The new Clinical Trial Regulation (CTR) explained

Safety monitoring and reporting

Session 2, November 23rd

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New concepts - Safety
Implementing Regulation for safety

- Currently being developed by the European Commission
- Supplementary legislation to the clinical trial (CT) Regulation (31st Jan 2022)
- Due to come into effect at the same time as the CT Regulation
- Describes how Member States (MS) will interact to assess safety reports
  - Who leads the safety assessment
  - Timelines for assessing safety reports
  - Risk based approaches to safety assessment by MS
  - Applies to ASRs and SUSARs only
- ‘Implementing act’ referred to in Art 44 of the CT Regulation
saMS

safety assessing Member State

• Lead member state for assessing safety issues linked with an active substance

• saMS selection for a new active substance:
  – 1. If one MS concerned volunteers – they become saMS
  – 2. If more than one MS concerned volunteers – selected based on expertise
  – 3. If no MS concerned volunteers – selected based on fair work share IT algorithm

• If new CT authorised with an active substance which already has a saMS, then this MS becomes saMS for this CT also

• Responsible for assessing:
  – ASRs (DSURs)
  – SUSARs
Lead saMS

• Where there are multiple active substances involved in a safety signal:
  – One saMS takes the lead and co-ordinates exchanges with other relevant saMS
  – Each relevant saMS still responsible for assessment of their active substance
  – Rely on volunteer for lead saMS

• Example: Drug class effect

• Rare occasion
Corrective Measures
CTR Art 77

• A Member State concerned may take the following measures on its territory:
  – revoke the authorisation of a clinical trial
  – suspend a clinical trial
  – require the sponsor to modify any aspect of the clinical trial
Corrective Measures
CTR Art 77

- saMS (or lead saMS) may propose recommended actions in relation to an active substance(s) following the assessment of:
  - SUSARs
  - ASR

- However regardless of saMS (or RMS) recommendation - **Overall responsibility for a CT remains with individual MSC**
Reduced safety reporting

- Article 41 - Two possible risk adaptations to safety reporting:
  - selective recording and reporting of AEs
  - adaptations to immediate reporting from the investigator to the sponsor, for certain SAEs

- Reduced safety reporting must be justified in the cover letter of CT application

- Applicable to low intervention CTs
Guidelines

Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use “CT-3” guideline will be replaced by the safety chapter in the Q+A document on the European Commission website.

https://ec.europa.eu/health/documents/eudralex/vol-10_en#fragment1
Transition Period

• SUSARs and other relevant safety information to be submitted under the legislation which the CT is governed under

• The same applies to ASRs
  – Exception: Where an ASR contains information on CTs that are governed under the Directive and CTs that are governed under CTR, the submission of the ASR is to CTIS (CTR). However sponsors are still obliged as of CT-3 to submit ASRs to Ethics Committees
ASRs
Annual Safety Reports
CTR Article 43
ASR - What stays the same?

- ASR usually per IMP, occasionally per CT (clinical trial)
- Definition of SAEs, SARs
- Content of the ASR
- Development Safety Update Report (DSUR) format as per ICH E2F
- Frequency of submission (annually) and Data Lock Point (DLP)
- Development International Birth Date (DIBD), alignment with International Birth Date (IBD) if authorised IMP
ASR – What is new?

• Single submission to CTIS - No direct reporting to NCAs or ethics committees

• Co-ordinated, workshared assessment:
  – Assessment led by saMS for ASRs per IMP/active substance
  – Assessment led by reporting MS for ASRs submitted per CT
  – All relevant reporting MSs and MS concerned have the opportunity to comment/raise queries, but saMS send any queries to the sponsor
  – saMS may propose corrective measures for Reporting MSs and MS concerned to consider for their specific CT

• Safety data for Auxiliary medicinal products can be included in section 7.2 of the ASR (Line Listings of SARs), separate ASR not needed
SUSARs
Suspected, Unexpected, Serious Adverse Reactions
CTR Article 42
SUSARs – What stays the same?

- Content of SUSAR reports (ICSR, ICH E2B)
- Timelines for submission of SUSAR reports:
  - 7 days for fatal and life-threatening SUSARs
  - 15 days for other SUSARs
- Reports submitted to and stored in EudraVigilance (EVCTM)
- HPRA will continue to facilitate submission of SUSARs to EudraVigilance for non-commercial sponsors *(must be pre-agreed with HPRA)*
- Reference Safety Information (RSI) used to determine expectedness
- MS concerned may choose to perform national assessments of SUSARs which occur in their territory
SUSARs – What is new?

• Co-ordinated, workshared assessment:
  – Assessment led by saMS
  – Should safety concern arise, all relevant reporting MSs and MS concerned have the opportunity to comment/raise queries, but saMS send any queries to the sponsor (via ad hoc CTIS case)
  – saMS may propose corrective measures for reporting MSs and MS concerned to consider for their specific CT

• No direct reporting to ethics committees and NCAs - reported to EudraVigilance only

• Sponsors encouraged to send safety profile changes sent to investigators, not individual SUSARs
Other safety notifications
## Safety notifications/information

<table>
<thead>
<tr>
<th>Type of notification/information</th>
<th>Article #</th>
<th>Sponsor reporting timeframe</th>
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<tbody>
<tr>
<td>Temporary halt or early termination by the sponsor for reasons of subject safety</td>
<td>Article 38</td>
<td>15 days</td>
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<tr>
<td>Other reporting obligations relevant for subject safety</td>
<td>Article 53</td>
<td>15 days</td>
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<td>• eg change in benefit risk</td>
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<tr>
<td>Urgent safety measures (USM)</td>
<td>Article 54</td>
<td>7 days</td>
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NEW!
Safety notifications/information

- All submitted to CTIS as an ‘ad hoc’ case
  - See training module 5, EMA website
- Will be assessed by:
  - MS concerned – if safety issue is linked to a national issue only (affecting Part II eg urgent update of ICF)
  - Reporting MS - if safety issue is linked to a specific clinical trial
    - Reporting MS may liaise with saMS if safety issue is linked to an IMP/active substance
Questions?

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