



EFPIA Position Paper on Reference Safety Information

Author: EFPIA * Date: September 2016 * Version: FINAL



Executive Summary

1. Recent EU national competent authority (NCA) focus on clinical trial (CT) reference safety information (RSI) has resulted in an increase in rejections of investigator brochure (IB) updates and CT Authorisations (CTA).
2. A stated NCA aim was to drive a more consistent approach to RSI in the EU, but despite understanding the need for this, sponsors are unable to achieve the objective because no detailed EU guidance document exists which reflects these updated expectations. This has resulted in the same RSI (as part of the same clinical trial) being accepted in one member state (MS) and rejected in another.
3. The current Commission CT-1 and CT-3 guidelines stipulate that the purpose of the RSI is to allow assessment of the expectedness of any adverse reaction that might occur during a clinical trial. Several of the NCA requests to include additional information and details in the RSI seem to go beyond the level of information that is needed for ADR expectedness assessment.
4. IB and CTA rejections are resulting in significant delay in EU CT start-up, confusion and frustration at clinical sites and an increase in negativity towards the EU as a location for clinical research.
5. The IB is a global communication tool to investigators, as well as driving the content for informed consent documents for study subjects (patients). A further unintended consequence of this situation is that investigators and patients outside the EU can be informed of new safety information when those within the EU are not because of the IB rejection.
6. To address this concern, EFPIA strongly considers that urgent action is needed by the CT Facilitation Group (CTFG) to generate an updated RSI guidance document that:
 - Includes transparent rationale behind the guidance provided.
 - Has agreement across the MS.
 - Provides clarity on how frequency and nature of adverse drug reactions (ADRs) can be optimally presented in the RSI to determine the expectedness of an ADR.

Such guidance could be in the form of a separate guideline or an updated Q&A and it would be important for Sponsors to have an opportunity to comment during the process.

- As CT safety management processes for commercial sponsors are usually global, the updated guidance will need a workable transition period to minimise the issues described in bullets 4 and 5.
- ICH could be considered as a forum to try and achieve global consensus in the longer term.



1. Background

In recent months, commercial sponsors have received an increasing number of comments on the location, the generation, the content and the management of RSI for CTs planned or conducted in the EU. The impact is significant as a recent EFPIA survey estimated that about 87.5% of members (14 out of 16 respondents) had received this feedback to date and that almost all IB updates and CT applications have been impacted.

In order to provide an idea of the extent and frequency of NCA feedback, examples are presented below with the number of EFPIA members impacted to date. Please note many sponsors have received contrasting requests from different NCAs on some of the topics highlighted below. This divergence will clearly further impede the ability of sponsors to remain compliant.

- 14 out of 16 (87.5%) of respondents received feedback that single cases should not be included in the RSI, despite the CTFG Q&A stating this assessment should be case by case¹.
- 13 out of 16 (81.3%) of respondents received request to include severity in the RSI ADR list.
- 10 out of 16 (62.5%) of survey respondents received discrepant advice as to whether or not non-serious ADRs can be included in the RSI and, if so, whether or not they should be clearly identified; including requested inclusion of this sentence: *'for the purpose of safety reporting the non-serious adverse reactions will be considered unexpected'*.
- 8 out of 16 (50%) of respondents have received questions on whether grouped MedDRA terms can be used to present frequency, or if this must always be presented by preferred term (PT).
- 7 out of 16 (40%) of respondents received feedback on ADR frequency aspects, including RSI frequency calculation methodology, namely calculating ADR frequency based on all events (serious or non-serious irrespective of causality assessment) or including only those occurrences assessed as suspected ADRs.

2. Problem Statement

In the EU, Section 7.2.3.2. of the CT-3 guidance² and the Clinical Trial Facilitation Group (CTFG) Q&A³ provide some details on the content of the RSI but do not specifically provide advice on how the various points covered above should be addressed.

For example, CT-3 section 7.2.3.2 Point 53 states: *'If the RSI is contained in the IB, the IB should contain a clearly-identified section to this effect. This section should include information on the*

¹ Question 4: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_05_CTFG_QnA_RSI.pdf

² http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf

³ http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_05_CTFG_QnA_RSI.pdf





frequency and nature of the adverse reactions. It appears that varying interpretation of the terms ‘frequency’ and, in particular, ‘nature’ has driven a lot of regulator feedback. This situation is further compounded by the fact that different terminologies are used e.g. CT-3 refers to ‘adverse reactions’ and CTFG guidances to ‘related adverse events’.

EFPIA’s interpretation (per comments below) is that there is confusion in:

- How an ADR is defined and included in the RSI
- Frequency calculation of ADR and
- What constitutes the ‘nature’ of an ADR

In the absence of specific guidance, the situation described is an inevitable consequence, one that requires urgent attention.

Lastly, we note that some EU regulators require that CTA amendments, which include an IB/ RSI change need to be approved before use of the RSI for expectedness reporting. Determining when such a change can be considered ‘approved’ at an EU level however, is operationally very difficult, as the approvals from individual EU NCAs are received at different time points. This requirement also delays communication of important safety information to ethics committees, investigators and patients (notably as a result of the subsequent delays in updating of the informed consent forms).

3. Single cases

There has been objection to the inclusion of single cases in the RSI. However the CTFG Q&A states that this assessment should be case by case.⁴ EFPIA supports the CTFG approach because a blanket non-inclusion rule would not permit a sponsor to include a single very well documented case of a clinically significant event which is classically drug related (especially if it involved a known class effect) e.g. Stevens Johnson Syndrome or cases including a positive de-challenge/re-challenge. We accept this is more likely the exception than the rule but strongly consider that sponsors should be allowed to use medical judgment for this decision if the circumstances warrant it.

4. Nature of ADRs

Wording used by regulators and in the CTFG guidance is not fully clear, as interpretation of the word ‘nature’ seems to cover a spectrum of terms including seriousness, severity or grade of the event.

⁴ http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_05_CTFG_QnA_RSI.pdf





4.1. Seriousness

The definition of 'serious' is defined on the basis of international consensus (ICH E2A)⁵, but it still requires medical judgment. Furthermore, as noted for 'severity' below, a particular AE term may be assessed as serious by one investigator and non-serious by another. As a result, inclusion of a category of 'serious ADRs' in the RSI is not considered helpful, as seriousness is determined per individual event reported in a case at an individual patient level, and not on how the aggregate level information in the RSI table is listed.

4.2. Inclusion of non-serious ADR in the RSI

Companies have received discrepant advice as to whether or not non-serious ADR can be included in the RSI and, if so, if they should be clearly identified. However, the CTFG Q&A explicitly states that *'The content of the Reference Safety Information should include a list of **all observed cumulative adverse reactions** (i.e. related adverse events, AR).'*

Sponsors have also received feedback that if non-serious ADRs are included in the RSI table, the Sponsor should add the following statement in the RSI: *'For the purpose of safety reporting in the clinical trials the non-serious adverse reactions will be considered unexpected'*. This statement is not considered appropriate, as, in line with discussions above, each event is assessed on a case by case basis and, if any AE described in a report is assessed as serious, unexpected and possibly related, it will be classified as such, irrespective of how it is presented in the RSI. Therefore, reporting of non-serious ADRs will occur in accordance with ICH E2A and CT-3 requirements.

We therefore support the CTFG Q&A but do not consider that the proposed statement should be included as it is unclear/ unhelpful.

4.3. Severity

Other than in oncology and some other specialised areas which more routinely use the highly structured and objective CTCAE scoring system, severity assessments are usually highly subjective and made at an individual patient and event level. For example, headache or abdominal pain may be assessed as severe by one patient but mild by another. It is not usually possible to assign a single severity score to an ADR listed in the RSI, as severity is likely to range from mild to moderate to severe, especially for ADRs that reflect subjective symptoms. In this circumstance, assigning severity to an ADR at an aggregate level is not helpful. Furthermore, determining whether a reported suspected SAE for an individual patient is expected or unexpected against a listed ADR in the RSI on the basis of increased severity (for example) is a matter of medical/scientific judgment by trained case management staff.

⁵ https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf





The 'nature' of ADR listed in the RSI of an IB is quite variable/ subjective, given the points raised above. Applying an inconsistent and somewhat artificial classification of severity, fails to take into account the important aspect of individual medical assessment of a case to determine what is serious and unexpected.

We understand that a key aim for EU key regulators is to strive for greater consistency in the development and use of RSI in preparation for implementation of the EU CT Regulation⁶ and that this will facilitate MS collaboration in the new EU database. EFPIA feedback has confirmed variability in sponsor response to the above feedback in the absence of an aligned EU position, suggesting current NCA RSI focus is failing to meet this consistency objective.

5. Frequency of ADRs

The use of all occurrences of ADR (serious and non-serious irrespective of causality assessment) to calculate the frequency of an ADR (at an aggregate level) is an established practice used for many years in RSI and product labelling. It is well known that calculating frequency on the basis of only those ADRs causally assessed by investigator or sponsor as 'suspected ADRs' at an individual patient level is very subjective and will inevitably underestimate frequency. This is the whole rationale, implemented many years ago, for moving collection of safety data from CTs from suspected ADRs to collection of all adverse events (AE) as individual case causality for 'suspected' ADRs can be highly variable. Basing frequency on only those cases considered to be 'suspected' contradicts these fundamental principles. As such, EFPIA consider that there is no scientific justification to change the basis for calculating frequency of ADRs now and that it should remain at an aggregate level based on all AEs for the particular medical concept listed.

6. Proposal

Based on the feedback provided by EFPIA members, it is very clear that prompt action is needed to avoid further perpetuation of the current issues in the development and management of the RSI. EFPIA therefore firmly consider that, as a matter of high priority, the CTFG should lead the development of an aligned EU guidance of sufficient granularity to ensure that it:

- Reduces IB/ CTA rejections
- Drives a consistent EU approach
- Allows flexibility for medical judgment and pragmatism in relation to how frequency and nature of ADRs (when clearly defined) can be presented in the RSI

A common position, at least in the EU countries, for determination of entry into effect of the amended IB/RSI for ICSRs expectedness reporting is also needed.

⁶ Article 44: http://ec.europa.eu/health/human-use/clinical-trials/regulation/index_en.htm





To ensure the final document is applicable in real practice, sponsors need to have an opportunity to review a draft prior to finalisation and EFPIA would be happy to provide assistance in this respect. Such an initiative by the CTFG would further enable and drive towards the common goal of consistency of implementation in the best interests of all stakeholders.

It is worth noting that this could be an update to the CTFG Q&A on RSI⁷ or full consideration of this issue in the anticipated Commission Q&A document that will replace the CT-3 guidance⁸ once the EU CT Regulation has been implemented.

Commercial sponsor CT safety monitoring processes are usually global and robust justifications are needed in the above guidance to support sponsors in changing global processes to comply, particularly if they conflict with guidance in other regions. A transition period will also be needed to ensure companies have time to implement and comply the guidance without unnecessarily delaying the start of clinical trials in the EU and ultimately access to new investigational medicinal products by study subjects.

7. Future considerations – international harmonisation

International harmonisation is desirable but the approach being adopted in the EU seems to be diverging from approaches being taken in other countries/regions and, notably the more risk based approach in the following US guidance⁹ and being further considered in 2015 US guidance¹⁰. For this reason, EFPIA consider that it would be worth raising the topic of ongoing CT safety monitoring at an ICH level to aim for international consensus.

⁷ http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_05_CTFG_QnA_RSI.pdf

⁸ http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf

⁹ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

¹⁰ <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm477584.pdf>

