



Seventh meeting of the CIOMS Working Group XII:
Benefit-Risk Balance for Medicinal Products – Update of CIOMS IV
11 April 2022, virtual meeting

Meeting Minutes

Participants

Guacira Corrêa de Matos (Anvisa), Brian Edwards (ASA BRAP, Husoteria)**, Scott Evans (GWSPH), Richard Forshee (FDA), Stewart Geary (Eisai), Luther Gwaza (WHO), Sanna Hill (CIOMS), Vicky Hogan (Health Canada), Claudia Ianos (Pfizer), Shuichi Kawarasaki (PMDA)*, Wataru Kuga (PMDA)*, Elaine Morrato (Loyola University)**, Shahrul Mt-Isa (MSD), Anthony Oladipo (AbbVie)*, Leo Plouffe (Bayer), George Quartey (Roche), Lisa Rodriguez (ASA BRAP, FDA)**, 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), Graham Thompson (FDA)*, Panos Tsintis (CIOMS Senior Adviser), Sebastian Vulcu (BI), Julie Williams (MHRA), Hong Yang (FDA), and Xi Sherry Zhang (Gilead).

Apologies: Patrick Caubel (Pfizer), Stephen Evans (LSHTM), Sergei Glagolev (Ministry of Health of Russia), Mari Kihara (PMDA), Shanthi Pal (WHO), and Qun-Ying Yue (UMC).

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

* New to the working group since the previous meeting

** Guest speakers at the meeting

Welcome and opening of the meeting

- Lembit welcomed the WG members and made the following announcements:
 - The WG welcomes new members: Carmit Strauss (Amgen), Barbara da Silva and her alternate Anthony Oladipo (AbbVie), Graham Thompson (FDA), and Wataru Kuga and his colleague Shuichi Kawarasaki (PMDA).
 - [The CIOMS Working Group XI: Patient Involvement in the Development, Regulation and Safe Use of Medicines](#) report is available for public consultation until 11 April 2022.
 - A new CIOMS WG will be launched at the end of May 2022 on Artificial intelligence in pharmacovigilance.
 - CIOMS Executive Committee General Assembly will convene in May 2022.
 - We are pleased to welcome guest speakers: Brian Edwards and Lisa Rodriguez from the American Statistical Association (ASA) Benefit-Risk Assessment Plan (BRAP), and Elaine Morrato from the International Society for Pharmacoepidemiology (ISPE) Benefit Risk Assessment, Communication and Evaluation (BRACE) Special Interest Group.
- Vicky chaired the meeting.

- The agenda was adopted.
- Kateriina was rapporteur at the meeting.

[American Statistical Association \(ASA\) Benefit-Risk Assessment Plan \(BRAP\) Taskforce](#)
[Brian Edwards, co-lead of ASA BRAP, Husoteria, and Lisa Rodriguez, co-lead of ASA BRAP, FDA](#)

- The presentation slides are available [here](#) and the below bullets include only points made at the meeting.
- As the two WGs are moving in the same direction, it is beneficial to enhance synergies to avoid unnecessary duplication.
- Brian commented that the BRAP Taskforce intends to publish its first outline document by August, while a section focusing on a survey and interviews will be published at a later stage.
- Q: As a part of the CIOMS WG XII report focuses on methods and benefit-risk (BR), are there any recommendations on methods specifically?
A: We aim to introduce different tools as resources for different circumstances.
- Another WG is currently being formed at the ASA which will focus on developing a tool to accompany BR assessment planning.
- Q: Is BRAP's aim to publish the results of the interviews, and after receiving feedback from stakeholders, to refine and re-publish the work?
A: While publication will follow, consultations will be prioritised over publication. Communication will be extremely important, so opportunities to present at meetings will be a valuable source of feedback, which will then be published in a format to be agreed, e.g. perhaps as an eBook rather than a journal. It will be an evolving, iterative process. Timelines will be decided in due course and CIOMS WG XII remains a valuable communication partner.
- Panos was one of the people interviewed for the ASA WG and he can expect to receive additional information about the results of the survey analysis.
- There are discussions within the leadership of the ASA working group about the design of the BRAP website to provide more links to papers and information about its current work.
- Hong is also a member of the ASA WG and will be approached in the future as communication between the two WGs is valuable. Leila Lackey, a former member of the CIOMS WG XII, who is still in contact with the CIOMS WG XII, is also a member of the ASA WG.

[International Society for Pharmacoepidemiology \(ISPE\) Benefit Risk Assessment, Communication and Evaluation \(BRACE\) Special Interest Group](#)
[Elaine Morrato, Chair of ISPE BRACE, Parkinson School of Health Sciences and Public Health, Loyola University Chicago](#)

- The presentation slides are available [here](#) and the below bullets include only points made at the meeting.
- The activities of the BRACE WG complement those of the BRAP, but differs in its particular focus on risk minimisation. Its documents will serve as valuable references for the CIOMS WG XII report.
- Q: Risk minimisation is a challenging area - can multiple approaches be used to assess risk minimisation within industry?
A: If risk minimisation is considered as a sub-branch of dissemination and implementation science, a multi-pronged approach is required, as is the use of mixed methods. Regulators seem to want more information, but until it is codified into regulation, it is difficult to deliver. The goal of minimising specific risk in each case should be kept in mind.
- Q: What might a more global approach look like to respond to regulatory demands for assessments in multiple jurisdictions, e.g. in Australia and China?
A: It should be made clear what a core safety issue is, which is consistent regardless of geography, and separately, what healthcare-contextual factors in each country are, as endpoints may vary depending on the healthcare context (e.g. relating to local delivery and resources). The underlying assumptions or contextual differences should be made clear and the approach adjusted accordingly.
- Q: One of the reasons for applying risk minimisation is to ensure a positive BR balance. Are there

publications or case studies about a case where an additional risk occurs and is removed? What is the impact on the positive BR balance?

A: There are examples of a drug with a risk, being regulated differently in different countries, and so showing how the context can affect the safe use of the drug. Elaine will send the bibliography for further research and more information. The valproate example was mentioned.

- Vicky thanked the presenters for their time and informative presentations.

Progress updates on chapter drafts

Subgroup 1 on Methods, presented by Leo

- The subgroup teams discussed the location of Section 3, *Considerations on Risk Methodology*, and decided to leave it in the Subgroup 1 chapter. The draft will be further refined and the team welcomes all feedback on its organisation and content.
- Section 3.10 *Evolution of benefit risk assessment: Methodologies*, the part discussing international guidelines, will be moved to the chapter 2 draft.
- The sub-section on the *Traditional methodological approach to inform the benefit-risk assessment leading to registration* does not currently include further details on alternative routes of approval, e.g. orphan drug approaches, single-arm studies, etc. After discussion, it was decided to provide more detail on the alternative pathways and the WG is invited to comment on this.
- The section on *Benefit-risk assessment in the post-marketing phase* provides an overview of the methods based on the CIOMS IV report. The team will draft a more detailed section considering the rapid developments in this area and cross-reference the section on the *Lifecycle approach to benefit-risk assessment* section in the chapter.
- Given the overall length of the draft chapter, any redundancies and overlaps with other sections will be considered at the editing stage.
- Vicky suggested for all subgroups to discuss each section with the WG to determine if the section contains enough detail on the topic. This would also help to identify overlaps.
- Section 3.11 *Patient-level benefit-risk assessment - a novel paradigm through drug development and lifecycle management* is a section drafted by Scott and may be included in the introduction or as a separate chapter in the report, including the more forward-looking discussions. The WG is invited to feedback.
- The concept of estimand and its relation to BR is relevant and will be addressed in the report. We need to be clear about what is being estimated, and the focus should be on the treatment effect, adherence degrees, and population parameters, as well as the ICH document; however, as estimand is somewhat separate to B-R, we should only cover the intersection of these topics. The report already has some content on estimand under intention-to-treat (ITT) and protocols.
- The Subgroup 1 team will reach out to Scott with a request to draft a section on estimand.
- Sections 3.14-3.16 will be organised under the section *Communicating the assessment* to include high-level discussion on the methods for communicating the assessment and refer to BRACE and similar initiatives. Once the draft is finalised, the WG will be invited to review it to decide whether to move this section to chapter 2.

Subgroup 2 on structured benefit-risk approach/framework, presented by Hong

- The subgroup has made good progress and the WG has already reviewed and commented on the content, structure and the flow of the document.
- Subgroups 1 and 2 have discussed overlaps and subgroup 1 has completed the first revision of its draft.
- The subgroup 2 draft will be revised to reflect the planned sections and subsections: The sections on *Risk Management* and *Benefit-Risk Conclusion* will be included in the section 2.2 on *Components of structured benefit risk assessment framework*.
- Panos felt that the section on *Risk Management* is written following a European Risk management plan (RMP) approach and suggested promoting a more universal core risk management approach. He suggested

adding the missing information to the ICH section on potential risks identified.

- The section on ICH needs to be revised and the same approach needs to be taken in the clinical overview when formulating recommendations on the BR framework, which is the basis for medicines approval.
- Panos agreed to send his more detailed comments to subgroup 2.
- It was agreed that the section *International Benefit-Risk Initiatives: The Heritage of CIOMS IV*, including content on the ICH guidelines and IMI-PROTECT, will be discussed in the introduction. The subgroup 2 will focus on the framework of methodologies and the different approaches.
- The lifecycle section overview includes an introductory paragraph describing the industry perspective and subgroup 2 would like to include similar information from the regulators' perspective in the introduction. Hong kindly agreed to reach out to different agencies and draft an introductory paragraph from the regulators' perspective.

Q 1: Regarding the lifecycle approach to BR and the BR assessment document as a standalone document, that can be included in others such as the Development Safety Update Report (DSUR) and the Periodic Safety Update Report (PSUR), what approaches could be considered to address this and where in the report is the best place to address this?

- Leo felt that for the sake of internal efficiency of a pharmaceutical company, there should be a standalone, core document on BR assessment. This way, the document could start early in the process, mature throughout the product lifecycle, and act as a feeder to all other documents, including the Development Risk Management Plan (DRMP), the investigator's brochure, and the submission document. The document could be covered in the section discussing the lifecycle management approach and aligned between the subgroups 1 and 2's drafts.
- In line with Leo's point, Carmit noted that there are industry publications, e.g. from Amgen, discussing the practise of utilising the standalone document on structured B-R assessment as a source for e.g. the DSUR, PSUR and the clinical overview. The document becomes a core structure in the B-R assessment and can therefore be used in different documents within the lifecycle. It could start at the end of e.g. phase II, when companies put in place the DRMP; the arrival of efficacy or safety data could trigger an update; and this would need to be discussed in the post-marketing setting too in relation to Risk Evaluation and Mitigation Strategies (REMS) data.
- Sabine felt the BR assessment document should be part of the lifecycle approach, but not as a standalone document; it is part of the changing dynamics of a medicine's life according to the context.
- Barbara added that the document would then also feed into the process that could be reviewed and modified within the context e.g. the DSUR and the PSUR; which would make the BR assessment document into a changing (shifting) assessment that is re-evaluated throughout the lifecycle.
- Panos felt that it may be advisable to have a B-R management type document. During the lifecycle, it is not something that is submitted to a regulator, but it is used for preparing submissions to the regulator by including something in the clinical overview, in the PSUR, and the DSUR. This is a good approach for the WG, which is also supported by the [CIOMS WG VI report on Management of Safety Information from Clinical Trials](#).
- The WG agreed that the document is to be discussed in the lifecycle section and that the usefulness of this type of document is best established early and then revised throughout the lifecycle. Subgroup 2 will briefly address the document and subgroup 1 will provide further details.

Q 2: Does the group provide recommendation on the order and hierarchy of key benefits and key risks within the value tree? Can this be addressed in the methodology section?

- No recommendations are currently included in the draft but it is a valuable point and some should be included.
- The section on the value tree will be discussed by Subgroup 1, including its applicability to other aspects of BR methodologies or assessment methods.
- The aim would be to introduce some hierarchy for the reader and list the most important key benefits first and then proceed from there in a descending order. A similar approach can be taken with risks, perhaps

putting the most clinically relevant risk at the top and then listing the others in order.

- Panos suggested researching for published examples.
- Leo and Richard agreed on working on trimming of the value tree by assigning a hierarchy to the list.
- Currently the value tree is included in both chapters and the sections should reference each other. The description of the hierarchy, including the trimming and assigning of weights, fits mainly in the Methods section and will be worked on collaboratively. The WG is welcome to send suggestions or examples to Subgroup 1.

Subgroup 3 on benefit-risk landscape, presentation by Steffen

- Subgroup 3 will review its draft in the light of feedback from the Co-Chairs and other subgroup Co-Leads. The subgroup will identify any missing information in the current draft and incorporate points from the presentations.
- Vicky suggested including information on the evolving nature of the area. Communication and input from various stakeholder groups, including patient groups, is essential and their philosophy and approach to BR assessment should be included in the chapter.
- Would other initiatives, e.g. ISPE and ASA, be discussed only in the introduction or would they fit into the context of the other initiatives as a whole?
- The subgroup 3 chapter will introduce the framework of the rest of the report and also mention other key initiatives, although it would be impossible to provide an exhaustive overview. The aim of this chapter is to be as comprehensive as possible and to state the original reasons for producing the WG report and to relate it to other work in this area.

Report glossary

- The glossary team convened on 4 April 2022 and discussed the merged list of terms and definitions submitted by the subgroups and the need for a separate glossary.
- The WG decided to pause defining any new terms for the time being and to review the terms and existing definitions with view to possibly drafting new definitions during the editing phase.
- The WG members are invited to propose a definition for the term “Benefit-Risk”, as it is a key term in the report, which could be included in the introduction. Other relevant terms can be defined within the chapters rather than in a separate glossary.
- The [CIOMS Cumulative Pharmacovigilance Glossary](#) is available as a resource for referring to terms relevant to the WG XII report. Relevant terms may be refined or redefined to specify their meaning in the report’s context and in light of its objectives.

Closing remarks and future meetings

- The Co-Chairs and Co-Leads will convene and discuss how to organise the report editing process and all members will be welcome to provide their comments.
- Thank you for everyone’s participation and effort to forward the WG agenda.