Anticipated changes to the detailed guidance CT3 and impact

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EV Info Day 19 Oct. 2010

The clinical trial directive requires:

- Investigators to report serious AE immediately to sponsor
- Sponsors
  - to collect and submit safety data from IMPs in clinical trials (SUSAR and Annual Safety Reports/ASR);
  - SUSAR reports to be entered electronically into Eudravigilance-CTM (EV-CTM);
- EMA to provide national competent authorities (NCAs) with access to the data in EV-CTM.
- Sponsors and MS to continuously monitor safety to protect clinical trial participants and public health;
- NCAs and ECs (Ethics committees) to receive SUSARs and annual safety reports;
- NCAs to suspend or prohibit a CT where appropriate;
- The Commission to provide detailed guidances.
The current situation

• 2 guidances:
  – Detailed guidance on the presentation of AR reports arising from CT on MP for human use (CT3) - April 2006
  – Detailed guidance on EV-CTM (CT4) - April 2004

• Some difficulties/issues

General issues

• Rules for Reporting of SUSARs are different or not clear
  – With impact on sponsors (unnecessary burden)
  – And on Eudravigilance (data quality);
• The communication of SUSARs to ECs is variable and excessive;
• Roles of National CAs and ECs need greater clarity;
• The content of the annual safety report is not harmonised.
• Too much SUSARs declared / not only Susars are declared
• NCAs do not receive automatically by EV-CTM the information they need to ensure their responsibilities (subject’s safety)
• Need for more harmonisation of decisions between NCAs
The responses

- **Short term (same regulatory framework)**
  - Strengthening implementing guidelines → CT3 revision
  - Strengthening cooperation of MS (CTFG)
    - Worksharing of assessment
  - Improving EV-CTM
    - According to NCAs/CTFG needs
    - Simplify trainings, new business rules, Q and A…(CTFG and EV-WG)

- **Mid term**
  - Revision of the CTD (Mid 2012)
    - e.g.
      - SUSARs to Ethics Committees
      - simplification

The new Commission’s CT3 guidance

- Public consultation until 10 September 2010
- Replacement of:
  - CT3 guidance;
  - CT4 guidance; and
  - Questions & Answers specific to adverse reaction reporting in clinical trials.
- **What is possible under the current legal framework (CTD)**
- Some cross reference to the new CTA guidance (CT1 – March 2010), ICH E2 A
- What’s new in the published draft?
• Reporting rules by investigators to sponsors
• Reporting rules by sponsors to:
  – NCAs
  – ECs
  – Investigators
  – Expedited SUSARs/yearly reports
• Functionalities of EV-CTM

Definitions

• CTD definitions
  – + comments from ICH E2A (no change)
• SAE:
  – “important medical event” may jeopardise the CT subject or may require an intervention to prevent seriousness = SAE
  – medical and scientific judgement to decide whether AE is serious
  – examples in ICH E2A.
1. Article 16 (1) of CTD: immediate reporting of SAE to sponsor + follow up
   • (except those identified in protocol or BI)
   • Times lines “immediate”: ≤ 48 hours
   • Purpose: ensure the sponsor has the necessary information to continuously assess the R/B balance of the CT

2. Non immediate reporting

3. Reporting of non serious AE
   • Article 16 (2) of CTD → protocol

Purpose of reporting to NCA-ECs

• Make regulators aware of SUSARs
  – Chapter 2C of ICH E2 A

• Give NCAs and ECs the possibility to:
  – take measures to protect the safety of CT participant
  – assess risk to the CT participant

⚠️ NCAs and ECs assess and take measures

No clear definition of respective roles
Focus on SUSARS exclusively

- Causality assessment between SAE and IMP: “a reasonable relationship should suffice”
- Unexpectedness
  - Reference Safety Information (RSI)
  - Significant info on specificity or severity of an expected AR
    → unexpected AR

Who does what?

<table>
<thead>
<tr>
<th>Seriousness</th>
<th>Causality</th>
<th>Expectedness</th>
</tr>
</thead>
</table>
| « usually the investigator » | « often made by the investigator » If sp. disagrees, no down grade. | • Sponsor
• Consultation of investigator |

SUSARs reporting rules

By Whom?
- By the sponsor of a CT in at least one MS

What?
- All SUSARs in that CT
  - Wherever it occurs (MS or 3rd country)
- All SUSARs same active substance
  - In a CT performed exclusively in a 3rd country
    • Same sponsor
    • Another sponsor part of same mother company or if development agreement
  - Transitional procedure, while waiting EVCTM enhancement:
    • In a CT in another MS, same sponsor or same mother company or if development agreement.

To whom?
- EVCTM + MS
AR not to reported as SUSARs

- Expected SARs, SAEs
- NIMP SAE without interaction with IMP
- SUSARs in a CT in EU by another sponsor
- Reports under the provision of pharmacovigilance (Dir 2001/83/EC) of authorised MP

Fatal or life threatening SUSARs

<table>
<thead>
<tr>
<th>Initial report</th>
<th>Follow up report</th>
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</thead>
<tbody>
<tr>
<td>• ≤ 7 days after knowledge of minimum reporting criteria (MRC)</td>
<td>• Within 8 additional days</td>
</tr>
<tr>
<td>• minimum reporting criteria:</td>
<td>• if information received after D15: 15 additional days</td>
</tr>
<tr>
<td>- EudraCT number</td>
<td>• only « relevant information »</td>
</tr>
<tr>
<td>- sponsor study number</td>
<td>• examples of non relevant information</td>
</tr>
<tr>
<td>- identifiable subject</td>
<td></td>
</tr>
<tr>
<td>- reporter</td>
<td></td>
</tr>
<tr>
<td>- SUSAR</td>
<td></td>
</tr>
<tr>
<td>- IMP</td>
<td></td>
</tr>
<tr>
<td>+ administrative info (eg receipt dates)</td>
<td></td>
</tr>
</tbody>
</table>

D0 | D7 | D15 | 15 days | 15 days
---|---|----|---|---
Receipt of MRC | Initial rep. | F. up. | Receipt new info. | F. up.
"Relevant information"

"Which is necessary in order to
– Verify whether the anticipated therapeutic and public health benefits continue to justify the risks
– And to process the report administratively"

• Medical judgement should be applied to identify relevant/non relevant information
• Examples of non relevant information

Addressees of SUSARs reports

• NCAs + EVCTM (+ ECs)
• EVCTM will be the transmission tool
• EVCTM capabilities to be improved
• Transitional period
How to report SUSAR: perspectives

- SUSARs reported by sponsors to NCAs through EVCTM
- 3 options:
  - Direct reporting to EVCTM is mandatory
  - Indirect reporting of national SUSARs to NCA is possible and NCAs enter in EVCTM
  - The sponsor chooses direct/indirect reporting
- Sponsor with no resource/experience
  - Indirect reporting
  - Outsource or delegate direct reporting to a partner

Transitional reporting procedures

<table>
<thead>
<tr>
<th>To MS</th>
<th>To EV-CTM</th>
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</thead>
</table>
| • all SUSAR in that CT  
• all SUSAR same active substance in a CT performed:  
  - in 3rd country  
  - in another MS | • MS where SUSAR occurred ensures it is reported in EVCTM:  
  - direct  
  - or indirect reporting  
• SUSARs in 3rd countries in a CT also performed in EU or not:  
  - direct report  
  - or sponsor chooses any MS concerned which ensures indirect reporting |
Format of reports

- ICH E2 B
- Note for guidance EV processing of ICSRs
- Data free text in English
- New process = EVMPD (EV medicinal product dictionary)
  - Populated by the sponsor
  - When and how?

SUSARs reporting to ECs

- Which EC?
  - Only the EC issuing the "single opinion"
  - Of the MS where the event occurs
- What?
  - Only SUSAR occurred in that MS???
  - Needs clarification
- Reporting procedures and time lines: same as for NCAs
  - No periodic reports anymore
- How?
  - Content needs clarification
SUSARs – information of investigators

• If appropriate:
  – Line listing of SUSARs + concise summary of the evolving safety profile of the IMP
  – “in period as warranted by the nature of development and volume of SUSARs”

Other issues (1)

• UNBLINDING
  – Reporting unblinded SUSARs is still the rule!
  – Exception may be possible
    • After agreement with NCA in the authorisation process
    • High morbidity/mortality CTs where efficacy end point may be also a SUSAR or mortality is the end point
      – DMC recommended
      – Composition and operation described in the protocol
  ➢ NO CHANGE
Other issues (2)

- **OTHER SAFETY ISSUES/NOT SUSAR**
  - Information/new event relevant to subjects’ safety
  - Or may require action: see chapter 3A2 of ICH E2 A
  - Not to be reported as SUSARs
  - but may require other action e.g.:
    - USM
    - Subst. Amendment
    - Early termination
  See CT1 guidance

\[\text{ICH E2 A} - \text{some events should be also reported to NCA even if no specific action (e.g. pregnancy, new significant non clinical result, overdose, lack of efficacy...)}\]

“Yearly reporting of SARs by the sponsor”

- “Annual safety report”
- Reference to the DSUR-ICH guideline
- Addressee: NCA and EC of the MS concerned
EV CTM functionalities (1)

- Provisions of EV-CTM
  - Overview of SUSARs in the Union as a whole and in each MS
  - Facilitated reporting to NCAs concerned (MNCTs)
  - Better communication between NCAs, Commission and EMA
- Basic functionalities allow for:
  - Direct reporting based on international formats
  - Some specific reports
  - Some queries

EV CTM functionalities (2)

- Enhanced functionalities
- Proposed by CTFG
- available after the transitional period
- Concept of “SUSARs relevant for MS”:
  - SUSARs on IMPs used in CT authorised by that MS
  - Link EudraCT and EV-CTM
- Daily messages – new SUSARs for all IMPs/CTs relevant for each MS
- Alerts of SUSARs relevant for MS for certain types of reactions, trials (e.g. FIH) or populations (e.g. healthy volunteers…) or active substance of interest
- More reports.
Conclusions

- New CT3 guidance
- Response to many calls from sponsors and NCAs (EV CTM) for short term improvements
- Limited to what is possible under the current legal framework
- Still needs clarification after the public consultation
- CTFG and EV WG have actively participated to the consultation
- In parallel, development of NCAs cooperation and EV CTM improvement.

Thank you