Council for International Organizations of Medical Sciences

Second meeting of the CIOMS Working Group (WG) XVI on the Development Safety Update Report (DSUR)

3 June 2025, virtual meeting

Minutes

Overview:

Summary

The CIOMS WG XVI convened its second meeting virtually on 3 June 2025. The meeting focused on the review and discussion of proposed revisions to the DSUR template, including subgroup presentation and feedback from WG members. The WG agreed to hold two virtual meetings in September and October 2025, with an in-person meeting planned for January 2026.

Minutes of discussion

1. Opening and welcome

- Lembit Rägo, CIOMS Secretary-General, welcomed all participants to the virtual meeting and opened with introductory remarks. (For a list of participants see Annex 1).
- He highlighted two recently published CIOMS guidelines:

  - The report on Severe Cutaneous Adverse Reactions (SCAR).
  - The report on Benefit-Risk Balance for Medicinal Products.
  - Both documents are publicly accessible via the CIOMS website. A limited number of printed hard copies are also available by request.
  - An updated version of the Glossary of ICH terms and definitions (Version 8) are to be published in June. The update incorporates new terms from recent ICH guidance documents. Future updates to the glossary are planned to occur at least twice annually, aligned with new ICH publications.
- Lembit also noted CIOMS' continued efforts to disseminate WG outputs more broadly through webinars, especially after new guidance publications. Webinars for the Severe Cutaneous Adverse Reactions and Benefit-Risk Balance for Medicinal Products reports are being planned for post-summer 2025 (likely September) to ensure maximum engagement.
- Agenda was adopted.
- Kateriina was rapporteur.

2. Presentation of Revised DSUR Template Proposal

- Tessy and Donald presented the work of the subgroup tasked with developing a revised DSUR template.
- The presentation was structured around three components:
  1. Conceptual framework for the revised structure
  2. A proposed roadmap aligning the current International Council for Harmonisation – Guideline E2F: Development Safety Update Report (DSUR) (ICH E2F) structure with the new format
  3. A draft table of contents for the updated DSUR template
- The approach was based on three main categories of content: (1) background data (non-clinical and clinical), (2) the company's internal signal detection and safety monitoring processes, and (3) benefit-risk considerations.
- The revised template aligns with ICH E2F principles (sections 1 and 2 were not revised).
- The overarching goal was to:
  - Streamline content;
  - Reduce redundancies;
  - Improve navigability and utility for both regulators and industry;
  - Maintain flexibility without sacrificing the integrity of required safety data.
- Key modifications include:
  - Merging or removing certain sections, with some data relocated to appendices (e.g. Reference Safety Information (RSI) changes):
  - Emphasis on signal evaluation as a unifying framework for multiple safety data components;
  - Restructured appendices, including expanded "Global Appendices" and minimised "Regional Appendices";
  - Proposal to keep post-marketing data only as part of signal evaluation, not as standalone sections.
- A clean draft template is under development and will be refined following feedback from subgroup members before circulation to the full WG.
- Presenters noted that proposals did not yet differentiate between early-phase and post-marketing trials due to time constraints but acknowledged the relevance of that discussion for the future.

3. Discussion and Reflections on the Proposed Template

Post-marketing Safety Data

- Beatrice questioned the removal of post-marketing data, noting its value in transitional situations (e.g. early post-approval).
- Donald and Tessy clarified that post-marketing data would be captured within signal evaluation if relevant and emerging.
- WG members suggested that clearer indexing or guidance within the template could aid users in locating such cross-cutting information.

Signal vs. Safety Monitoring Terminology

- Several WG members expressed concern about using the term 'signal' in a clinical trial context, as it is traditionally associated with post-marketing pharmacovigilance.
- Alternatives such as 'safety monitoring', 'safety issues', or 'safety concerns' were proposed.
- Donald noted variability across companies in terminology use but emphasised that guidance can include a glossary to clarify terms.

Risk Minimisation Measures

- The need to explicitly reflect on the effectiveness and adequacy of risk minimisation strategies within the DSUR was stressed.
- A new or expanded table was proposed to show:
    - Safety concern status (start/end of reporting period);
    - Risk minimisation measures;
    - Updates or changes to measures (e.g. protocol amendments).
- The inclusion of this table in the main body (rather than appendices) was strongly recommended to improve accessibility and training value.

Benefit-Risk Assessment

- The appropriate treatment of benefit-risk, especially in early-phase development was discussed.
- There was broad agreement that even in the absence of confirmed efficacy, anticipated or theoretical benefits should be described.
- The group agreed to retain the current ICH format for benefit-risk sections while ensuring alignment with the new CIOMS guidance.

Guidance and Glossary Needs

- The importance of accompanying the template with clear guidance and terminology definitions was underlined.
- Concepts such as Adverse Drug Reaction (ADR), RSI, and 'new risk' vary across contexts and must be clearly explained to aid understanding, particularly among smaller sponsors and Contract Research Organisations (CROs).

Feedback Integration and Project Structure

- Antonella clarified that comments submitted reflected input from the Clinical Trials Coordination Group (CTCG) safety subgroup.
- Peter suggested a more structured approach to advancing the work:
    - Divide specific sections (e.g. RSI, risk display, data sources) among small teams for focused development
    - Avoid over-editing during plenary calls
- Donald and Tessy confirmed that the subgroup would finalise the draft based on initial feedback and then circulate it to the full WG.

Next Steps and Publication Outlook

- The final product will be a CIOMS WG report with recommendations. All CIOMS outputs are advisory.
- Engagement with ICH or external stakeholders will be considered once the proposal reaches a mature draft stage.
- WG members were encouraged to promote and present the evolving work at relevant scientific conferences.

4. Presentation on Safety Reporting in Combined Trials – Insights from the COMBINE Programme

- Corina introduced the European COMBINE programme, launched in late 2024, aimed at optimising the regulatory environment for combined studies, i.e. clinical trials that involve medicinal products in conjunction with in vitro diagnostics (IVDs) or medical devices.
- She explained the regulatory context in Europe: while the Clinical Trial Regulation (CTR) introduced centralised submission via the Clinical Trials Information System (CTIS), the Medical Devices Regulation (MDR) and the In Vitro Diagnostics Regulation (IVDR) still operate with national-level submissions. This fragmented regulatory pathway may cause delays in initiating combined studies.
- Combined studies, by definition, require simultaneous compliance with CTR, MDR, and IVDR, making safety reporting particularly complex.
- To address this, a cross-sectoral project (Project 2) was launched under the COMBINE programme, involving stakeholders from clinical trials, medical devices, IVDs, ethics committees, and EMA.
- The project began in February 2025 and focused on:
    - Comparing safety reporting obligations across CTR, MDR, and IVDR.
    - Identifying practical challenges from stakeholders (industry, investigators).
    - Proposing harmonised solutions, possibly including a guidance document and legal recommendations.
- Corina emphasised that serious adverse event (SAE) reporting in such trials presents unique challenges:
    - Different definitions of ‘seriousness’ across the regulations.
    - Overlap of responsibilities (e.g. when an SAE could be caused by the IMP or the device).
    - Additional concepts such as ‘indirect harm’ from IVDs (e.g. misdiagnosis leading to incorrect treatment).

- Corina proposed that CIOMS WG XVI consider how to integrate relevant safety aspects from such trials into the DSUR, given their growing prevalence in precision medicine and advanced therapy settings.

5. Discussion on Integration of Combined Trials into the DSUR Framework

- Peter asked how IVDR and MDR reporting obligations might be incorporated into the DSUR and whether reciprocal integration (from DSURs into medical device frameworks) was being considered. He noted the challenge of doing this in a globally harmonised way.
- Corina responded that while the focus is on improving benefit-risk transparency in combined trials, such integration is not yet reflected in DSUR templates. She emphasised the importance of reflecting impacts regardless of the source (IMP, device, or IVD).
- Pete referenced early ICH E2F drafts that aimed to evaluate not just product-related safety, but the safety of study procedures overall. He welcomed Corina's proposal as aligned with this original intent.
- He noted that Donald and Tessy's draft already moves in this direction by supporting better structuring of safety data beyond traditional adverse reactions.
- Beatrice highlighted the value of a holistic benefit-risk assessment that includes all components of a study.
- However, she cautioned that the DSUR remains, by definition, a report on the investigational medicinal product (IMP). Expanding it to cover full study safety might dilute its regulatory purpose.
- She proposed that references to combined product risks could be included in the section on safety monitoring activities, provided there is clarity about causality and attribution (i.e. IMP vs. device).
- Antonella added that CTR already requires sponsors to notify regulators of any event that significantly affects the benefit-risk profile of the trial, not limited to the IMP.
- She noted that such events must be reported both on an expedited basis and periodically (e.g. in the DSUR or ASR), supporting the notion that existing frameworks can accommodate some of these broader concerns.

Practical Integration Approaches

- Tessy supported the idea of pragmatic integration. She proposed:
    - Clearly identifying combined trials in the DSUR introduction.
    - Integrating relevant issues into sections such as "Actions Taken for Safety Reasons" or signal detection, depending on the nature of the event.
    - Ensuring transparency and consistency throughout the document.
- Lembit noted that CIOMS WG XVI should provide at least high-level guidance on how safety data from combined trials might be addressed in the DSUR. He acknowledged that while DSURs may not cover all aspects in depth, even brief recommendations could help guide sponsors in responding to emerging trial designs.

Technical Considerations and Regional Practices

- Donald queried whether combined trials generally align with IMP development programmes.
- Corina explained that many current examples involve biomarker-driven IVDs embedded in clinical trials, often without parallel authorisation, or involve delivery devices and software.
- Antonella and Corina noted that in many countries, including Italy, medical devices fall under the responsibility of separate authorities, and integration across regulatory databases remains

limited. Carmen added that in Switzerland, Swissmedic oversees combined studies, but the review is internally structured: the department responsible for medical devices leads the evaluation, while a separate department handles the review of medicinal product component.
- Beatrice elaborated on US practice, noting that combined studies are managed under the IND framework, with only significant events being escalated to FDA or IRBs.

6. Next steps / next meeting

- Lembit proposed the idea of hosting a CIOMS webinar on the current DSUR revision project to raise awareness of the issues identified with the current DSUR format and highlight the working group's efforts toward a more functional model.
- Two options were presented:
    - Wait until the report is finalised before launching a public webinar (usual CIOMS practice).
    - Alternatively, host an interim webinar on ongoing work to stimulate broader engagement.
- There was general openness to both approaches, depending on timing and need.

In-Person and virtual meetings

- No in-person meeting will be planned for 2025. The first in-person meeting is tentatively scheduled for January 2026.
- Indra kindly volunteered to explore the possibility of hosting the January meeting in Barcelona, subject to confirmation with the local office.
- It was agreed that two virtual meetings will be scheduled before the January in-person meeting to:
    - Review progress and maintain engagement with the full working group.
    - Facilitate decisions on subgroup deliverables.
- The first virtual meeting is tentatively targeted for mid to late September 2025, with a second to follow in October or November. CIOMS Secretariat will help schedule the meetings.
- Beatrice will deliver a presentation during the September meeting on key concepts from the new CIOMS report on Benefit-Risk Balance for Medicinal Products, with potential application to the revised DSUR.

Workstreams and Subgroup Organisation

- The subgroup will:
    - Finalise the integrated working draft of the revised DSUR template by late June 2025.
    - Circulate the draft to the full working group for feedback.
    - Flag sections that require more detailed subgroup discussion.
- The full group will then be invited to join targeted subgroups based on interest and expertise. These will work on discrete content areas and guidance topics throughout Q3/Q4 2025.
- It was agreed that subgroup leads will be identified once priority sections are confirmed in the subgroups' review meeting.
- Corina will convene a small subgroup in autumn 2025 focused on combined trials, building on her earlier presentation. Volunteers already include Elena and Beatrice (mapping US and possibly Japanese frameworks).

- CIOMS Secretariat will distribute Doodle polls for scheduling the next two virtual meetings, coordinate communication regarding subgroup formation and participation and support logistical planning for the in-person meeting.
- It was agreed that timely progress updates from the drafting subgroup will be shared with the broader group to maintain transparency and engagement.

7. Closing remarks

- Lembit thanked all participants for their commitment and contributions. He acknowledged the considerable progress already made and encouraged members to maintain momentum.

Annex 1: List of participants

Participants

Antonella Caselli (Italian Medicines Agency), Carmen Campanile (Swissmedic), Peter De Veene (MSD), Mamiko Konishi (Eisai), Pete Nash (Gilead), Beatrice Panico (Individual expert), Donald Puccio (Pfizer), Kateriina Rannula (CIOMS), Lembit Rägo (CIOMS), Tessy Ruijgrok (Biogen), Anita Shenoy (AbbVie), Corina Spreitzer (Austrian Medicines Agency), Indra Purevjal (Bayer), Mutsuhiro Ikuma (PMDA), Elena Prokofyeva (FAMHP), Wang Xiangyu (NMPA), Wang Haixue (NMPA), Maria Grazia Malpezzi * (Italian Medicines Agency).

*Alternate

Apologies
Eun Mi Kim (WHO), Andrzej Czarnecki (Eli Lilly), Juliana Dornelles (ANVISA), and Richard Pendlebury (Novartis).