8th meeting of the CIOMS Working Group WG XIV on Artificial Intelligence in Pharmacovigilance

7-8 March 2024, Geneva, Switzerland

Minutes

Summary

The CIOMS Working Group XIV on Artificial Intelligence in Pharmacovigilance held its 8th meeting in Geneva, Switzerland, on March 7-8, 2024. The chapter teams gave progress updates, an editorial team was formed, and 9 guiding principles were established, which will form the main framework of the future report. The next in-person meeting will be held in September, while smaller subgroups will continue working virtually.

Minutes of discussion

Day 1

1. Opening and welcome

Hervé le Louët, CIOMS President, welcomed the members to the 8th meeting of the CIOMS Working Group XIV on Artificial Intelligence (AI) in Pharmacovigilance (PV).
Lembit Rägo, CIOMS Secretary General, added his words of welcome and opened the meeting as Chairman for the two days (for a list of participants see **Annex 1**)

Lembit made the following announcements:

- This year CIOMS will celebrate its 75th anniversary.
- The CIOMS Working Groups (WGs) WG XII Benefit-risk balance for medicinal products and WG XIII Real-world data and real-world evidence in regulatory decision making are finalising their reports after addressing numerous public comments. The WG XIII report will be published before summer, WG XII report before end of the year.
- Introduction to MedDRA Labeling Grouping (MLG): A standardized approach to grouping adverse reactions in product safety labels has been published and is available on the CIOMS website (https://doi.org/10.56759/hmku5307).
- CIOMS WG Severe Cutaneous Adverse Reactions to Drugs (SCAR) is reaching maturity for public consultation, aimed to be released before the summer.
- CIOMS Glossary of ICH terms and definitions: Version 5 and CIOMS Cumulative Glossary with a focus on Pharmacovigilance (Version 2.1) are available on the CIOMS website. A special anniversary edition of the CIOMS Glossary will be printed in hard copies to mark the anniversary.

The meeting agenda was adopted.

2. Reflections on the artificial intelligence landscape

- Walter opened the session, acknowledging the challenges faced in drafting chapters 1-3 due to the rapidly evolving field of artificial intelligence (AI). He noted that defining the group's specific contributions would be beneficial, especially considering the unforeseen relevance of generative AI, which was not initially considered at the start of the WG.
- Niklas highlighted the importance of settling on a definition of AI to maintain the group's focus, recommending Jeff Aronson's definition as a starting point:

  "Artificial intelligence n. a branch of computer science that involves the ability of a machine, typically a computer, to emulate specific aspects of human behaviour and to deal with tasks that are normally regarded as primarily proceeding from human cerebral activity. (Latin: *artificialis*, from *ars*, *artis*, art, and *facere* to make; *intelligens*, prp of *intellegere*, to understand, from *inter*, between, and *legere*, to choose)"
- It was suggested that, due to the risk of the content becoming outdated rapidly, the group should aim for targeting the principles for using AI rather than specific current applications, as principles evolve at a slower pace compared to the available technology.
- Bob pointed out a gap in the document regarding how quality assurance should be managed for AI systems, and Denny chimed in with his experience of having to repeatedly revise his section of chapter eight due to the rapid progression of AI becoming a commodity in PV workflows.
- The WG agreed to contact International Society for Pharmaceutical Engineering (ISPE) regarding their work related to AI.
- Further discussions ensued about the need for transparency in AI applications and the potential impact of foundational models developed by large organisations on the field of PV, with a focus on qualifying AI models based on performance in specific use cases rather than the intricacies of their training.
- The group acknowledged the significance of clear guiding principles, particularly as they set the standard for industry, academia, and regulatory authorities. Additionally, the limitations and pitfalls of AI were recognised as crucial elements that must be expanded upon in the document to provide a comprehensive understanding of what AI can and cannot do.
- Monica introduced the Brazilian perspective, highlighting the importance of model development, deployment plans, privacy, and data protection.

3. Progress updates on chapter drafts

Chapters 1-4

Walter, Niklas and Beth gave the chapters 1-4 team's presentation. The following represents the discussion points raised after the presentation. All materials presented during the meeting are available in the WG private member area.

- Does chapter 3 have sufficient substance to stand alone?
- The chapter's main focus is to delineate the scope of the document clearly, ensuring that the content emphasizes principles over practical implications, to avoid the document becoming outdated upon publication. The chapter also provides an orientation to the report's structure and guides the reader through the chapters.
- In chapter 4, there are currently twelve guiding principles adopted from good manufacturing learning practice for medical device development.
- Discussion centered on whether any principles are missing or need to be elaborated upon.

- The chapter's current format, which includes extensive discussion on specific topics, led to consideration of whether these topics should be relocated to ensure that the guiding principles remain high-level and do not lose impact.
- The conversation touched upon the potential overlap of industry and regulatory perspectives.
- Chapter 4 aims to present high-level guiding principles that provide a framework for the entire guidance, threading through all chapters.
- A discussion ensued regarding the necessity of twelve guiding principles specifically for AI and why it may differ from other methodologies.
- The importance of addressing the uncertainty around AI outputs and the need for more complex oversight was underscored.
- The group sought to clarify the main message to readers regarding the preconditions required for AI-generated data to be as reliable as that from deterministic systems.
- A reflection on the content and flow of messages within the chapters was proposed to ensure balance and clarity.
- The WG should agree on the referencing software used and contribute to adding references in the document for a more comprehensive overview.
- Benny will reach out to ISPE for potential collaboration on AI guidance.

Glossary development

- Julie was thanked for beginning to populate the glossary with key terms.
- The group was urged to review the glossary critically to ensure it includes the most critical topics and that consensus is reached on the definitions, particularly of artificial intelligence and machine learning.
- The proposal was made for chapter leads to suggest terms for the glossary from their respective chapters, as it serves as a quick reference for readers to understand terms within the document's context.
- The group considered whether to include 'take-home messages' in boxes within each chapter for enhanced readability and immediate understanding.

Chapters 5-7

Thomas updated the WG on chapters 5-7 progress.

- Robert discussed the possibility of consolidating regulatory perspectives and high-level principles in the beginning of the document for clarity and coherence. There was a suggestion that this could involve bringing all the regulatory content together and possibly restructuring the document to align with this consolidated perspective.
- Satoko suggested a gathering of all regulators to ensure alignment and consensus on the text, as she had not yet received feedback on her contributions and had only recently reviewed others' parts.
- The need to identify major themes and principles recurring throughout the document, such as human-computer interaction and performance evaluation was emphasised.
- The idea of consolidating text by theme was reiterated and it was proposed having a medical writer or someone with AI safety background to help consolidate the pieces together.
- Walter raised the issue of using examples to make abstract concepts more tangible, although cautioning that the fast pace of AI development could quickly date these examples. He also suggested cross-chapter collaboration to identify overlaps and ensure consistency.

- Lembit reflected on the balance between detail and educational value in CIOMS documents, suggesting that the educational nature of the documents is one of their added values. He also mentioned the common practice of including case studies as an appendix rather than in the main body to avoid dating the document.
- The WG agreed on the importance of consolidating the text related to similar topics and focusing on establishing guiding principles before further editing. It was acknowledged that some principles might change over time but would still provide a foundational framework for the document. The group looked forward to more detailed work in smaller sessions.

Chapter 8

Denny and Ravi gave an overview of chapter 8 progress.

- The future role of AI in pharmacovigilance is expected to shift towards a more predictive science, leveraging vast datasets to hypothesise and identify potential risks ahead of time.
- There is a call for transparency in AI processes, emphasizing the need for clarity on human accountability in AI-generated outcomes.
- From a regulatory perspective, uniform rules are hoped for, and regulatory oversight is likely to expand as the field grows.
- Lembit discussed the continuum of risk-benefit assessment and how AI might support this process, as well as the role of AI in assisting healthcare providers with benefit-risk assessments for individual patients.
- The discussion touched on the possibility of current guiding principles evolving, especially in the context of predictive modeling and validation practices.
- A suggestion was discussed to break the vision into short-term and long-term perspectives to provide concrete guidance while remaining flexible.
- The role of regulatory expectations was emphasized, with industry participants expressing a desire for clear guidelines on what to demonstrate during inspections.
- The WG discussed the potential structure of the document, weighing whether to organise it by life cycle stages or principles.
- The idea of using diagrams or workflows to illustrate the application of principles throughout different stages of AI development was considered.
- The WG agreed that while the document should stay at the principal level to avoid getting too prescriptive, it should also provide clear, applicable guidance for different stages of AI integration.
- Several members suggested focusing on establishing principles first and then addressing use cases and text consolidation.
- There is a call for volunteers from regulatory bodies to join Chapter 8 discussions, reflecting a collaborative approach to developing the document.
- A governance bridge model is referenced as a way to visually represent oversight across different stages of AI development, which could aid readers in navigating the document.
- The group acknowledges the rapid pace of AI development and the necessity for regulations to adapt accordingly.
- There is a consensus on the importance of principles such as accountability, which is expected to remain a core tenet regardless of AI's autonomy.

Exchange with Transcelerate Digital Health Team. Presentation and Discussion

Elivia Ambler, Rajesh Ghosh, Clint Craun, and James Whitehead from the Transcelerate team gave an online presentation about their initiatives and collaborative efforts within the pharmaceutical industry. WG members unable to join in person were able to join the online session. The following only represents discussion points that followed the presentation:

- The importance of transparency about AI use with consumers and healthcare professionals was stressed to ensure they are informed about the data usage and technologies applied.
- Transcelerate pointed out the complexity of implementing AI in healthcare due to varying international healthcare systems and regulatory bodies.
- There was a consensus that while regulations may pose challenges, they are necessary for ensuring privacy and responsible AI use. Global operations of companies mean navigating different regulatory landscapes, which poses unique challenges.
- A discussion ensued on advancing regulations to facilitate the integration of AI in pharmacovigilance, referencing the FDA's approach to regulating continuously learning AI systems.
- The group discussed how current regulatory frameworks could be adapted to support innovations in pharmacovigilance.
- The dynamic nature of digital health solutions and AI demands a regulatory approach that can accommodate the evolving landscape.

Breakout sessions

- The WG split into two subgroups: one set of members from regulatory bodies to discuss the guiding principles and the other to discuss use cases.
- Following the breakout sessions, the two groups provided updates on their discussions, and the following points summarise the discussions that took place.
- A proposal was made to restructure the entire document to be organised according to the guiding principles, potentially creating a chapter per principle. A consensus was reached on a list of **nine guiding principles** after a review of documents from regulatory agencies.
- Some members expressed concern over the magnitude of the undertaking and the redundancy it might introduce. It was agreed that it would be necessary to map the existing document content against the newly formed principles.
- The mapping will determine how existing content fits within the new structure and where changes or consolidations are necessary.
- The outcome of this mapping exercise will be to ensure that all principles are covered and the document does not repeat content unnecessarily.

On use cases

- The WG debated whether to include actual industry use cases or rely on published use cases.
- A preference emerged for use cases with existing publications for the depth of analysis they provide.
- There is potential for the inclusion of generative AI use cases, though they may not be widely published yet.

The meeting was adjourned.

DAY 2

Hervé and Lembit welcomed the WG and thanked all for the fruitful discussion the previous day.

- As a summary of the dicussions held the previous day, Walter reported a breakthrough in reconsidering the structure of the document, acknowledging new major authority documents introduced since the working group's initiation.
- The WG had identified nine common principles across these documents which could serve as a new logical structure for the document: **Transparency, Accountability, Explainability, Risk Based Approach, Validity and Robustness, Human Oversight, Fairness and Equity, Data Privacy, and Governance.**
- There is a potential need for revising the introductory sections to align with these principles.
- More details on principles are needed before reworking the existing content.
- The use cases bsugroup highlighted the importance of real use cases, POCs, and papers published. Most illustrative use cases will be selected according to the finalised list of guiding principles.
- The WG discussed the integration of use cases into the appendix as examples to highlight the guiding principles.
- There was a consensus on the need for alignment on key glossary terms during the drafting process.The WG will reconvene after breakout sessions to consolidate findings and make any necessary revisions.
- There was an exercise to map existing content to these new chapters, some content may appear in multiple chapters due to overlap.
- A need was identified to develop more content around certain principles like a Risk-Based Approach, Explainability, Fairness, Equity, and possibly Data Privacy.
- Five use cases, mostly from publications, were identified for inclusion in the document.
- Use cases from the industry are being considered for inclusion, with one currently in use by the FDA and another from industry practice.
- A suggestion was made to include experiences from companies using AI in pharmacovigilance, alongside literature.
- The group discussed whether to include industry vendors and consultants in the feedback process, weighing the benefit of their early input versus waiting for public consultation.
- Satoko will reach out ot PICS AI-ML Working Group about their expectations concerning the CIOMS WG XIV, AI in PV document.

4. Forming teams and timelines

- **An Editorial team** was formed: Taxiarchis Botsis, Julie Durand, Satoko Hirokawa, Denny Lorenz, Niklas Noren, Beth MacEntee Pileggi (coordinator), Monica da Luz Carvalho Soares, and Walter Straus. Editorial team is tasked with restructuring the document to align with the newly identified guiding principles. They aim to share the first draft with the full WG by **28 June 2024.**

- **A Definitions team** was formed: Douglas Domelik (coordinator), Neal Grabowski, Thomas Henn, Vijay Kara, Benny Ling, and Manuela Messelhäuser, and is responsible for creating consensus definitions for the guiding principles. The aim is to have the final draft ready by **12 April 2024.**
- **Use case team** was formed, with Arvind Bellur taking the role of the coordinator. The team will assign specific use cases to team members for development and summary and decide on how these use cases align with the guiding principles and include them in an appendix of the document. The aim is to have the first draft ready by **10 May 2024** and to finalise the draft with the full WG by **24 May 2024.**
- The WG aims to have the full draft ready for public consultation by the end of the year.

5. Next meeting

- The next in-person meeting will be kindly hosted by Merck KgaA and held 24-25 September 2024 in Dramstadt, Germany. CIOMS Secretariat will begin planning the meeting with the coordinator from Merck.
- Subgroups will continue their work virtually.
- CIOMS Secretariat will assist with scheduling virtual meetings.

6. Closing remarks

Hervé and Lembit thanked the WG for the successful meeting and for the progress made.

7. Annex 1: List of participants

Participants

Elivia Ambler (TransCelerate) **, Robert Ball (US FDA), Luisa Barrios (Merck Sharp & Dohme), Arvind Bellur (CSL Behring), Adrian Berridge (Takeda), Taxiarchis Botsis (Johns Hopkins University School of Medicine, US), Hua Carroll (Biogen), Clint Craun (TransCelerate) **, Douglas Domalik (AstraZeneca), Julie Durand (EMA), Piero Francesco Franco (Pfizer), Rajesh Ghosh (TransCelerate) **, Neal Grabowski (Sanofi), Thomas Henn* (Unither), Satoko Hirokawa (Health and Youth Care Inspectorate, Netherlands), Kirsten Egebjerg Juul* (Danish Medicines Agency), Vijay Kara* (GlaxoSmithKline), Dieter Kempf (Genentech, Roche), Benny Ling (Health Canada), Denny Lorenz (Bayer), Hervé Le Louët (CIOMS), Yusuke Matsunaga (Pharmaceuticals and Medical Devices Agency, Japan), Manuela Messelhäusser* (PEI), Niklas Norén (World Health Organization / Uppsala Monitoring Centre), Beth MacEntee Pileggi (Johnson & Johnson), Monica da Luz Carvalho Soares (ANVISA, Brazil), Ravi Patel (Unither), Kateriina Rannula (CIOMS), Lembit Rägo (CIOMS), Hans-Jörg Römming (Merck Group), Irene Scholz (Swissmedic), Walter Straus (Moderna), and James Whitehead (TransCelerate) **.

Apologies

Justyna Amelio (AbbVie) **, Russ Altman (Stanford University, US), Andrew Bate (GlaxoSmithKline) **, Yauheniya Cherkas (Johnson & Johnson) *, Selin Cooper (Abbvie) *, Shaun Comfort (Genentech)*, Flávia Moreira Cruz (ANVISA, Brazil) **, Jean-Michel Dogné (University of Namur), Julie Girod (Sanofi) *, Kendal Harrison* (The Medicines and Healthcare Products Regulatory Agency, UK), Stephen Heaton* (CIOMS), Kostadinos Kidos (Takeda), Yuki Kikuchi* (Pharmaceuticals and Medical Devices Agency, Japan), Roli Mathur (India Council Medical Research), Richard McAteer* (Health Canada), Eva-Lisa Meldau (WHO) *, Dirk Mentzer (Paul-Ehrlich Institute), Nicolas Perez * (Swissmedic), John Reinhard Pietzsch* (Bayer), Stephen Rosenfeld (North Star Review Board), Thomas Stammschulte (Swissmedic) *, Phil Tregunno (The Medicines and Healthcare Products Regulatory Agency, UK), Panos Tsintis (CIOMS Senior Adviser) **, and Brian Yau (WHO).

*Alternate
** Attended virtual sessions