



Eleventh meeting of the CIOMS Working Group XII:  
Benefit-Risk Balance for Medicinal Products – Update of CIOMS IV  
12 October 2023, virtual meeting

## Meeting Minutes

### Participants

Guacira Corrêa de Matos (Anvisa), Scott Evans (GWSPH), Richard Forshee (FDA), Stewart Geary (Eisai), Wataru Kuga (PMDA), Sanna Hill (CIOMS), Vicky Hogan (Health Canada), Claudia Ianos (Pfizer), Mutsuhiro Ikuma (PMDA), Leo Plouffe (Gilead), Lembit Rägo (CIOMS), Barbara da Silva (AbbVie), Sabine Straus (MEB, Chair of PRAC), Carmit Strauss (Amgen), Stéphanie Tcherny-Lessenot (Sanofi), Graham Thompson (FDA), Panos Tsintis (CIOMS Senior Adviser), Maria Verdugo (AbbVie), Hong Yang (FDA), Qun-Ying Yue (UMC), and Xi Sherry Zhang (Gilead).

Apologies: Patrick Caubel (Pfizer), Stephen Evans (LSHTM), Sergei Glagolev (Ministry of Health of Russia), Shuichi Kawarasaki (PMDA), Luther Gwaza (WHO), Shahrul Mt-Isa (MSD), Shanthi Pal (WHO), George Quartey (Roche), Tomas Salmonson (former Chair CHMP), Steffen Thirstrup (EMA), Sebastian Vulcu (BI), and Julie Williams (MHRA).

Alternates who did not attend: Karen Kaplan (MSD), Sara Khosrovani (MEB), Eun Mi Kim (WHO), Hussein Laljee (Gilead), and Fumihito Takanashi (WHO).

### Welcome and opening remarks

- Lembit welcomed the Working Group (WG) members.
- The CIOMS WG XIII on [Real-World Data and Real-World Evidence in Regulatory Decision Making](#) completed its Public Consultation on the 14<sup>th</sup> of July and received over 900 comments.
- A new WG – CIOMS WG XV on Harnessing the potential of pharmacoepidemiology for public health – will be launched during 2-3 November in Geneva, Switzerland.
- The agenda was adopted.

### Reflections from the chair

- The previous minutes were accepted.
- Vicky commended the WG members on the exceptional effort made during the past years while working through the challenging pandemic years.

### Update on Public Consultation

- The draft report received a total of 566 comments including 276 comments from the public and 290 comments from peers.
- Regarding the work process, the Editorial Team will be working in track changes, responses to comments will be logged and made accessible to WG members, and the WG will have an

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- opportunity to approve the report before publication.
- The responses to comments will be categorized according to: “No action needed”, “Edit/comment considered but not implemented”, “Edit implemented”, and “Edit implemented with small change”, with a short justification to explain why the decision was taken.
- CIOIMS often receives questions during Public Consultations such as the following:
  - Q: Does CIOIMS publish the Public Consultation comments or how they were dealt with?  
A: No, but we keep tight, transparent records so that we can respond to queries.
  - Q: What does it mean to be listed as a commentator?  
A: In the appendix of the report, we will list the commentators who gave consent on their comment form. We received requests from 3/23 of the public commentator companies / organisations for them to not be named in the final report. For completeness, we will write: “A few organisations did not consent to be published in this list”.

### Foreword

- Vicky will take ownership of the comments that are left behind once the Subgroup Co-Leads have selected comments for actioning within their chapters.
- The content will be updated once the rest of the report has been updated to ensure there is no conflict.

### Executive summary

- Stéphanie will take ownership of the comments that are left behind once the Subgroup Co-Leads have selected comments for actioning within their chapters.
- The content will be updated once the rest of the report has been updated to ensure there is no conflict.
- There were some requests for the scope and for some terminology definitions to be clarified, e.g. patient.

### Chapter 1

- The Subgroup Co-Leads have reviewed the Chapter 1 comments and identified the ones that apply to Chapter 1. These will be addressed. A follow up meeting is planned for diving the tasks for the next steps.
- Some broader comments have also been identified that apply to the full document, e.g. relating to the audience or terminology, e.g. “net clinical benefit” or defining “integrated benefit-risk assessment”. These will be brought to the Editorial Team’s attention via Sanna.

### Chapter 2

- The Chapter team already started addressing the comments.
- Some comments will apply to several chapters. These will need to be discussed for consistency, e.g. there is some redundancy between Chapters 2 and 3, although some repetition is intentional.
- The Chapter team consulted the full WG about some specific questions:
  - OTC and lifecycle – these topics will be covered in more detail in Chapter 4.
  - There was a request for recommendations for the event that there is an option to conduct an assessment in the pre-clinical time – this depends on companies and the information available, the disease state, and the decision needed to be made; it is likely the BRA will be more qualitative; the BRA should begin as early as possible (we say this already in the report).
  - RWE for post-marketing BRA – this is important and perhaps not emphasised enough in the report.
    - Add examples to Chapter 2, examples of rare diseases and vaccine efficacy/effectiveness validation, maybe to Chapter 4 too.
    - Add a reference to [CIOIMS Working Group XIII – Real-World Data and Real-World](#)

### [Evidence in Regulatory Decision Making.](#)

- Carmit already added some text on RWE to the lifecycle section and she will add text to earlier areas too.
- RWE is not recent, approvals have used RWD&RWE for long time, [see some articles from European and FDA context outside of RCTs.](#)
- Consider the rolling submissions of Covid-19 vaccines.
- We may require a fair amount more emphasis on RWE including in the Foreword under the new concepts and in the Executive Summary.

### [Chapter 3](#)

- Claudia received many thanks for her work in addressing the comments.
- Claudia has addressed the minor comments in the chapter (some require input from the authors), Claudia has also addressed all comments on pragmatic trials and uncertainties, and the Chapter 3 team will be reviewing the BR team section.
- The next step is to divide sections among the original authors where comments need to be addressed by the original authors.
- The patient input illicitation section by Stéphanie in particular requires some editing.
- Claudia mentioned that many of the references have lost their correct places.
- Add cross reference to Chapter 4 to the OTC section.
- Add cross reference to Chapter 4 to the Combination products section.

### [Chapter 4](#)

- The American Statistical Association brought forward some comments about BRA in rare diseases.
- Based on comments and on discussions with the Editorial Team, two new topics have been added:
  - Non-prescription products (including switch to OTC) (add cross reference to Chapter 3);
  - Combination products (add cross reference to Chapter 3).
- We received a request for a definition for legacy products and advanced therapy medicinal products, etc. Stéphanie will check first if the other chapters have these.
- Add a reference CIOMS WG XIII for the use of RWE.
- Clarify the link to patient input. Consider adding a cross reference to Chapter 3 or a link to CIOMS WG XI.
- Add more examples of data sources, methods, etc.

### [Appendix](#)

- The case study comments will be addressed by the Chapter teams.
- It may be worth re-naming case study A.2 to bring out more the process and the Monte Carlo simulation.

### [Implementation activities](#)

- Webinars. We may wish to hold one or two region-specific webinars. The PowerPoint slides would be made available following the webinars.
- Speaker engagements, such as DIA Meetings.
- Please a scientific article in an open access journal.
- eTraining -modules. A couple of former CIOMS report publications, e.g. the [Drug-Induced Liver Injury](#) (DILI), have been accompanied by e-learning modules: please see [here](#). The WG XII report could have a similar set of modules to help bring the report to e.g. resource-limited settings or to even seemingly advanced settings. The DILI e-modules were created with the Uppsala Monitoring Centre. Now over one year on, we have around 150 people graduating from the course each month. This has been a positive, much appreciated experience.

- Volunteers for the implementation team are invited to come forward. All are invited to start thinking about what their contribution may be. [Post-meeting comment: Leo has volunteered to participate in the team.]
- Leo and Hong were invited to speak at the ASA and DIA Quarterly Seminar on 2 October to present about the CIOMS WG XII report (Biopharmaceutical section scientific seminar). Hong has received several other invitations too.
- All are welcome to present at speaker engagements. We encourage everyone to share information so that all are aware. CIOMS would like to make details available via the CIOMS quarterly Newsletter that is distributed to 15,000+ people globally.

### Next steps

- The WG members agreed to hold the next full WG meeting in about one month's time.
- At this time, we will share the full combined chapters for everyone's visibility.

### Any other business

- There was a discussion about collaborative work spaces. Due to the technological and legal complexities, there has not been a satisfactory solution identified. The best solution at this stage of report production seems to be working consecutively on the draft.

### CIOMS Working Group XII structure

Chairwoman: Vicky

Co-Chair: Patrick (currently less active in this capacity) supported by Claudia

Co-Chair: Scott

Subgroups and Co-Leads (Co-Leads' names are underlined)

<b>Subgroup 1</b>	<b>Subgroup 2</b>	<b>Subgroup 3</b>
<b>Methods</b>	<b>SDA</b>	<b>Benefit-risk landscape</b>
Including integrated B-R methodologies / patient level	Structured descriptive assessment	
<u>Leo</u>	<u>Hong</u>	<u>Steffen</u>
<u>Richard</u>	<u>Sherry/Hussein</u>	<u>Tomas</u>
Claudia	Stewart	<u>Graham</u>
Patrick	Barbara/Maria	Sabine/Sara
Scott	Stéphanie	Guacira
Stephen	Carmit	George
Shahrul/Karen	Sebastian	Shanthi
Stéphanie	Julie	
Luther	Mutsuhiro/Shuichi	
Ying	Wataru	
Panos		