Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

StEM – Reference Safety Information Update

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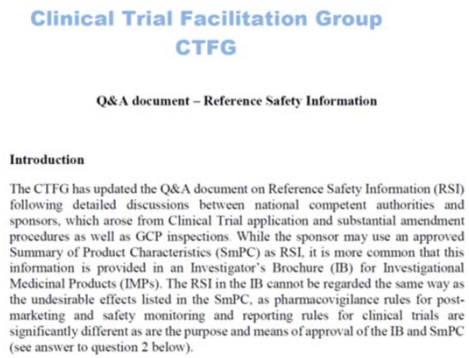
Reference Safety Information (RSI)

- Reference safety Information (RSI) is addressed in a recently updated guideline
- Q&A from Clinical Trials Facilitation Group (CTFG): http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf



Clinical Trial Facilitation Group
CTFG

Q&A document – Reference Safety Information

Introduction

The CTFG has updated the Q&A document on Reference Safety Information (RSI) following detailed discussions between national competent authorities and sponsors, which arose from Clinical Trial application and substantial amendment procedures as well as GCP inspections. While the sponsor may use an approved Summary of Product Characteristics (SmPC) as RSI, it is more common that this information is provided in an Investigator's Brochure (IB) for Investigational Medicinal Products (IMPs). The RSI in the IB cannot be regarded the same way as the undesirable effects listed in the SmPC, as pharmacovigilance rules for post-marketing and safety monitoring and reporting rules for clinical trials are significantly different as are the purpose and means of approval of the IB and SmPC (see answer to question 2 below).

Reasons the guidance needed updating

- RSI serves 3 purposes:
  - Information for the investigator
  - Basis for expectedness for SUSAR reporting
  - Basis for annual safety report

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- There was
  - Inconsistency among sponsors
  - Inconsistency among member states
  - Multiple GNAs
  - Findings in GCP inspections

Aim and Content of Q&A

- Written as 18 Q&A
- Aligned with EMA SmPC guidance, ICH E2A, Dir,. 2001/20/EC, CT-1, CT-3 and CT Reg. 536/2014
- For sponsors:
  - To provide updated details on RSI requirements based on shared experiences since 2013
  - To reduce complexity and confusion in relation to RSI generation
  - To ensure consistent approach by sponsors to allow for supervision of CTs e.g. valuable interrogation of EV database by NCAs
- For Member States:
  - To support and ensure harmonised requirements and decisions

Q1 – Purpose and content

- 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 expectedness** of all “suspected” serious adverse reactions (SARs) that occur in clinical trials

A separate section **means it is clearly identifiable and distinct from other tables or lists of events** seen in previous clinical trials, for example those in section 5 of the IB (Human Data)

It is acceptable to incorporate it into Information for the Investigator / CCDS / DCSI, provided the section can still be identified

Severity

- **Only previous SERIOUS ARs can be considered as expected**
- Non-serious reactions can be included in a table elsewhere in the IB

The listed adverse reactions should be **based on reactions previously observed** and not on the basis of what might be anticipated from the pharmacological properties of a medicinal product, others in the same class or based on what is predicted from preclinical data (with no clinical data)

- If previously unseen reactions are included then there is no regulator oversight of any new safety signal

Frequency

- **Preferred to be in categories** recommended for the SmPC (CIOMS)
- If there are an insufficient number of subjects exposed to the IMP to use these categories (e.g. during the early stages of product development), **consider expressing the observed adverse reactions as a number**, together with the number of patients exposed.
- **Reactions that have occurred once cannot usually be considered expected** and a robust justification should be provided if these are included in the RSI.

Q3,4,5 - format

Table 1.0 Serious Adverse Reactions for the IMP considered expected for safety reporting purposes.

preferred terms (PTs)

calculated on an aggregated level; based 'suspected' SARs to the IMP

body system organ class →

SOC	SARs	Number of subjects exposed (N) = 328		
		All SARs	Frequency of fatal SARs	Frequency 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)

expected expected

8

If the SmPC contains the RSI then section 4.8 lists those events considered as expected.

These events are generally accepted as the IMP has been through the MAA assessment process and sufficient safety data is available, even if not given in detail in the SmPC.

A substantial amendment is ALWAYS required to update the RSI.

New preferred terms added must be justified (the DSUR can act as the justification document)

If the RSI is updated without approval then the regulator has no opportunity to disagree with the proposed events and loses clarity of oversight

The RSI can be updated at any time if approved via a substantial amendment

However

- **This will amend SUSAR reporting** from the time of approval
- **The RSI for the DSUR can only be the one in effect at the start of the reporting period**. Therefore any change in the middle of the reporting period will require re-evaluation of events no longer deemed SUSARs (as they require notification as SUSARs in the DSUR report)

When do I need to be compliant?

- Start now!!
- CTFG RSI Q&A cover note
  - A 1-year transition period will apply for the duration of 2018 (i.e. from 1/1/2018 to 31/12/2018) before the recommendations outlined in the Q&A are strictly enforced by national competent authorities. During this period, clinical trial applications and/or substantial amendment dossiers will not be rejected if the RSI is not completely in line the Q&A, and when the IB contains a clear RSI section that is fit for purpose is submitted
  - The national competent authorities represented at CTFG plan to implement the guidance more strictly from 1/1/2019, and submission of an application and/or substantial amendment with an RSI that does not comply with the guidelines outlined in the Q&A risks being rejected.

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2018_03_CTFG_RSI_Q_A_Covernote.pdf

Questions?

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