Anticipated changes to the detailed guidance CT3 and impact

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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 frame work)
  - 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 untill 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?

Content

- 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 E2 A.

Investigators

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) → IB / SMPc
  - Significant info on specificity or severity of an expected AR → unexpected AR
- Who does what ?

Seriousness	Causality	Expectedness
« usually the investigator »	« often made by the investigator » If sp. disagrees, no down grade.	• Sponsor • Consultation of investigator

SUSARs reporting rules

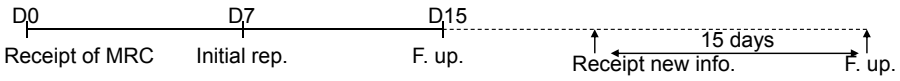
By Whom?	What ?	To whom ?
• By the sponsor of a CT in at least one MS	• All SUSARs in that CT – Wherever it occurs (MS or 3rd country) • All SUSARs same active substance – In a CT performed exclusively in a 3rd country • Same sponsor • Another sponsor part of same mother company or if development agreement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

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



“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

To MS	To EV-CTM
• all SUSAR in that CT • all SUSAR same active substance in a CT performed: − in 3rd country − in another MS	• MS where SUSAR occured ensures it is reported in EV-CTM: − 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 dictionnary)
  - 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

⚠ ICH E2 A - 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