the treatment administered in the clinical trial.



Is the serious adverse reaction expected or unexpected?
The determination of whether an event is expected or unexpected is assessed based on the reference safety information (RSI).

Example: In the case of authorised medicinal products, the RSI is often section 4.8 of the summary of product characteristics (SmPC). Therefore, an adverse reaction appearing in the SmPC section 4.8 is expected, and an adverse reaction not appearing in section 4.8 of the SmPC is unexpected.

SUSAR (suspected unexpected serious adverse reaction)	A suspected **unexpected** serious adverse reaction means a serious adverse reaction, the nature, severity or outcome of which is not consistent with the RSI.
ASR (annual safety report)	Annual safety report: It is expected that any relevant safety information will be described in the annual safety report. The report is expected to include a list of SARs and SUSARs and an assessment of whether these events give rise to updating the protocol. Likewise, the annual safety report is expected to include an assessment of whether the benefit-risk balance is changed or unchanged, meaning if the trial may continue or if a protocol amendment is required for it to continue.

Annual safety reports must be prepared and reported for all trials

Once a year, the sponsor must summarise cumulative safety information in the annual safety report. Based on this report, the safety of the trial is evaluated, including if the benefit-risk balance has changed and whether, on the basis thereof, the trial may continue. The annual safety report ensures the continuous safety assessment and may therefore not be exempted despite any applied risk-adapted adverse events management.

The annual safety report must describe the risk-adapted approaches as provided in the clinical trial protocol, under which the report has been prepared.

4. Risk assessment of a clinical trial

The level needed for adverse event recording and reporting depends on the evidence base of the investigated medicinal product. As mentioned earlier, risk-adapted adverse event management must be justified on the basis of a trial-specific risk assessment.

A risk assessment means the identification of potential risks associated with the concerned trial, based on the safety of the participants, the investigational medicinal product and the trial design and methods. A number of different factors influence the extent to which the safety of the trial participants is affected in the trial, e.g. the status, type and safety profile of the medicinal product, the difference between intervention and normal clinical practice, and the complexity of the trial. The risk assessment and the associated risk categorisation of a trial are described below in Figure 2, points 1-4.

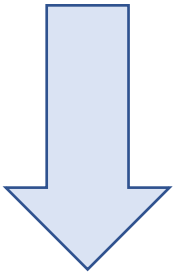
Figure 2. Risk assessment of a trial for the purpose of applying risk-adapted adverse event management.

1) Consider the RISK FACTORS likely to impact the safety of the trial participant

At least the following points must be considered and addressed in a risk assessment:

- Whether the medicinal product is authorised, including the total exposure of the medicine and whether the available safety data of the medicinal product provides sufficient grounds to implement risk-adapted adverse event management.
- The type of medicinal product/intervention (e.g. mechanistic characteristics, pharmaceutical form, route of administration).
- Indication, including the difference between intervention and normal clinical practice.
- Population, including age, gender and other patient characteristics.
- Dose and treatment regimen compared to the authorised dose and treatment regimen described in the product information, including the use of combination therapy or other medicines given concurrently, including an assessment of whether this may lead to serious or more frequent adverse reactions, new adverse reactions or new drug interactions.
- Complexity of the trial design.

See Appendix 3 for more considerations of risk factors likely to impact the safety of trial participants.



2) Assess the RISK LEVEL based on the difference between intervention and normal clinical practice

What is the risk posed to the patient compared to the standard treatment?
What are the risks, and how can they be handled?

INCREASED RISK FOR PATIENTS

"Low-risk" trial = **risk level 1**	**"Medium-risk"** trial = **risk level 2**	**"High-risk"** trial = **risk level 3**
➢ The investigational medicinal product(s) is/are authorised ➢ The intervention is comparable to standard treatment ➢ The intervention and the medicinal product's evidence base and safety profile are robust, also in relation to rare adverse reactions ➢ Expected new signals are minimal Application of risk-adapted adverse event management can generally be justified. See examples in Appendix 4.	➢ The investigational medicinal product(s) are authorised, but are used for an unapproved indication ➢ The intervention is not significantly different from the standard treatment, and the safety profile is expected to be comparable ➢ The safety profile of the medicinal product is robust Application of risk-adapted adverse event management can be justified if based on a trial-specific risk assessment. The risk assessment and justification should address the risk factors listed under point 1) of this figure. See examples in Appendix 4.	➢ Investigational medicinal product or indication is not authorised ➢ The intervention has not been studied before or is significantly different from the standard treatment ➢ The intervention and the safety profile of the medicinal product have not been sufficiently studied, and evidence on the efficacy and safety of the product is insufficient ➢ The investigational medicinal product is authorised but subject to stricter national reporting requirements or additional monitoring. See point 2 in section 2. Thorough adverse event management is needed to safeguard patient safety and to ensure the collection of data on the safety profile of the medicinal product. Full adverse event management is expected, unless adaptation can be justified on robust grounds based on a trial-specific risk assessment. See examples in Appendix 4.

3) Assess if risk-adapted adverse event management may be justified

Based on the above risk assessment, a risk-adapted approach to recording and reporting of adverse events may be possible if sufficiently justified.

Even so, borderline cases may exist, which means that an assessment of the individual protocol and trial design is needed to determine the required level of adverse event management. In borderline cases, variables like the duration of treatment, whether or not a life-threatening disease is involved, knowledge of the product's mechanistic effects, as well as non-clinical signals, along with data from the clinical development and the total exposure of the medicinal product, may determine which approach is justifiable. This must be seen in the context of the robustness of the safety profile, also in relation to rare adverse events.

If there are doubts about whether the evidence base of the product's safety is sufficiently known or whether the intervention may expose the patient to a risk, conservative/full adverse event management must be applied.

See section 5 on risk adaptation in the management of adverse events.

4) Dedicate a section in the protocol specifically to the justification of risk-adapted adverse event management

This justification must at least include the following:

- Risk assessment of the trial and justification of the level of risk chosen for the trial.
- Description of risk-adapted adverse event management, including reasons why certain SAEs are not be recorded or not immediate reported to the sponsor.
- Considerations about the risks associated with the chosen risk-adapted adverse event management:
  - For trial participants?
  - For data integrity?
- How risks in the trial can be prevented and/or reduced?

The extent of the justification depends on the level of risk associated with the trial.

5. Risk-adapted adverse event management in a clinical trial

In general, all adverse events must be recorded and all serious adverse events must be reported to the sponsor, unless the risk-adapted adverse event management is supported by the risk assessment documented in the protocol.

Authorised medicinal products have generated a sufficient evidence base for their use with respect to the populations and indications as described in the SmPC, and the safety of authorised medicinal products is monitored on an ongoing basis (see Appendix 5). In relation to clinical trials with authorised medicinal products, it may therefore be possible to adapt recording and reporting of adverse events proportionate to the risk level of the trial. Conversely, it can usually not be justified to reduce the recording and reporting of adverse events for trials with non-authorised medicinal products.

The protocol must always provide justification for any risk-adapted approach on the basis of a trial-specific risk assessment and if there is a risk of new, more serious or more frequent adverse reactions. Regardless of the selected approach, the investigator must always have the possibility of recording any event and reporting these to the sponsor if the investigator finds this relevant/necessary.

The possibility of applying a risk-adapted approach to the recording and reporting of adverse events and adverse reactions from investigator to sponsor is described below in Table 1 and Tabel 2. SUSARs must always be reported by the sponsor to the EudraVigilance database regardless of the risk-adaptation applied to adverse event management, as stipulated in the CTR[6]. Likewise, the sponsor is required to submit annual safety reports (ASRs) via CTIS[7].

Table 1. Risk-adapted adverse event management based on the level of risk associated with the trial

Risk level:	**Risk level 1 = "Low"**	**Risk level 2 = "Medium"**	**Risk level 3 = "High"**
Recording of adverse events			
Is risk-adaptation for **AE recording possible**?	YES – AE recording can be exempted	YES – AE recording can be exempted	NO[b)] – all AEs must be recorded
Is risk-adaptation for **SAE recording possible**?	YES – SAE recording can be exempted	YES[a)] – SAEs pursuant to a predefined list in the protocol can be exempted from recording	NO[b)] – all SAEs must be recorded
Is risk-adaptation for **SAR recording possible**?	YES – only suspected unexpected serious adverse reactions (SUSARs) must be recorded	YES[a)] – SARs pursuant to a predefined list in the protocol can be exempted from recording	NO[b)] – all SARs must be recorded
Reporting of serious adverse events from investigator to sponsor			
Is risk-adaptation for **SAE reporting to sponsor possible**?	YES – SAE reporting can be exempted	YES[a)] – immediate reporting of recorded SAEs can be exempted, but must be reported to the ASR	NO[b)] – all SAEs must be reported immediately to sponsor
Is risk-adaptation for **SAR reporting to sponsor possible**?	YES – only suspected unexpected serious adverse reactions (SUSARs) must be reported immediately to sponsor	NO[b)] – all recorded SARs must be reported immediately to sponsor	NO[b)] – all SARs must be reported immediately to sponsor
Sponsor's reporting obligations			
SUSAR reporting	SUSARs must always be reported by the sponsor to the EudraVigilance database.		
Annual safety report (ASR)	The ASR must always be submitted by the sponsor via CTIS. See also section 3.		

[a)] Must always be justified based on the trial-specific risk assessment

[b)] Generally not possible, unless robust justification provided

[6] Find more information about reporting to the EudraVigilance database on the website of the Danish Medicines Agency.

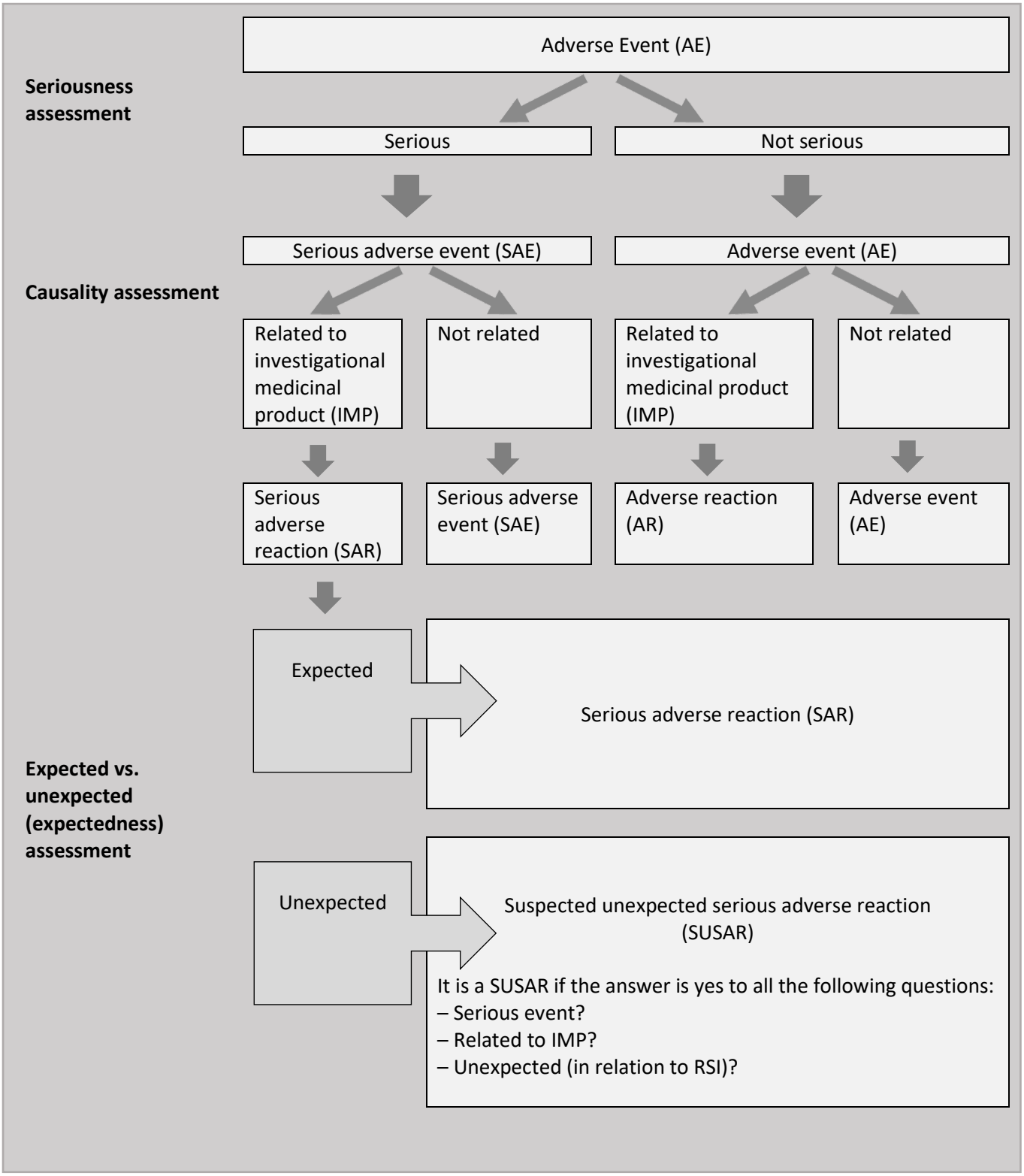
[7] Clinical Trials Information System (https://euclinicaltrials.eu/)

Tabel 2. Description of risk-adapted adverse event management.

Description of risk-adapted adverse event management based on the risk level	
Adverse event management at <u>risk level 1:</u>	The investigator must at least record adverse events satisfying all the following three criteria: 1) The adverse event must be serious (serious adverse event, SAE) 2) The adverse event must be suspected to be related to the investigational medicinal product (serious adverse reaction, SAR) 3) The adverse event must <u>not</u> appear in section 4.8 of the summary of product characteristics. In reality, it is the investigator who must assess expectedness when only suspected unexpected serious adverse reaction (SUSARs) are to be recorded. The investigator must report all recorded adverse reactions (subject to the above requirements) to the sponsor within 24 hours. The investigator must always have the possibility of recording and reporting any event to the sponsor if the investigator finds this relevant/necessary and this must be stated in the protocol.
Adverse event management at <u>risk level 2:</u>	In general, all SAEs must be recorded, but the sponsor may include in the protocol a predefined list of SAEs not to be recorded. This could be SAEs either associated with the investigational medicinal product or an underlying disease. SAEs in this category could be administrative/planned hospitalisation, exacerbation of underlying disease, or in the case of the treatment of intensive-care patients expected to have a critical disease course involving, for example, multiple organ failure. SAEs that are related to the investigational medicinal product (=SARs) and are listed in section 4.8 of the product information (known adverse reactions) may generally be exempted from recording. In case of that other SARs than expected (known adverse reactions, see 4.8 of the product information) will be exempted from recording, this must be further justified. Any SAEs and/or SARs exempted from the recording must always be clearly stated and justified in the protocol. The reporting of SAEs to the sponsor within 24 hours can be omitted, if predefined in the protocol and justified. However, all SAEs recorded and deemed related to the intervention (causal relationship) must be reported immediately to the sponsor. In other words, <u>all recorded SARs</u> must be reported to the sponsor within 24 hours. If SARs are exempted from immediate reporting due to the fact that they are recorded as part of the clinical trial's primary or secondary efficacy endpoints, continuous safety monitoring must be ensured through a DSMB. Please see point 4 in section 2. For SAEs exempted from immediate reporting, it is important to note that all SAEs recorded but not reported immediately, must still be reported to the sponsor no later than before preparation of the ASR, and the specific frequency of reporting must be stated and justified in the protocol. The investigator must always have the possibility of recording and reporting any event to the sponsor if the investigator finds this relevant/necessary and this must be stated in the protocol.
Adverse event management at <u>risk level 3:</u>	It is expected that all AEs/SAEs are recorded, and that all SAEs/SARs are reported to the sponsor within 24 hours. Risk-adaptation is in general not possible, unless the sponsor can provide a robust justification based on a trial-specific risk assessment.

6. Appendix

Appendix 1 – Assessment of events and adverse reactions in a clinical trial



Appendix 2 – Description of selected terms

Adverse event (AE):

Any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

Seriousness criteria:

The event is serious if at least one of the following criteria applies:

- *inpatient hospitalisation or prolongation of existing hospitalisation*
- *results in persistent or significant disability or incapacity*
- *results in a congenital anomaly or birth defect*
- *is life-threatening*
- *results in death*

Serious adverse event (SAE):

Any untoward medical occurrence that at any dose requires inpatient hospitalisation 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.

Causality assessment:

A causality assessment is used to assess if an event is related to investigational medicine/intervention or not. In determining whether an adverse event is an adverse reaction, consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the investigational medicinal product based on an analysis of available evidence.

In the absence of information on causality provided by the reporting investigator, the sponsor shall consult the reporting investigator and encourage him to express an opinion on this issue. The causality assessment given by the investigator shall not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor shall be provided with the report.

The WHO-UMC's method may be used to make the causality assessment:
https://www.who.int/docs/default-source/medicines/pharmacovigilance/whocausality-assessment.pdf

Serious adverse reaction (SAR):

Is an SAE in which the event is assessed to be related (see causality assessment) to the investigational medicine and/or intervention.

Suspected unexpected serious adverse reaction (SUSAR):

A serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information. Whether an incident is unexpected or expected is determined based on the reference safety information.

Reference safety information (RSI):

The determination of whether an event is expected or unexpected is assessed in relation to the reference safety information (RSI). Often, parts of the product information or parts of the Investigator's Brochure (IB) are used as RSI for the investigational medicinal product.

Example:
In the case of authorised medicinal products, the RSI is often a part of the summary of product characteristics (SmPC), i.e. an adverse reaction appearing in the SmPC, often section 4.8, is expected; an adverse reaction not appearing in the product information is unexpected.

Annual safety report (ASR):

Any relevant safety information is expected to be described in the annual safety report. A list of SARs and SUSARs is expected, including an assessment of whether these events give rise to updating the protocol.

The annual safety report must describe the risk-adapted approaches subject to which it has been prepared.

Likewise, the annual safety report is expected to include an assessment of whether the benefit-risk balance has changed or is unchanged, meaning if the trial may continue or if protocol amendments are required for it to continue.

It is possible to submit a single safety report on all investigational medicinal products used in a clinical trial, see article 43(2) of the CT regulation.

Appendix 3 – General considerations about risk factors and risk minimisation measures

The following may be considered in connection with the risk assessment (list is non-exhaustive):

- Does the trial population consist of healthy trial subjects or patients?

- Is the investigational medicinal product authorised, and is it used in compliance with what has been approved and described in the product information? If not, consider the following:
  - *Are there changes to the dosage regime/route of administration?*
  - *Are there changes to the population/indication?*
  - *How will these changes impact the safety of trial participants?*

- What are the known/expected risks, both in relation to the trial design and/or the investigational medicinal product?
  - *Have these risks been addressed in normal clinical practice?*
  - *If the adverse reaction profile of the investigational medicinal product is unknown, which risks are expected based on non-clinical data and/or based on the knowledge from other medicinal products containing the same active substance?*
  - *Is the duration of treatment supported by previous experience?*
  - *Is there a risk of dosing errors?*

- Are there any risks of interactions with other treatments given concurrently that could increase the risk to trial participants?

- Is there a need for further safety monitoring of the trial participant in addition to that provided in standard treatment? This could be additional laboratory tests, ECG, imaging, biopsy, more frequent visits to the doctor.

- Are further risk minimisation measures needed? The following may be considered:
  - *Restrictive inclusion and exclusion criteria, e.g. exclusion of persons with a particular risk due to secondary diseases, resulting from impaired kidney/lung/heart/liver function or the use of certain medicinal products.*
  - *Adjustment of treatment regimen and duration, including sufficient monitoring and facilities, rescue medicine and the presence of trained (emergency) staff when relevant.*
  - *Stopping criteria or (dose) modification of the investigational treatment, e.g. using a protocol-specified treatment algorithm or an independent Data Safety Monitoring Board (DSMB).*
  - *Focused recording of adverse events and adverse reactions, e.g. organ-specific events or events giving cause for specific concern; reporting to the sponsor and authorities must comply with the legislative requirements at all times.*
  - *Further safety monitoring, e.g. by way of experts in the disease, in its routine treatment and in the investigational medicinal product/study treatment; an independent DSMB for the assessment of new safety data and benefit-risk balance.*

Appendix 4 – Examples of clinical trials at the different risk levels

Examples "low-risk" trials (risk level 1):

- Low-intervention trials[8]
- Trials with authorised medicinal products involving an approved indication in which the intervention is normal clinical practice.
- Trials with authorised medicinal products involving a well-established off-label indication which is normal clinical practice and supported by published evidence.

Examples of "medium-risk" trials (risk level 2):

- Trials with authorised medicinal products involving an unapproved indication in which the studied indication/population/treatment DOES NOT differ significantly from the authorised indication or normal clinical practice, and where the safety profile is expected to be the same.
- PK/PD trials with data available from other authorised medicinal products in the same pharmacological class.

Examples of "high-risk" trials (risk level 3):

- Trials with non-authorised medicinal products or authorised medicinal products with limited knowledge about adverse reactions[9].
- Trials with authorised medicinal products involving an unapproved indication in which the studied indication differs significantly from the approved one, e.g. another disease area or a special population such as children for which the safety profile of the intervention has not been established despite the status of the medicinal product.
- Trials with combination treatment with two or more medicinal products, posing a risk of drug interactions and where it is not possible to break down the adverse event management on the individual medicinal products.
- Trials with modified medicinal products without a marketing authorisation, for example a new formulation/pharmaceutical form.
- Trials in which the medicinal product is used in combination with medical devices or other medicinal products with an expected synergistic effect (e.g. electroporation).

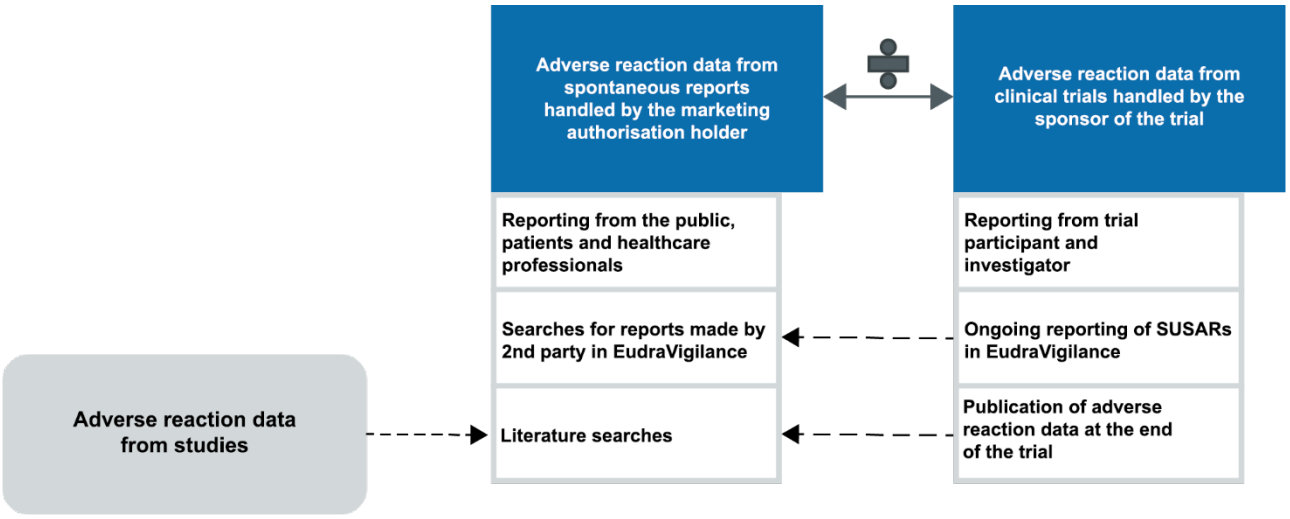
[8] Under article 2(3) of the CTR, a low-intervention clinical trial is a clinical trial which fulfils all the following conditions:
   a. the investigational medicinal products, excluding placebos, are authorised;
   b. according to the protocol of the clinical trial, i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and
   c. the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned;

[9] Including authorised medicinal products subject to additional monitoring and stricter reporting requirements

Appendix 5 – Evidence generation and data sources for authorised medicinal products

Medicinal products used in clinical trials are categorised as investigational medicinal products whether or not they have a marketing authorisation. Consequently, adverse event data collected in a clinical trial are not automatically sent to the marketing authorisation holder. Instead, alternative mechanisms ensure that the marketing authorisation holder can gain a complete overview of emerging safety data. One such mechanism is the sponsor's ongoing reporting of SUSARs to EudraVigilance database which are searchable by the marketing authorisation holder. Another mechanism is the literature searches made by the marketing authorisation holder which aim to identify publications containing safety data related to the concerned medicinal product (Figure 3).

Figure 3 Safety data sources for authorised medicinal products



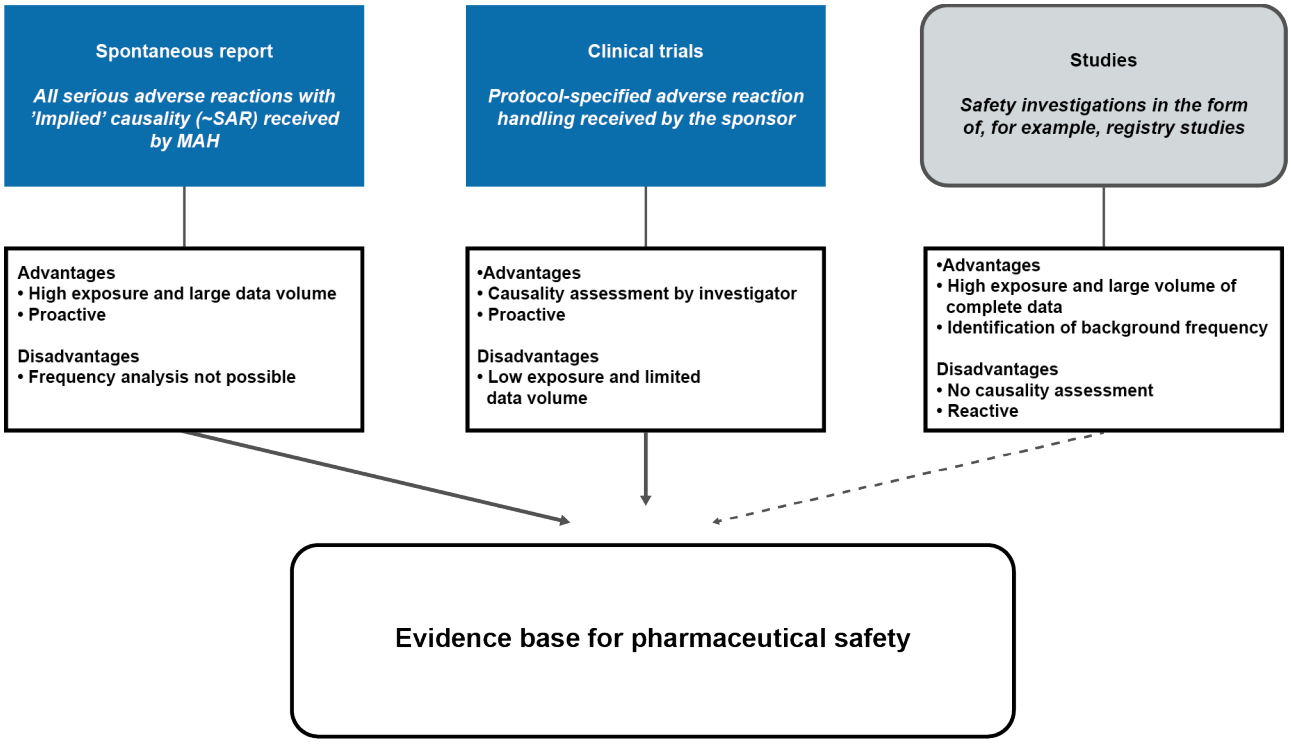
As illustrated in the figure above, literature searches will also identify adverse reaction data from other sources, such as registry-based studies. This reveals a complex array of data sources that collectively provide a comprehensive evidence base for the safety of the medicinal product.

Each source of adverse reaction data has its advantages and disadvantages concerning the quality of the evidence it provides, emphasising the importance of all data sources in enhancing the knowledge about pharmaceutical safety. Spontaneous reports related to authorised medicinal products generate a substantial volume of data. However, the lack of background frequencies is a significant disadvantage compared to controlled clinical trials, where frequency comparison is possible. While registry studies allow for such comparisons, they lack the medical causality assessment that are conducted for each recorded adverse event in a clinical trial (Figure 4).

Where the array of data sources is complex when it comes to authorised medicinal products, the sole source of evidence is clinical trials when it comes to non-authorised medicinal products. In this case, the safety profile has not been validated by means of a marketing authorisation application, and no post-marketing monitoring has begun. Hence, thorough adverse event management is essential, above all to safeguard the safety of patients and, secondly, to ensure a fit-for-purpose evidence for any future marketing authorisation application.

Exposure will be lowest in the development phase and will in most instances increase significantly once the product receives marketing authorisation. In the first two years following market placement in the EU, the medicinal product is subject to additional monitoring. The additional monitoring may be extended, reflecting the need for further evidence, and hence is important to consider when evaluating the product's exposure and evidence base for setting the necessary risk level of adverse event management.

Figure 4 Evidence base for safety data



7. Change log

Changes from version 1.0 to 2.0:

Version 2.0 includes the following updates:	• Section 2.2: New wording concerning additional monitoring list in the EU. • Section 2.4: Clarification and new wording concerning trials with high mortality and establishing DSMB. • Section 2.5: Clarification of which events must be included in ASR. • Editorial changes throughout the document, including changes to the layout.