Tenth meeting of the CIOMS Working Group XII:
Benefit-Risk Balance for Medicinal Products – Update of CIOMS IV
23 May 2023, virtual meeting

Meeting Minutes

Participants

Guacira Corrêa de Matos (Anvisa), Scott Evans (GWSPH), Richard Forshee (FDA), Stewart Geary (Eisai), Eun Mi Kim (WHO), Wataru Kuga (PMDA), Luther Gwaza (WHO), Sanna Hill (CIOMS), Vicky Hogan (Health Canada), Claudia Ianos (Pfizer), Mutsuhiro Ikuma (PMDA), Shahrul Mt-Isa (MSD), George Quartey (Roche), Lembit Rägo (CIOMS), Tomas Salmonson (former Chair CHMP), Barbara da Silva (AbbVie), Carmit Strauss (Amgen), Stéphanie Tcherny-Lessenot (Sanofi), Graham Thompson (FDA), Sebastian Vulcu (BI), Julie Williams (MHRA), 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), Shanthi Pal (WHO), Leo Plouffe (Gilead), Sabine Straus (MEB, Chair of PRAC), Steffen Thirstrup (EMA), and Panos Tsintis (CIOMS Senior Adviser).

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

Welcome and opening remarks

- Lembit welcomed the participants.
- The CIOMS WG XIII on Real-World Data and Real-World Evidence in Regulatory Decision Making is anticipated to start its Public Consultation around the same time as the WG XII.
- The CIOMS publications continue to be downloaded intensively, with the Glossary of ICH terms and definitions being one of the most popular publications.
- Mari Kihara has left PMDA and she has been replaced by Mutsuhiro Ikuma at the WG XII.

Reflections from the chair

- Vicky commented on the WG's positive progress in general and through the pandemic. She feels we are in the home stretch to the report completion and expects the document to be a valuable resource to industry, regulators and academic in the years ahead.

Discussion on new items

Foreword, presented by Vicky

- Vicky highlighted the new features of the report and welcomes feedback.
- Richard appreciates the Foreword.
- Hong proposed including a mention of "additional quantitative analysis as part of the structured benefit-risk approach/framework as applies to all BRAs" in the Foreword and the Executive summary, bearing in mind that many readers will still be thinking in terms of "quantitative and/or qualitative approaches". This was accepted.

Executive summary, presented by Stéphanie

- Stéphanie provided high-level content on the chapters.
- Hong's comment as above applied to the Executive summary too and it was accepted for the Executive summary too.

Discussion on the chapters

Chapter 1: Benefit-risk landscape, presented by Graham and Tomas

- Figure 1 was updated with help from Claudia and Shahrul.
- The comments received from the previous WG-internal review have been addressed.
- We need to ensure that the flow of the document works well from the Foreword and the Executive Summary, through the chapter on Benefit-risk landscape, and all the way through the other chapters, ensuring consistency throughout.

Chapter 2: Structured benefit-risk approach/framework, presented by Hong

- The chapter is complete.
- During recent subgroup meetings, there were some comments made about consistency and clarity of terminology: SBRA for structured benefit-risk framework has been used to refer also to a document i.e. the final BR summary. We need to use a clearly defined term consistently across chapters.
- There was a discussion about potentially combining Tables 2 and 15 but it was decided to keep them as they are. The discussion centered around how both tables are about sources of uncertainties and could potentially be combined into a single table for efficiency but the tables can also be argued to serve different purposes: Table 2 lists areas to consider when drafting a qualitative BRA whereas Table 15 gives potential sources of uncertainties to consider during the process; and therefore it was decided to keep both tables. In the introduction to Table 2 we will mention that it provides information to consider in terms of uncertainties for BRAs in general. We will refer the reader to Table 15 for further sources of uncertainty in the methodologies section.

Chapter 3: Benefit-risk methods, presented by Richard

- The chapter is in good shape and ready for further review.

Discussion on the case studies

A.1, Rotavirus vaccine: how to inform BR with an emergence of intussusception, presented by Hong

- This case study was completed a while ago.
- The rotavirus case study is used by both Chapters 2 and 3. It is described in one place in the report (A.1) and both chapters have their own discussion of it to bring out their own points, thereby removing repetition.
- For Chapter 2, this case study is used to focus on how to model and incorporate different types of input i.e. additional quantitative analysis to support the structured framework.

A.2, Rotavirus vaccine: focusing on BR methods including Monte Carlo simulation, presented by Richard

- For Chapter 3, this case study is used to focus on the Monte Carlo simulation methodology.

B, BR balance for oral anticoagulants, presented by Hong

- This case study was completed a while ago.
- This case study shows a different quantitative analysis.
- A minor edit was made to be in line with Chapter 3: using BR ratio as an endpoint has a drawback and therefore a limit was added.

C, Two regulatory agencies conduct BR differently on Nerlynx nilotinib, presented by Sanna

- Sara at MEB will be re-submitting the case study by the end of the week.
- Report reviewers are encouraged to propose cross-references from other places from the report to help bring to life the points being made in the report.

Outstanding issues to address prior to Public Consultation, presented by Sanna

- There are many small details in the draft report to address such as confirming cross-references between sections and proposed track changes e.g. acronyms.
- The provisional meeting for the Co-Chairs and Subgroup Co-Leads of 25th of May was confirmed to discuss the small details with more time.
- In preparation for the meeting on the 25th of May, Sanna will share the updated version of the draft report. Any updates received in the meantime will be implemented.
- Also in preparation for the meeting, Sanna will re-send her email regarding asking for information about the sources of the tables and figures in the report. She will also briefly group the topic areas we need to focus on most e.g. inconsistencies of terminology.
- The CIOMS office will contact the owners of the tables and figures used in the report to request permission to reproduce/adapt the tables and figures. We need to at least begin the process of requesting permission and we can include a disclaimer for the Public Consultation if needed.

Comments from WG members – open discussion

- Barbara commented on her appreciation for the exposure to all the experts in the areas of BR and the educational opportunity. She felt the format and experience of the WG have been good, and that the report will be an excellent reference going forward.

Next steps and closing statements

- Tomas commented that small details such as cross-references within the document missing are not a reason to delay the Public Consultation.
- Lembit agreed with this. The WG can also review in parallel with the Public Consultation and this also helps to finalise the report.
- Vicky expressed a wish to uniformalise terminology between chapters (benefit risk, benefit-risk, benefit:risk), and although this has been addressed, some other terminology issues may exist.
- Sherry made the point that BRA is referred to as a process but also as a document. This has happened in multiple places e.g. in Table 2. In Chapter 3, this is clearer with the use of SBRA. If the changes can be sent by email, Sanna can make the changes in the master document. We need consistency in the use of terminology.
- The Subgroup Co-Leads to go through their sections of the report to check if their terms are used consistently.
- When we decided to not have a glossary, we agreed to not have any terms whose definitions do not exist/conform to the definitions given in the CIOMS Cumulative Glossary, with a focus on Pharmacovigilance (Version 2.1) - please note this is now already the next version - were to be defined in the footnotes, such as “BRA”, “Key risk” and “Product lifecycle”. Only “Traditional clinical trials” was included as a footnote. Some of the new definitions are critical for understanding the report. The Subgroup Co-Leads need to bring definitions from their chapters to the meeting on Thursday 25th of May and the task of defining them will be assigned to the most appropriate WG member.

- Using exiting authoritative, adjudicated definitions will help the field. “Key risks” and “Key benefits” were defined in the ICH document on benefit risk assessment (Revision of M4E guideline on enhancing the format and structure of benefit-risk information in ICH).
- CIOMS has recently published a Glossary of ICH terms and definitions.
- If a suitable definition cannot be found in any of the above sources, we will need to draft a de novo definition.
- It was decided that we should delay the Public Consultation by a week to address the terminologies.

Public Consultation process

- We discussed the draft Comment form.
- Vicky proposed a text improvement to the form, which was implemented live during the meeting.

Editorial team volunteers

- The Editorial team should have representation from the different chapter teams, the WG stakeholder groups, and geographic areas. WG members are encouraged to volunteer.
- As soon as we have the Public Consultation comments, we will need to have an Editorial team to begin working through the comments. Sanna will be sending out Doodle polls for September.
- Initial volunteers included Vicky, Claudia, Stéphanie, Barbara, and Carmit.
- Lembit and Sanna will work through the initial set of comments (e.g. where commentators have suggested including point X which has actually been covered already under title Y) during very late August and very early September.

Next working group meeting

- Lembit views the function of the next WG meeting as seeking the WG’s endorsement for the final publication.
- The timing is a little unpredictable as it will depend on how many comments we receive from the Public Consultation. End of September or early October could be realistic for a virtual meeting. We can postpone if needed. We can schedule two meetings and use the earlier meeting slot if we can.
- The second meeting could be used for an implementation team meeting. Implementation team activities may include:
    - webinar to introduce the report to the target audience(s);
    - scientific article for an open access journal;
    - some WG XII BR e-learning modules.
- Vicky felt the implementation team work could begin sooner rather than later. WG members can begin thinking about what contributions they could make.

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)

Subgroup 1 **Methods** Including integrated B-R methodologies / patient level	**Subgroup 2** **SDA** Structured descriptive assessment	**Subgroup 3** **Benefit-risk landscape**
Leo	Hong	Steffen
Richard	Sherry/Hussein	Tomas
Claudia	Stewart	Graham

Patrick
Scott
Stephen
Shahrul/Karen
Stéphanie
Luther
Ying
Panos
Barbara/Maria
Stéphanie
Carmit
Sebastian
Julie
Mutsuhiro/Shuichi
Wataru
Sabine/Sara
Guacira
George
Shanthi

Glossary team: Vicky, Hong, Leo, Steffen, Panos, Stephen, and Lembit