Medicines and Healthcare Products Regulatory Agency (MHRA), UK, Inspectorate Comments on the public consultation of CT3

MHRA welcomes the opportunity for review of the proposed document and has a number of comments and suggestions.

General

1. As CT3 will be replacing CT3 and CT4, it would be useful if the document contained a table and flow chart for ease of reference to clarify reporting requirements (CT4 currently contains such tables).
2. As CT3 will also replace the Q&A document relating to adverse reaction reporting, it is suggested that the text from the current Q&A is used where appropriate and a check is performed to ensure that the Q&A clarifications have been completely captured in the revised guidance.
3. The title of the guidance should be clarified. The title refers to adverse events; however, the guidance covers only serious adverse events.
4. The concept of serious adverse reactions resulting from study procedures has been removed. In addition, lack of efficacy in life-threatening conditions, important pre-clinical findings have also been removed and no longer require reporting (please refer to section 5.1.1.2 of the current CT3). This is important information as it may lead to an urgent safety measure, or a protocol amendment and may have an impact on the risk/benefit ratio of the study.
5. Clarity is requested in the headings to reflect that it is expedited reporting of individual cases that is being referred to, and not periodic reports. This has led to some confusion, for example in section 4.6 it should be clear that this is limited to expedited reporting. Article 51 suggests that safety reporting falls either under 2001/20 or 2001/83. However, SUSARs can be reported under 2001/20/EC as expedited individual reports, but are also required to be included in periodic safety update reports, under 2001/83.
6. There should be clarity within the document when referring to reporting. The investigator is required to record all adverse events in the medical notes, regardless of whether these are to be expedited. Adverse events may then be reported to the Sponsor, for example, through CRFs, although again these would not always be expedited. All SAEs must be expedited by the investigator to the Sponsor (unless identified in the protocol as not requiring immediate reporting), and then all SUSARs must be expedited by the Sponsor to the regulatory authorities/Ethics committees. Often the term “reporting” is used when what is meant is “expedited reporting”. This may confuse users of the guidance document.
7. Does EudraVigilance permit reporting to the CT module if there is no trial site in the EU e.g. for third country trials? If a trial is being conducted exclusively outside the EU and the sponsor is conducting no other trials with the same IMP in the EU, by a sponsor who is the MAH of the product in the EU, there may be no EudraCT number. To which module should these reports be sent?
8. There is inconsistent use of the term patient and participant throughout the document. Suggest using participant, as this guidance also covers healthy volunteer studies.

Specific

Paragraphs 12 and 14. Suggest that these sections are combined to give one definition of serious adverse event.

Paragraph 18. It would be useful to add some examples to illustrate what types of events might typically not be reported. The important point here is that these events do not tell us anything more about the safety profile of the IMP, but they do tell us about efficacy i.e. time to disease progression. For example, disease defining events, or endpoints. In HIV trials there are certain events such as Kaposi's' Sarcoma that are disease defining and protocols often state that these need not be reported in an expedited manner. Endpoints for cardiology trials, such as myocardial infarction, also illustrate the point.

Paragraph 19. 48 hours is stated as the timeframe for reporting SAEs to the sponsor. Could the Commission explain the reasoning behind this? In general, 24 hours is expected (and often what is required of investigators as set out in the protocol).

'Non-immediate reporting' - This paragraph does not have a number. Also this paragraph requires clarification (see general point 6). We suggest rewording to, 'the investigator shall report to the Sponsor within the appropriate timeframe as specified in the protocol'. This paragraph may be better placed earlier in the document, for example immediately after 18.

Paragraph 28. We suggest inserting, 'which does not result from a <u>possible</u> interaction with an IMP, is by definition not a SUSAR'.

Paragraph 30 This section appears to be redundant.

Paragraph 36 We suggest re-wording for clarity, 'The Sponsor is responsible for ensuring only serious adverse reactions are expedited '.

Paragraph 37 Suggest using 'expedited' rather than 'reported'. The use of reported can be confusing here (refer to general comment 6), for example, an investigator reading this guidance will still need to report non-serious AEs and unrelated SAEs into the medical notes and, where required, in the CRF.

Paragraph 39 This should be combined with 37.

Paragraph 40 It would be useful to include the type of factors that could be considered when assessing causality e.g. temporal relationship; is the event expected with the disease; does the subject have pre-trial medical history relevant to the event; does the event disappear when the drug is stopped (and re-start when it is recommenced), is the event known to be something that occurs with the product or class of products.

Paragraph 41 We suggest replacing this with the text from the current version of CT3, in section 4.2.4, as this is clearer.

Paragraph 42 We suggest that this Could be amended to ' The sponsor is responsible for assessing expectedness and ensuring that only unexpected serious adverse reactions are reported.

Paragraph 43: We suggest: Replacing ‘applicable product information' with 'Reference Safety Information (e.g. IB or SmPC)'

Paragraphs 44 and 45. It is highly recommended that this text is removed or amended. The sponsor is in the best position to assess expectedness and not, in most circumstances, an individual investigator, and the normal process is that sponsors perform the assessment of expectedness based on the current reference safety information (except in rare circumstances where the responsibility may be delegated by the sponsor to an investigator). It would not routinely be expected that individual investigators would comment on expectedness (this does not happen in most trials). In multi-centre clinical trials, the sponsor is in the best position to perform consistent assessments of expectedness. Delegating this responsibility to individual investigators is not always appropriate and can lead to inconsistency and under-reporting.

It is strongly recommended that the text on expectedness in the existing guidance is retained i.e.:

“The definition of the term “unexpected adverse reaction” is given in Article 2(p) of Directive 2001/20/EC taking into account comments in Annex 1. Adverse reactions should be considered as unexpected if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information for the IMP. The expectedness of an adverse reaction shall be determined by the sponsor according to the reference document. The reference document is, as a general rule:

- the investigator's brochure for a non authorised investigational medicinal product,
- or the summary of product characteristics for an authorised medicinal product in the European Community, which is being used according to the terms and conditions of the marketing authorisation). When the investigational medicinal products has a marketing authorisation in several Member States with different summary of product characteristics, the sponsor should select the most appropriate summary of product characteristics, with reference to patient safety, as a reference document for assessing expectedness. The reference document is the same for the whole clinical trial in all the Member States concerned. It should be clearly identified in the protocol and attached to the Clinical Trial Application, in an acceptable language and mentioned in the covering letter.”

Paragraph 46 In the last point we suggest adding, for clarity, ‘or who holds a development agreement with the Sponsor and, therefore, has access to those safety data’.

Paragraph 48 In the heading 4.5 ‘reported’ should be replaced with ‘expedited’. Likewise the first sentence ‘report’ should be replaced by ‘expedite’. In addition a reference to the guidance on NIMPs should be included here.

Paragraph 56 We suggest that calendar days is specified and we also suggest replacing ‘brought to the attention of’ with ‘received by’.

Paragraphs 63 and 64. The reporting and follow-up reporting timelines are clarified in the Q&A and we suggest using the Q&A wording here (as it is clearer).

Paragraph 80 and 81 Contains a typographical error - should read EVCTM.

Paragraph 84 If the directness of the report does not change the format there is no need to state this here, therefore, we suggest removing this.

Paragraph 91 We suggest re-wording to, ‘For example, the information on SUSARs could be aggregated in a line listing’.

Paragraph 95 It is essential to reach agreement, and this should be in the protocol. We suggest rewording to, ‘Under these and similar circumstances, agreement must be reached’

Section 5 heading ‘annual’ would read better than “yearly”.