



Eighth meeting of the CIOMS Working Group XII:
Benefit-Risk Balance for Medicinal Products – Update of CIOMS IV
14 September 2022, virtual meeting

Meeting Minutes

Participants

Guacira Corrêa de Matos (Anvisa), Scott Evans (GWSPH, Chair of PRAC), Stephen Evans (LSHTM), Richard Forshee (FDA), Stewart Geary (Eisai), Luther Gwaza (WHO), Sanna Hill (CIOMS), Vicky Hogan (Health Canada), Claudia Ianos (Pfizer), Mari Kihara (PMDA), Wataru Kuga (PMDA), Shahrul Mt-Isa (MSD), Leo Plouffe (Bayer), George Quartey (Roche), Lembit Rägo (CIOMS), Tomas Salmonson (former Chair CHMP), Barbara da Silva (AbbVie), Sabine Straus (MEB, Chair of PRAC), Carmit Strauss (Amgen), Stéphanie Tcherny-Lessenot (Sanofi), Steffen Thirstrup (CORS), Panos Tsintis (CIOMS Senior Adviser), Sebastian Vulcu (BI), Hong Yang (FDA), Qun-Ying Yue (UMC) and Xi Sherry Zhang (Gilead).

Apologies: Patrick Caubel (Pfizer), Sergei Glagolev (Ministry of Health of Russia), Shuichi Kawarasaki (PMDA), Shanthi Pal (WHO), Graham Thompson (FDA), and Julie Williams (MHRA).

Alternates who did not attend: Karen Kaplan (MSD), Sara Khosrovani (MEB), Hussein Laljee (Gilead), and Maria Verdugo (AbbVie).

Welcome and opening of the meeting

- Lembit welcomed the WG members and made the following announcements:
 - On the 6th of September, CIOMS published the [Patient Involvement in the development, regulation and safe use of medicines report of the CIOMS Working Group XI](#).
 - On 15th of September, CIOMS will publish the [CIOMS Cumulative Glossary with a focus on Pharmacovigilance \(Version 2.0\)](#).
 - On 26th of September, CIOMS will publish the [Glossary of ICH terms and definitions](#).
- Vicky chaired the meeting.
- The agenda was adopted.

Progress updates on chapter drafts

Subgroup 3 on Benefit-risk landscape, presentation by Tomas and Steffen

- The subgroup is updating its draft and will share the updated text soon.
- The authors do not want to make the introductory chapter too long.
- The report is to focus on medicines. Many of the principles can be applied beyond pharmaceutical products, e.g. to devices and diagnostics, as there are commonalities, but we do not have substantial expertise and stakeholders in the WG from these other areas, and so we cannot cover them in depth.
- The Methods subgroup section can be shortened but Leo would like to have at least a paragraph on considering different therapeutic options, i.e. different B-R methods relating to e.g. devices, surgeries and

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- pharmaceutical options. This comparing of apples and oranges is a key concept under the Methods section.
- For industry, often an analysis will involve a combination product e.g. a drug and a device, and so it may be helpful to include some information on combination products.
 - There are differences in terminologies across different jurisdictions, e.g. in the European context, ‘medicines’ includes vaccines and biologicals, but this is different in e.g. Canada. Include a note about this in the introduction.
 - Stephen requested to avoid using the term ‘drugs’, as this does not include ‘vaccines’. He considers ‘medicines’ as including ‘drugs’ and ‘vaccines’, and prefers ‘medicines’ to ‘pharmaceuticals’, although the latter does also encompass ‘drugs’ and ‘vaccines’.
 - Our original remit included cell / gene therapy, alongside biologics and vaccines.
 - In Canada, natural health products are regulated, which can be considered medicines if a claim is made. Are those meant to be included in the focus of this guideline? We could add a note to say this report may be useful when carrying out BRA for e.g. natural health products although this is not the focus of the report.
 - In Europe, a natural substance could be a medicinal product if a claim is made and data is provided for quality, efficacy and safety. Under the medicines legislation of Europe:

Medicines

Substances independent of origin used to treat or prevent disease, or to make diagnosis.

Medicines legislation, Europe

- From the CIOMS Working Group XI report glossary:

Medicinal product

Any substance or combination of substances:

- presented as having properties for treating or preventing disease in humans; or
- which may be used in or administered to humans either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Modified from: European Parliament. Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the Community code relating to medicinal products for human use. (PDF) Article 1(2).

Note: In other jurisdictions, this may be called a medicine, medical product or a drug, and may include biologicals and vaccines.

- The above definitions were largely appreciated. They were considered as if reduced/expanded versions of one another.
- The report’s target audience was re-confirmed as pharmaceutical companies and regulatory agencies. This confirmation had been considered necessary because recently there had been some discussions about individual patients’ BRA. Lembit confirmed the target audience, i.e. not individual patients. [Post-meeting note: academics are the only other stakeholders represented in this WG.]
- Stephen added that in the light of the CIOMS WG XI report publication, we should say we are talking about the patients’ B-R, and the report may be of value to individual patients as they assess their own risks. It may be helpful to have patients read the report before its publication. We are working for the benefit of patients, not for the benefit of companies and regulators. Panos added that the WG XI report had an early section written in patient-friendly language and this could be considered for the WG XII report too. Perhaps Lembit could consider a patient representative drafting a piece in plain language or reviewing the report? Lembit felt we could consider this for an Executive Summary at a later stage. Tomas added that there is an increased emphasis on communication as an outcome of BRA to allow other stakeholders, and in particular patients, to take informed decisions.

Subgroup 2 on Structured Benefit-Risk Approach/Framework, presented by Sherry, Hong and the wider team

- The subgroup 2 used a slide set to work through a number of questions e.g. on:
 - moving the figure on the “Timeline of Global Benefit-Risk Initiative” and its accompanying text from Chapter 2 to Chapter 1.
 - How to handle the difference in a product’s risk and the B-R balance for using the product (dependent e.g. on the indication, intended population, etc.).

Subgroup 1 on Methods, presentation by Leo, Richard and the wider team

- The subgroup 1 used a slide set to work through number of questions e.g. on:
 - Approaches in the post-marketing phase.
 - CIOMS WG IV report’s 5-6 examples on the post-marketing phase in the form of signals.
 - As the WG XII report is focusing on the lifecycle approach, we need to look at the post-marketing phase.
 - Subgroup 1 will cover only the methods aspects as Subgroup 2 will covers post-marketing also under its Lifecycle section.
 - ‘Specificities of Benefit-Risk Methods for Special Situations’ to be a standalone Chapter 4
 - Concepts and methods are quite different, consider e.g.:
 - Orphan diseases;
 - Late lifecycle products.
- Here is [FDA’s guidance on RWE](#).
- Relevant article published last month: "[Visualizations throughout pharmacoepidemiology study planning, implementation, and reporting](#)".
- Key benefits and key risks are discussed in [ICH M4E\(R2\)](#).

Report glossary

- The WG XII glossary team preferred to wait for the [CIOMS Cumulative Glossary with a focus on Pharmacovigilance \(Version 2.0\)](#) to be published and for the WG XII draft to mature in order to review which terms may need to be defined by WG XII, if any.
- It is becoming clearer now that we may need to focus on terms such as ‘BRA’, ‘Key risk’, and ‘Product lifecycle’.
- ‘Key risk’ is not in the Cumulative Glossary and this will probably need to be defined as there is a difference between the pre- and post-marketing meanings.
- Terms and definitions can be put in footnotes for the time being. If the WG XII does not go ahead with a glossary, the terms and definitions can be picked up from there towards the CIOMS Cumulative Glossary.

Next steps

- Week commencing 26th of September: Sanna to combine chapters, format, and circulate to WG [done].
- Week commencing 3rd of October: Subgroups to start finalising their drafts.
- Friday 11th of November: Subgroup Co-Leads to email finalised drafts to Sanna.
- Week commencing 14th November: Sanna to combine chapters.
- Thursday 17th November: Sanna to circulate combined chapters for reviewing, WG members will be given goals on what is expected (is something missing, are concepts clear), Vicky to provide a feedback form, subgroups will have about a month to review, feedback is expected by cob 16th of December.
- Next full WG meeting for mid-end January 2023. This may be an hour-long meeting with an open agenda to discuss remaining issues. We can also talk about the possibility of a public consultation.