CTFG
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Clinical Trial Facilitation Group CTFG comments on the European Commission public consultation document CT3: draft detailed guidance on the collection, verification and presentation of adverse reaction reports arising for clinical trials on medicinal products

CTFG welcomes the public consultation document revising the detailed guidance on safety reporting in clinical trials (CT) and is delighted to comment it.
CTFG strongly supports the objectives to simplify and harmonise rules for safety reporting with the objectives to facilitate the conduct of CT in EU and to ensure CT participants safety.
The new CT3 is supposed to replace the current CT3 guidance but also the CT4 on Eudravigilance database and the Commission's questions and answers (Q and A) on CTs safety.

1. General comments

1.1. The new guidance should detail roles and responsibilities of all stakeholders as in the previous guidance: investigators, sponsors, National Competent Authorities (NCAs), Ethics committees (EC) and EMA.

- Although paragraph 25 gives the same roles to the 2 bodies, the guidance should clarify the <u>responsibility of the NCAs and of ECs</u> in clinical trials safety monitoring, which can be derived from the directive. Indeed, as it is the responsibility of NCAs to ensure public health, as only NCAs have access to Eudravigilance database, as only NCAs can inspect CTs, as only NCAs can suspend or stop a CT, then the responsibility to assess CT safety data is for the NCAs. EC is responsible for assessing ethical aspects of CTs. In that situation, we believe that there is a need for the 2 bodies to communicate and this should be better described in the guidance in order to avoid any national specificity during the transposition of the guidance.

- Furthermore, and according to the title of the guidance, guidelines should be given on <u>sponsors responsibilities regarding collection and verification of adverse event/reactions</u> ; this is why we would strongly suggest:
  - o that the Commission reintroduces section 4.2 of the previous guidance in the new CT3.
  - o that a new section is included in the guidance proposing the topics to be covered in the safety assessment section of a CT protocol. As a matter of fact, protocol is the document that should guide the investigators to ensure that in the clinical trial, all sites apply the same criteria with respect to adverse event collection and reporting ; however many protocols are very deficient regarding such procedures. CTFG will be happy to work on such a list.

1.2. The new guidance is shorter as references to other guidelines are given and therefore may be more difficult to read, particularly for academic sponsors; lack of table of contents does not make the guidance very clear.

1.3. According to ICH E2A, we believe that some other safety issues not falling within the definition of SUSARs may require rapid communication to regulatory authorities (this is the wording of chapter 3A2 of ICHE2A guideline) because they might influence the benefit-risk assessment of the IMP or of the CT, such as increased frequency of an expected serious adverse reaction, lack of efficacy, major safety issue from non clinical studies, serious reactions related to misuse, medication errors and overdose, serious adverse reactions linked to a NIMP…

However, those events may not require a urgent safety measure by the sponsor nor a substantial amendment nor an early termination of the CT as stated in Section 4.11.3. and the guidance does not cover them.

We would like to stress again the need to clarify section 4.11.3 in order that these information are reported to NCAs on an expedited basis, as it is required in the current guidance and the ICHE2A guideline. Section 5.1.1.2 of the current guidance should be reintroduced.

1.4. All Q and As should be integrated in this guidance (eg. Q and A 2 to 9).

2. Detailed comments

2.1. What SUSARs to be reported?

- As over - reporting is one of the most important issue, it should be said clearly that SUSARs to be reported are only those related to IMP (paragraph 46).

- Paragraphs 46 and 92 should also clearly state that only unblinded SUSARs are to be reported to NCAs and to EV-CTM, as a general rule.

- Furthermore, for trials in high morbidity or high mortality disease (paragraph 96), sponsors shall appoint (and not "are encouraged to appoint") a DSMB and its composition and rules should be attached to the protocol.

- Section 2.3.2. "…serious adverse event, as well as possible guidance in the IB": the possible guidance should be preferably in the clinical trial protocol rather than in the IB.

- *The guidance should give details on when SUSARs reporting should start. From the international birthday to all concerned MS?*

2.2. Causality

It should be clearly specified in chapter 4.3.2, that :

- Only cases of SUSARs, for which a reasonable causal relationship between the event and the IMP has been established by the sponsor and/or the investigator, should be reported to the NCAs and to EVCTM,
- Events with no reasonable causal relationship with the IMP do not need to be reported.
- Causality should be assessed by the investigator and/or the sponsor; the sentence "the assessment of causality is often made by the investigator" in paragraph 40 should be deleted.

2.3. Expectedness:

- Who should assess expectedness of an adverse reaction (section 4.3.3) is not clear. It should be the responsibility of the sponsor who is generally the one with the best knowledge on the IMP ; this rule is in the current guidance and there is no reason to change it. Furthermore, in the directive 2001/20/EC article 16.1, it is stated that investigators shall report SAE to the sponsor and in article 17 that the sponsor shall report SUSARs. Therefore it is unclear why the investigator should assess the expectedness.

- The choice of the reference safety information (RSI) needs further clarification. CTFG recommends the following:
  - Always use the same wordings (replace "product information" by "reference safety information" (paragraph 43)) in order to avoid misinterpretation.
  - Clarify that the RSI is:
    - the investigator's brochure, for a MP not authorised in any member state (MS) or used outside the conditions/terms of its marketing authorisation;
    - the summary of product characteristics (SmPC) for an authorised IMP in any MS which is being used in the CT according to the terms and conditions of the MA.
  - As mentioned in CT1, it should be reminded here that when the IMP has a MA in several MS with different SmPC, the sponsor should select the most appropriate SmPC, with reference to patient safety, as the reference document for assessing expectedness.
  - The RSI is the same for the whole clinical trial in all the MS concerned. It is clearly identified in the protocol and in the cover letter and attached to the CTA in an acceptable language.
  - A change in the RSI should be accepted by all MS concerned before it can be implemented for expedited reporting.
  - For ASRs, the RSI to use is the one in effect at the start of the reporting period.
  - The investigator's brochure should clearly describe in the section "summary of data and guidance for investigators" what are the expected adverse reactions.

- Paragraph 34 should also mention section 2C of ICHE2A, where it is said that reports which add significant information on specificity and severity of a known serious AR constitute also unexpected adverse events.

2.4. Reporting of SUSARs:

- Minimum reporting criteria
  - Paragraph 60: it is not clear whether the "relevant information" detailed in this paragraph corresponds to the "minimum reporting criteria" mentioned in paragraph 56 (we guess yes; so, harmonisation of wordings is necessary).
    Furthermore, it should be précised that all the criteria are needed to initiate a SUSAR report to the NCA.
    In paragraph 60, it should be mentioned that the valid EudraCT number is only required "if appropriate", since not all CTs have an Eudract number.
  - The minimum requirements detailed in this new CT3 guidance and those detailed in the current version of the "note for guidance EudraVigilance human – processing of safety messages and individual case Safety reports (ICSRs)" by EMA should be in accordance.

- Content: recommendations on the "content of initial reporting" (Section 4.7.1.2.) and on the "content of follow up information" (section 4.7.2.2.) should be applied not only to life - threatening SUSARs but also to all other SUSARs. So, section 4.8. regarding the reporting of non fatal and non life-threatening SUSARs should be identical to section 4.7., especially the content of initial and follow-up reporting. One exception is the timeframe of initial reporting of 15 days.
- Section 4.6: This is a guideline on clinical trials, and only for sponsors which are outside of pharmacovigilance requirements. Therefore, it has not sense and it may be seen as a supplementary complexity to give such a detailed description of pharmacovigilance legislation. Points 49 and 50 should be deleted.

2.5. What SUSARs Ethics Committees are supposed to receive and how is not clear in the guidance (section 4.9).

Should ECs receive on an expedited basis only the SUSARs occurred in the trial for which they gave the opinion? Only those occurring in their territory? All the SUSARs that NCAs will also receive?

We recognise that the directive requires EC to receive SUSARs. We would recommend:
- only ECs who gave the opinion on the CTs should receive SUSARs;
- they should receive only SUSARs occurring in subjects included in the concerned CTs in their country.

2.6. DSUR/ASR:

The guidance introduces the Development Safety Update Report (DSUR) that should replace the Annual Safety Report when the ICH E2F guideline is published and implemented.

We would suggest the Commission:
- to clarify the fact that this ICH guideline is to be applied by all sponsors including non commercial sponsors.
- to publish the templates of DSUR for non commercial sponsors, as an attachment of the guidance.
- to set up a centralised notification of the DIBD (development international birthdate), and to give further details on when (at the time of the CTA application), by whom (sponsor) and how (in EudraCT or EV-CTM) the DIBD has to be notified.
- to set up a single European electronic repository of DSUR in order to simplify the process.
- to clarify which is the information on DSUR, Ethics Committees should receive. As proposed in the DSUR guidance (ICHE2F), ECs should receive only the executive summary of the DSUR.

2.7. EV-CTM:

We fully endorse the need to improve EV-CTM functionalities in order to make it the single CT safety database in Europe.

However, legislation can request the general use of an application only when all people who should comply with the legislation are able to use it. In order to achieve that, EV-CTM functionalities should be improved, the registration procedure simplified and the costs for the users (sponsors) should be reduced to a minimum.
- A first description of the NCAs needs in terms of improvement of EVCTM in order to achieve the principle of a single EU database has been provided to

EMA and the Commission by the CTFG. The basic and enhanced functionalities should cover the NCAs' description of needs for SUSARs assessment delivered by CTFG. All those functional specifications should be taken into account with a time frame announced for their implementation.

- With the view to simplify EV-CTM to allow all sponsors to enter SUSARs, we believe that:
  - The currently mandatory courses on Eudravigilance-CT M should turn to be on-line.
  - A procedure that would avoid the sponsor to fill in the same information in both the EV-MPD and in the CT application form to be loaded in EudraCT is needed.

- Further provisions should be given in the guidance regarding how and when sponsors should populate EV medicinal product dictionnary; how and when EudraCT and EV-CTM will be linked.

- Indirect reporting of SUSARs to EV-CTM: we understand that 3 options should be offered to Member State (MS) to organise SUSARs reporting in EV-CTM.
  - 4.7.3.2. (76) With regard to the sponsor, we may suggest that a differentiation is needed between commercial and non-commercial sponsors as well as small enterprises. Only for the later two, the paragraph 76 should be applicable.
  - Regarding SUSARs from 3rd countries (section 4.7.3.3.), we do not agree with the option that lets the sponsors choose the MS who will enter those SUSARs in EVCTM, since some MS will not be able to offer such an option. The wording should be modified and replaced by "or chose any on MS concerned which offers/or agrees with the MS ensuring indirect reporting" (paragraphs 80 and 81). Furthermore this should be limited only in cases where the sponsor is not able to report directly.
  - In paragraph 89, it should be pointed out that according Article 17(3)(a) of Directive 2001/20/EC Ethics Committees (EC) do not have access to EVCTM, since this database is only accessible for the Commission, the Agency, and the NCAs.
  - Indirect reporting should not be acceptable when the advanced functionalities of EudraCT and EV-CTM are in place.

2.8. Information of investigators (paragraph 91):

We note that the recommendations proposed by the Commission are not laid down in the CTD.

Adding a time frame for providing the line listings would be appreciated. We would like to suggest quarterly reports.

The sponsor should though be aware of the fact that in the case of a significant safety issue following either the receipt of an individual case report or the review of aggregate data, he should inform investigators as soon as possible.

The recommendation should be given that communication to investigators should be concise and practical, avoiding overloading with non analysed individual reports.