AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

The Reference Safety Information: Introduction of the Regulatory Aspects

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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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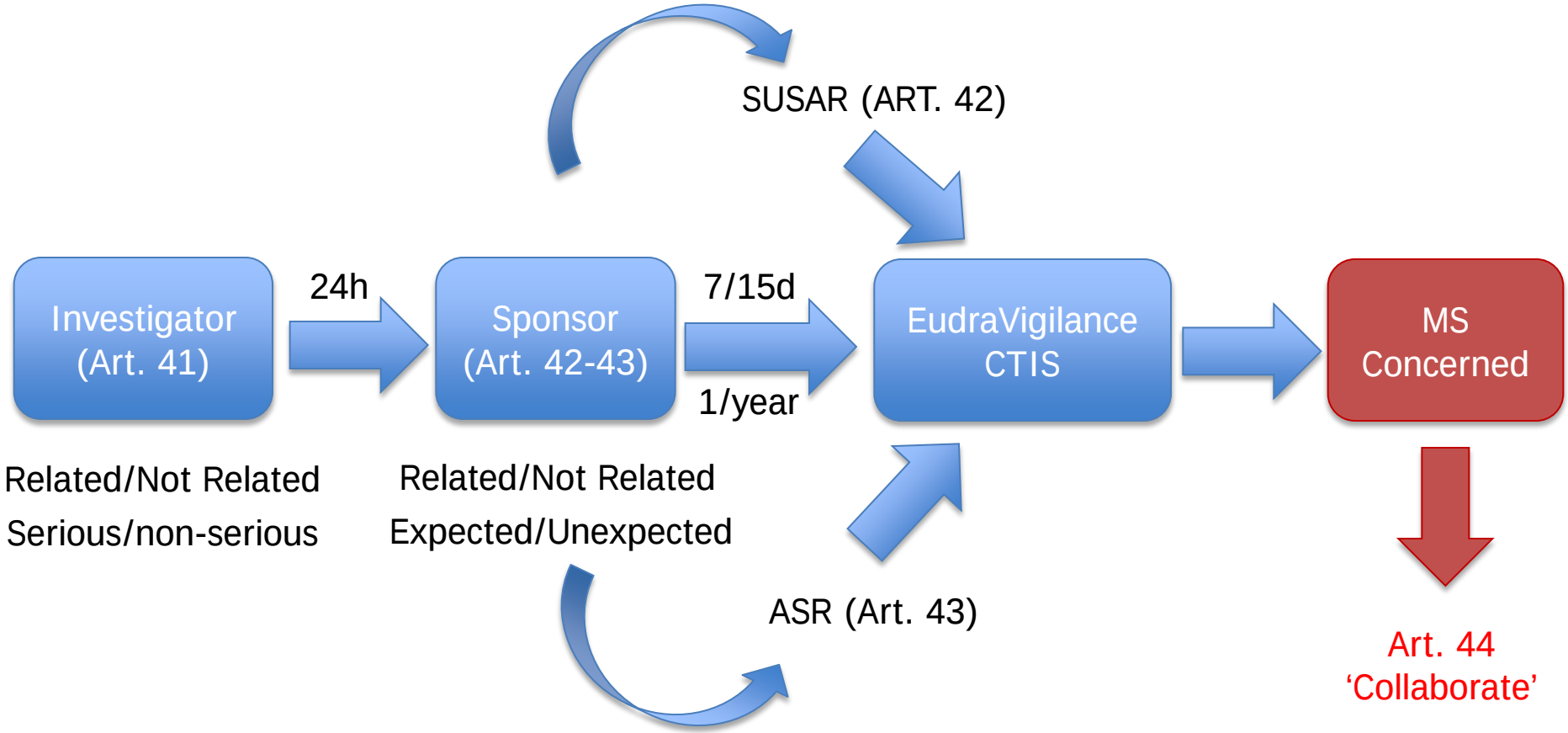
N.B. I am not receiving any compensation

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

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

Expectedness assessment

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

No non-clincal data, potential risks or **unrelated** SAE should be 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.

Fatal and life-threatening SARs should be always considered unexpected. Life-threatening SARs inclusion in the RSI is possible only if supported by a reasonable justification based on medical judgment.

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 teh 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

N.B. 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.

Example of an RSI table

Table 1.0 Serious Adverse Reactions for the IMP considered <u>expected</u> for safety reporting purposes.

SOC	SARs	Number of subjects exposed (N) = 328		
		All SARs	Occurrence of fatal SARs	Occurrence of life-threatening SARs
		n* (%)	n (%)	n (%)
Gastro-intestinal disorders	Diarrhoea	25 (7.6)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	ALT increase	12 (3.6)	0 (0.0)	0 (0.0)
	AST increase	9 (2.7)	0 (0.0)	0 (0.0)
Cardio vascular disorders	Myocarditis	33 (10.0)	0 (0.0)	2 (0.6)

n = number of subjects who have experienced the SAR

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)
- Life-threatening suspected SARs that are not considered to be ‘expected’.
- 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.

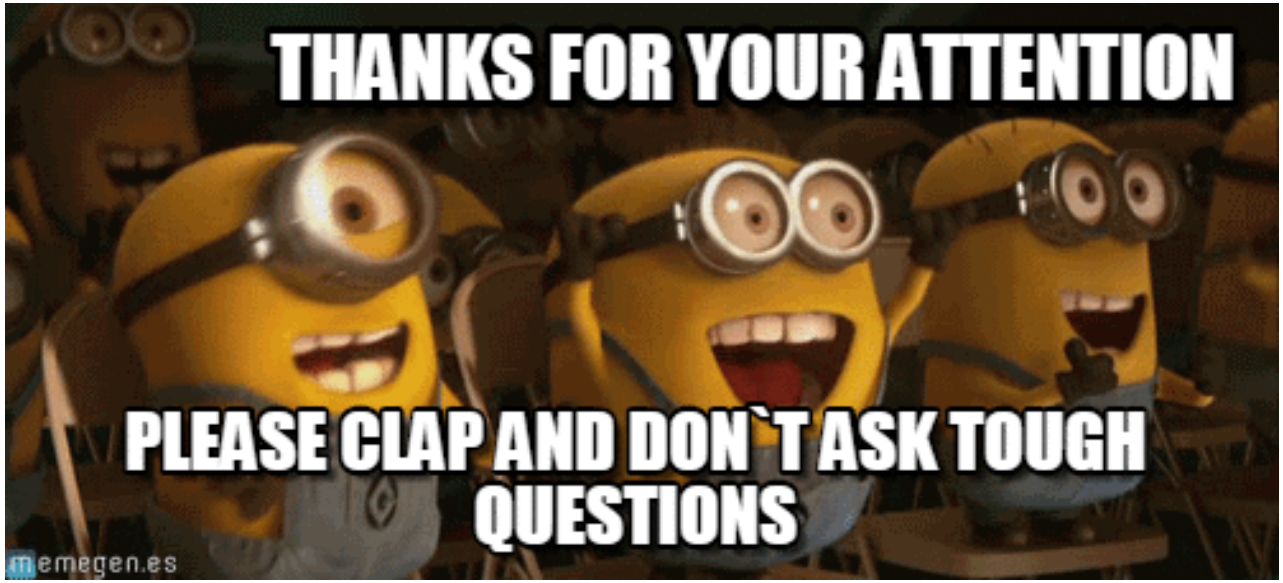
In these cases, a clearly defined section of the IB called RSI should still be present, followed by a brief text stating that no SARs are considered expected by the sponsor for the purpose of expedited reporting.

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



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