AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

# Guidance on Use of new RSI and Outstanding Issues: Regulators Perspective

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# Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

| Interests in pharmaceutical industry | NO | Current | From 0 to 3 previous years | Over 3 preavious years |
|---|---|---|---|---|
| *DIRECT INTERESTS:* | | | | |
| 1.1 Employment with a company: pharmaceutical company in an executive role | X | ☐ | ☐ | ☐ mandatory |
| 1.2 Employment with a company: in a lead role in the development of a medicinal product | X | ☐ | ☐ | ☐ mandatory |
| 1.3 Employment with a company: other activities | ☐ | ☐ | ☐ | X optional |
| 2. Consultancy for a company | X | ☐ | ☐ | ☐ optional |
| 3. Strategic advisory role for a company | X | ☐ | ☐ | ☐ optional |
| 4. Financial interests | ☐ | ☐ | ☐ | X optional |
| 5. Ownership of a patent | X | ☐ | ☐ | ☐ optional |
| *INDIRECT INTERESTS:* | | | | |
| 6. Principal investigator | X | ☐ | ☐ | ☐ optional |
| 7. Investigator | X | ☐ | ☐ | ☐ optional |
| 8. Grant or other funding | X | ☐ | ☐ | ☐ optional |
| 9. Family members interests | X | ☐ | ☐ | ☐ optional |

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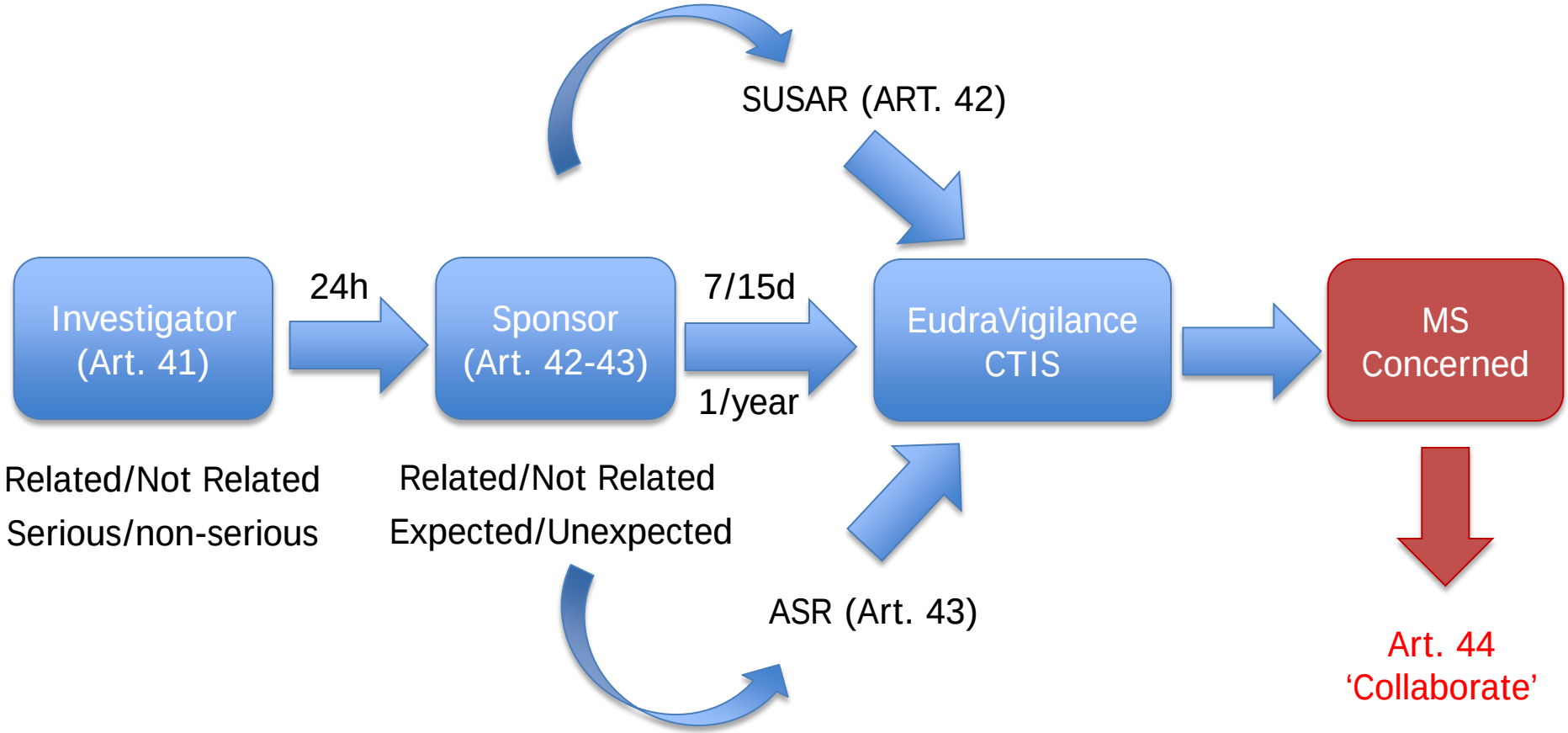
N.B. I am not receiving any compensation

# Safety Reporting under Reg. 536/2014



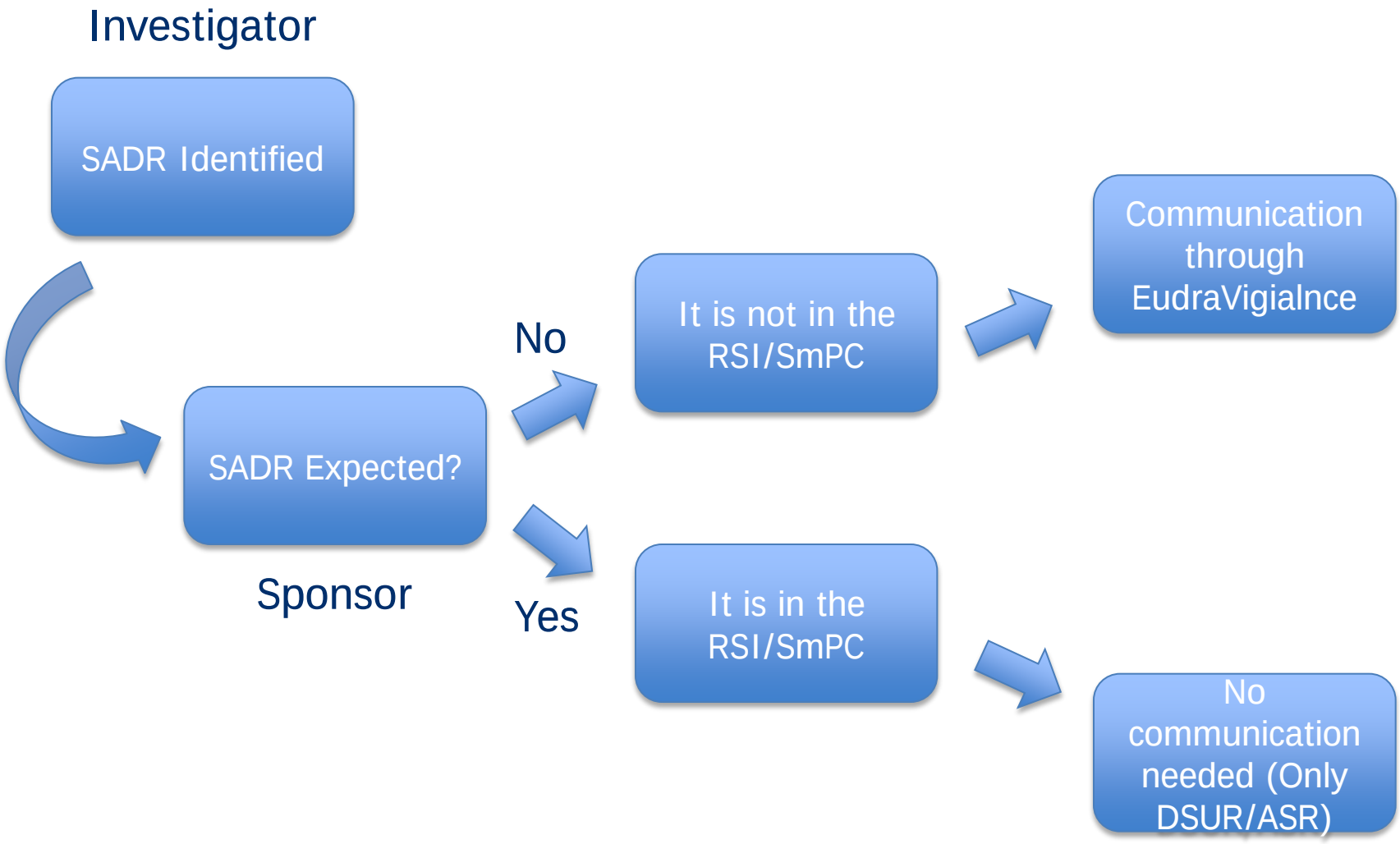
# What is a SUSAR?

S = Suspected: the relationship with the IMP is suspected by either Investigator and Sponsor.

U = Unexpected: The AR has not been finally linked with the IMP

S = Serious: results in death, is life- threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect or is otherwise medically important

AR = Adverse Reaction: noxious and unintended responses to an investigational medicinal product related


Investigator
SADR Identified
SADR Expected?
Sponsor
No
Yes
It is not in the RSI/SmPC
It is in the RSI/SmPC
Communication through EudraVigialnce
No communication needed (Only DSUR/ASR)

# Reference Safety Information

The RSI is a list of **expected serious** adverse reactions, which are classified using Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA).

It is used for the assessment of the expectedness of all 'suspected' serious adverse reactions (SARs) that occur in clinical trials.

An expectedness assessment is required to be conducted by the sponsor on each 'suspected' SAR to determine expedited reporting of SUSARs.

It is not a simple list of SAR occurred in clinical trials, but it includes only the SAR considered expected and therefore with no need to be transferred to the NCAs

# Reference Safety Information

RSI is aimed at:

- Giving safety information
- Reporting information for annual safety report
- Assessing expectedness in SUSAR

A CTFG QnA Document was provided in 2013, however:

- Various methods for generating RSI exist among CT sponsors
- Inconsistencies in approach among sponsors limits the value of SUSARs: Supervision of CT and patients safety
- Different assessment of the RSI by the NCAs

# New updated document was needed: CTFG QnA document 2017

CTFG Q&A document includes 18 questions (EMA SmPC guidance, ICH E2A/E2F, Dir. 2001/20/EC, CT-1, CT-3 as well as Reg 536/2014)

<u>Aimed at giving clear indications to the Sponsors:</u>

- To provide updated details on RSI requirements based on shared experiences since 2013
- To reduce complexity & confusion in relation to RSI generation
- To ensure consistent approach by sponsors to allow for supervision of CTs

<u>Aimed at giving clear indications to the NCA assessors:</u>

- To support and ensure harmonised requirements & decisions

# Expectedness assessment: General rules

1. Evidence of a **causal relationship** between the event and the IMP exists.

The Causal Relationship should be demonstrated by the Sponsor. Information on the process of selecting 'suspected' SARs as expected should be given in full transparency.

2. The SAR should have been occurred **more than once**. Otherwise the inclusion should be supported by a reasonable justification based on medical judgment.

Occurrence of a 'suspected' SAR on more than once is not sufficient to determine expectedness

3. Non-clinical data, potential risks or **unrelated** SAE should be **not included** in the RSI.

The expectedness should not be based on what it might be anticipated from the pharmacological properties of a medicinal product or the compound class

# Expectedness assessment: Fatal/Life-threatening SARs

**Fatal and life-threatening SARs** should be always considered unexpected

As a general rule, sponsors should not expect an IMP to cause Fatal and/or Life-threatening SARs

Life-threatening SARs in the RSI acceptable only if strongly justified

Fatal SARs can only be considered expected if clearly stated in SmPC (IMP with MA)

Adequate risk mitigation measures should be taken

# Which document should contain the RSI

The Sponsor should provide information on where the RSI is located. This information can be given to the NCA in the cover letter of Clinical Trial Application

| IMP | DOCUMENT |
|---|---|
| No MA in EU | Investigator's Brochure |
| MA in the EU (used according with the authorized terms) | Investigator's Brochure/SmPC |
| MA in the EU (used outside the authorized terms) | Investigator's Brochure |

The RSI should be located in a specific section of the IB, different from the general safety information on the IMP.

# Format of the RSI

- The RSI should be presented in the form of a table, with the nature of the ‘expected SARs’ expressed by body system organ class and using preferred terms (PTs) followed by the frequency.

- If under development in different medical conditions, separate tables by indication may be appropriate, if adequately justified by the sponsor.

- The frequencies of the expected SARs listed in the RSI are preferred to be in categories in analogy to the recommendation for the SmPC (section 4.8.) where possible. If there is an insufficient number of subjects exposed, the number of observed ‘suspected SARs’ for each ‘expected SAR’ should be provided, together with the number of patients exposed.

# What should not be included in the RSI

- Adverse events considered unrelated to the IMP
- Non-serious ARs,
- Fatal ‘suspected’ SARs (unless included in SmPC)
- AR identified in non-clincal settings, even if considered potential risk for humans.
- SAR that have occurred only once, unless there is a very strong plausibility of a causal relationship with the IMP and a robust justification based on medical judgment is provided.
- SARs that are expected for similar products within the therapeutic class, which did not occur in subjects taking the IMP.

# RSI with no expected SAR

There may be situations where there the IMP is not expected to cause any SARs. For example:

- Early in the clinical development
- Later in clinical development, some ‘suspected’ SAR cases may have occurred, but upon evaluation of the available cumulative evidence are not considered to be ‘expected’ SARs by the sponsor.
- Treatment with certain IMPs does not result in the occurrence of SARs.

In these cases, a clearly defined section of the IB called RSI should still be present, followed by a brief text stating that no SARs are considered expected by the sponsor for the purpose of expedited reporting.

# How and When the RSI should be updated

- A substantial amendment is always required to be submitted if there are changes to the RSI.
- Any addition of SAR in the RSI should be adequately justified by the Sponsor
- Usually within the scope of the annual update of the IB.
- Consequent update of the protocol should be considered in case of specific safety issues.

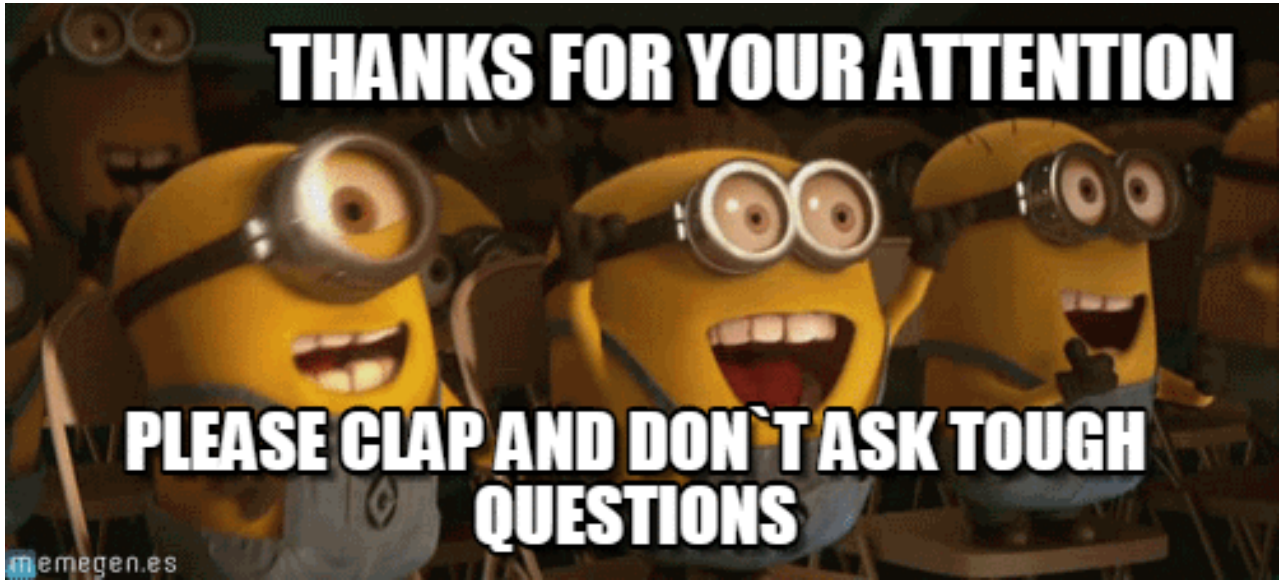
# Conclusions: why the RSI is important

- It determines what SUSARs we receive: by agreeing to an RSI we are agreeing to events NOT being SUSARs
- To assess new safety information that may impact on the risk benefit/ratio of the trial
- To determine if as a result the IMP and its dosing regimen are still appropriate for the trial population

# Conclusions: Recommendations

- To update the IB a 1-year transition period was given. The transition period expired on 31/12/2018
- The IB should be updated in case of relevant changes occur in the RSI. It is highly recommended to update the RSI annually (annual update of the IB).
- Justify the inconsistencies with the CTFG recommendations.
- The RSI should be clearly distinguishable from the other safety information related to the IMP. A specific section of the IB should be dedicated to the RSI
- It is not acceptable to consider the entire Summary of Data and Guidance for the Investigator section of the IB to be the RSI.

Comply with the CTFG recommendations lead to harmonization

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