Third meeting of the CIOMS Working Group XII:
Benefit-Risk Balance for Medicinal Products – Update of CIOMS IV
8 September 2020, virtual meeting, hosted by CIOMS

Meeting Minutes

Participants

Guacira Corrêa de Matos (Anvisa), Scott Evans (GWSPH, Chair of PRAC), Stephen Evans (LSHTM), Richard Forshee (US FDA CBER), Stewart Geary (Eisai), Luther Gwaza (WHO)*, Sanna Hill (CIOMS), Vicky Hogan (Health Canada), Sara Khosrovani (MEB), Leila Lackey (US FDA CBER), Kitami Noriaki (PMDA), Leo Plouffe (Bayer), George Quartey (Roche), Qun-Ying Yue (UMC), Lembit Rägo (CIOMS), Kateriina Rannula (CIOMS), Cheryl Renz (AbbVie), Sabine Straus (MEB, Chair of PRAC), Stephanie Tcherny-Lessenot (Sanofi), Steffen Thirstrup (CORS), Panos Tsintis (CIOMS Senior Adviser), Mariko Tsukuda (PMDA), Sebastian Vulcu (BI), Julie Williams (MHRA), Hong Yang (US FDA CBER), and Xi Sherry Zhang (Gilead).

Apologies: Patrick Caubel (Pfizer), Sergei Glagolev (Ministry of Health of Russia), Takahiro Goto (WHO), Shahrul Mt-Isa (MSD), Shanthi Pal (WHO), Tomas Salmonson (former Chair CHMP), Stephanie Storre (Swissmedic), and Hervé Le Louët (CIOMS).

Alternates did not attend: Karen Kaplan (MSD) and Hussein Laljee (Gilead).

* New to the working group since previous meeting.

Prior to the meeting

- The minutes of the 2nd WG virtual meeting held 29-30 April 2020, hosted by Pfizer were approved by absence of comments.

Welcome and opening of the meeting

- Lembit Rägo, CIOMS Secretary-General, welcomed the members and thanked everybody for joining the meeting, acknowledging that some of the members are extremely busy. He continued to introduce the agenda and commended sub-groups for their good progress, making a suggestion to find further solutions to the excessive workload within the working group. He invited all members to participate in a short discussion towards the end of the meeting, concerning the experiences and lessons learned from COVID-19 as well as the challenges of introducing the vaccine to the global population, while considering balancing benefits and risks and general development of understanding on the topic.
- The agenda and the working mode were adopted.

- Kateriina Rannula was rapporteur at the meeting.

Subgroup 1: METHODS, presented by Leo Plouffe

The Subgroup 1 documents are available at the CIOMS website for WG XII, under password-protection.

Discussion

- Leo introduced the latest table of contents:
    - He proposed to start the modified way of working, to receive further feedback on the team, further fine-tuning or adding to the topics;
    - given the prominence of COVID-19, the collaboration between the UK NHS and DSRU is a topic worth considering;
    - with the focus on the major regulatory agencies: the US FDA approach EMA, PMDA, any proposals of any further affirmation would be welcome;
    - there is a necessity to align on the nomenclature, the concept of the patient-level integrated B-R assessment;
    - having identified a number of Special Situations, he stated that COVID-19 would be a more recent example of urgent situations.
- He concluded by saying that the current proposal is based on everyone´s comments with a possibility of further adjustments to be made. Any feedback and discussion from the other two groups with the aim of avoiding possible duplication would be welcome.
- Leo also introduced the sub-teams for September – December 2020: group members were given a topic to choose from the table of contents and to develop it into an advanced draft. The draft would then be shared with the broader group and a new topic could be chosen.
- He continued to list the names in the pairings and respective future work hours: Scott, Qun-Ying and Richard could each dedicate 8 hours in total; Luther, Sharul and Stephanie about 24-48 hours in total, Patrick and Leo about 24-48 hours in total. Stephen would act as an overarching reviewer for the work of the three groups.
- Richard thanked Leo for preparing and explaining their work and expressed his appreciation for everyone trying to find time to continue with the topics during these difficult times.
- Stephen expressed satisfaction with the suggestions from sub-group 1.

Subgroup 2: Structured Descriptive Assessment Chapter, presented by Cheryl Renz.

The Subgroup 2 materials are available at the CIOMS website for WG XII, under password-protection.

Discussion

- Cheryl started by explaining that team members were consulted on the particular topics they would be most interested in providing information about as well as on the time resources, which resulted in devising a three-month and a six-month plan.
- She continued that for the three-month plan and for some topics included, the writing process could be started immediately, whereas other topics would require further exploring in order to determine the information to be included.
- Experts within the sub-group and other groups would be consulted in order to avoid duplication. The six-month plan involves members actual writing process on different topics in the chapter.

- Cheryl agreed with Leo that certain areas present a risk for duplication and suggested for some of the team members to discuss more specifically what is being envisioned behind their topics.
- She also stated that with the structured approach to B-R chapter, their ultimate goal is to describe the process of undertaking the effort either in an industry or regulatory setting and assemble the information. Following that they aim not to discuss the details about visualization or patient preference, but to present in the structured approach where that methodology could best be used.
- Cheryl suggested an offline meeting with Leo to share and compare what is included in the work of their subgroups, to which Leo agreed.
- Vicky expressed satisfaction with the proposed plan and suggested to organize a meeting with the sub-group co-leads as soon as Cheryl would find it necessary.
- Richard felt that it would be beneficial to mention and reinforce the notion of multidisciplinary teams in the different themes and parts of the document, as it is an important concept that deserves attention.
- Stephen emphasized the need to consider how to involve B-R from both observational and randomized data and how to introduce different perspectives in disciplines that often have different approaches and knowledge.
- Stephen went on to elaborate on different theoretical knowledge underpinning of what is being assessed, evident in the example of COVID-19. With regards to the knowledge about convalescent plasma being used in many areas, weaker evidence for its efficacy would be accepted in terms of statistical power than it would be for a new drug in that area. He expressed uncertainty to whether the amount of theory can be captured.
- Vicky commented that the use of convalescent plasma and what level of evidence would be needed to determine the favourable B-R balance could be captured in the examples.
- Stephen agreed and continued by comparing Remdesivir and convalescent plasma, with the R-B of convalescent plasma being quite negative, whereas due to the theoretical knowledge it should be more positive. General knowledge of Remdesivir would be much more limited in terms of theoretical basis for it and would require stronger evidence for the efficacy than convalescent plasma. He added that the groups might be able to describe similar concepts in the examples, but rather in a form of a discussion, without definite answers.
- Panos addressed a question to the WG members from FDA: having read the publication that Leila circulated previously, has FDA used the framework mentioned during the pandemic treatment, plasma or any other new drugs?
- Leila responded by saying that she does not possess information whether there are examples for COVID-19 therapeutics or treatments yet.
- She added that if she were to advise an FDA reviewer on the topic, she would incorporate it into discussion of the context of the decision as it is the context that informs of the tolerance for uncertainty.
- Leila continued to elaborate that there are rare diseases of which FDA had many examples where different types of evidence was accepted: uncontrolled trials, unrandomized trials, due to the difficulty of perhaps running control trials or what is known about the product.
- Richard agreed with Leila and added that FDA had issued an emergency use authorization for convalescent plasma, which he shared with the working group.
    - https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
    - FDA Clinical Memo for COVID-19 convalescent plasma: https://www.fda.gov/media/141480/download
- Richard appreciated Stephen´s comments regarding the prior knowledge and added that in the case of convalescent plasma, a robust safety database exists with the risks well characterized and low.

- Richard added that in their sub-group, there were discussions of using real-world evidence and B-R assessment as a part of their chapter. He found the B-R assessment tools for quantifying uncertainty extremely helpful when trying to integrate real-world evidence into B-R decisions.
- Cheryl returned to chapter 2, relating to Stephen's comments to their intended work in subgroup II and added that sub-group 2 had also intended to highlight the various data sources that can form a structured B-R approach, and this is also an example of where to try to avoid duplication.
- She continued that besides also highlighting the roles that different professionals serve in a multidisciplinary team, highlighting uncertainty would also be necessary. She also felt that the examples of challenging B-R decisions would be most informative.
- Vicky thanked Cheryl and added that perhaps in the discussion about uncertainty there should be some input into at least one of the three sections' work on tolerance of risk, as brought up by Stephen and Richard, as tolerance of risk is a key factor in development of a B-R assessment.

Subgroup 3: Introductory chapter: Benefit-risk landscape, presented by Leila Lackey (US FDA CBER)

The Subgroup 3 materials are available at the CIOMS website for WG XII, under password-protection.

Discussion

- Leila commented on having discussed the shift in approach and people's capacity within their sub-group and there were two volunteers to work on some examples: George to work on Zelnorm and Sara and Sabine to work on Neratinib.
- She added that for the examples, the aim was to highlight the nuances of B-R assessment by incorporating cases with different decisions made either in different regions or regarding the view of the B-R.
- Leila mentioned that their group had progressed more on the writing, so she had proposed to do work more on the topic of the shift to the lifecycle approach.
- Leila also suggested that there might be some parts of the text produced by other sub-groups to be added to the introductory chapter.
- Stephen enquired about the document´s availability and Leila confirmed it to be found in the WG coworking section of the CIOMS website.
- Vicky suggested the co-leads to share the materials with other subgroups and have discussions internally about what aspect of the topic each group is focusing on, and asked Sanna to circulate the materials as well.

Plenary discussion on new work approach. Proposal for a standardized format for the CIOMS WG XII report case studies. Presented by Vicky Hogan (Health Canada).

Document is available at the CIOMS website for WG XII, under password-protection.

- Vicky suggested that the working group should discuss the first draft of the proposal for a structured approach on developing the examples.
- She continued that the proposal was developed after evaluating the examples included in CIOMS WG IX, titled "Practical Approaches to Risk Minimization for Medicinal Products".
- She found that the CIOMS IX examples:

    - follow a loose structure and have very little commonality between the examples, also, it was more difficult to follow the examples.
    - many of the case study examples had different approaches to risk minimization and they often compared only the EU and the US;
    - did not follow a structured approach, some information on the examples was provided in narrative text while in others in bullet point form;
    - sometimes provided a summary table of published papers on drugs, the table would better suit a reference section or bibliography rather than the examples.
- Vicky stated that the goal of the proposal is not to reach a definite conclusion but to investigate if the group agrees to the attempt to structure the approach or the format of the examples included in the guidance.
- Vicky suggested that everybody provides her with comments on the document which she would then refine over the following months rather than discuss immediately.
- She proposed to use the summary table at the beginning of each example as it makes finding the information easier but deciding what kind of detailed information is to be added, needs further discussion.
- She mentioned that the proposal might require some more additions to it, as it might not accommodate everybody's examples.
- She added that in CIOMS IX working group the focus was not on B-R assessment, but on risk minimization, so they summarize the risk minimization tools that were used for that particular drug and included an introduction and background or both.
- Stephen responded by commending the proposal and added that although he was not on CIOMS IX, he was on CIOMS X, and they should have had similar discussions there as well.
- Stephen asked whether it would be possible to share the proposal with some of his colleagues and Vicky agreed as she found that it would be beneficial for Stephen's colleagues to provide their comments.
- Cheryl offered the following points for consideration:
    - Having a structured way of presenting cases is beneficial, it provides information on what to anticipate when reading through case examples;
    - when thinking about the template to use for examples, the purpose of the example is important, because the structure may vary depending on what is being demonstrated;
    - it would be advisable to thoroughly consider how to structure the example, because working group 2 should use the same structure in the example added to chapter II.
- Panos welcomed Vicky´s proposal and added that as he was part of CIOMS IX, they would have appreciated a common way of presenting the examples. As they did not have time to reach a consensus, individual members developed examples on their own.
- Panos also commended the use of bullet points and the idea of adding a summary to the beginning. He also suggested to aim for shortness.
- Vicky elaborated on Cheryl's comment saying that according to her understanding a similar structure can be deployed suggesting a section of methodology stating that the method followed was the structured descriptive assessment. The example then could be presented using the structured descriptive assessment. Any additional information provided would still follow the same structured format as the rest of the examples.
- Scott commented that perhaps more topics could be added to the proposal. He continued by emphasizing that the document should include information about B-R being more than just the sum of benefits and harms, and that B-R should come into design and conduct of studies as well as into development programs.
- He also suggested that as a trial protocol has an efficacy section and a safety section as well as efficacy endpoints and safety endpoints - there should be a third section on B-R that should have integrated B-R endpoints, and they should be part of protocols.

- Scott commended the structured approach but proposed to modify it to address some of the limitations: using the outcomes to describe, what is happening to the patient, rather than using the patient to describe what happens to the outcomes.
- Scott also voiced a concern about reinforcing existing approaches that need to be adjusted and improved.
- Vicky agreed with Scott about adjusting the existing knowledge and suggested a requirement within the methodology section to discuss the limitations of the method.
- Panos added that during the face-to-face meeting it was discussed and agreed that the new way of looking at the patient and looking at outcomes would be clear when the data is available. The suitability and examples would then be discussed by the methodology group.
- Cheryl agreed that what Scott had summarized would be something to add to the methodology chapter, to state what we believe would be the optimized way of looking at the data constituting a key part of the chapter I group, to which Leo also agreed.
- Vicky proposed to add a separate section to discuss the limitations of the methodology, if needed. She also suggested to decide on the type of examples that should be presented in the document.
- Stephen suggested to reduce the amount on risk minimization, as it is not the topic of this CIOMS group.
- Richard commented that he would not advise to completely eliminate risk minimization, because sometimes it affects the B-R balance and Panos agreed by saying that some formal frameworks, e.g. FDA, mention risk management.
- Vicky agreed that risk minimization could be added in a section of limitations as a discussion on how to improve the B-R assessment following the methodology
- Cheryl agreed with Vicky's proposal for structured approach and following the debate about the risk minimization, urges everybody to consider what the other parts of the guidance will and should include.
- Vicky added that it needs some consideration of how to include all information relevant to some examples and not to the other, without limiting anybody.
- Vicky concluded the discussion by requesting everybody to send their further comments during the next three-week period, after which she can compile a second draft and discuss it with the co-leads. Further comments will be welcome for the second draft as well.

- Vicky introduced the newest working group member, Luther Gwaza from WHO, who joined the group during the last meeting, April 29-30, but had not formally introduced himself then. Luther is working in the WHO as a technical officer in the Regulation and Safety Unit, Regulation and Prequalification Department and Access to Medicines and Health Product Division of the WHO and he has joined subgroup I, Methodology group. Vicky welcomed Luther and added that the working group is looking forward to his participation in CIOMS XII.
- Luther thanked everyone and said that he is looking forward to working with all members of the group.

- To conclude the meeting, Lembit expressed gratitude to the working group for their work, time and dedication, and agreed that the heads or the co-leads of the sub-groups should organize a meeting to discuss the aforementioned topics in order to prevent overlapping.
- Lembit added that in case the subgroups should require any help from the secretariat, the secretariat will certainly do their best to help, by organizing a zoom conference or assisting in any other way necessary.
- Vicky reminded all working group members to consider the proposal and send their comments during the 4-week period. She agreed that after receiving the comments the group will ask Sanna to organize a zoom conference.

- Following the conference Vicky would compile a second draft, again followed by a zoom conference for co-leads.
- Vicky thanked everybody for attending, for their continued efforts and for all the hard work that the members are doing under various challenges.

General discussion

Challenges experienced / lessons learned from COVID-19; challenges of making the COVID-19 vaccine available to the global population; how the views on balancing B-R are evolving in light of COVID-19.

- Cheryl commented that it had certainly been a different working situation for everyone and would appreciate if anyone shared their experience of working in a pandemic when B-R decision-making is paramount. Also, whether anybody would share their experience of working on a vaccine or any other new development product to address the pandemic.
- Stephanie shared her experience saying that working on a vaccine for COVID-19 has been an interesting challenge, in terms of real life and on the topic of B-R as well. She added that they are expecting results to be ready to launch the vaccine.
- Cheryl enquired about the company's routes of informing the public about the safety and effectiveness of the vaccine, as there will be perhaps suspicions about the vaccine due to its rapid development.
- Stephanie responded that the communication will be more transparent, and the information communicated more regularly with each new evidence. Generally, a more conservative approach was used. More communication to scientific community and also to general public can be noted.
- Lembit enquired about the process of linking communication to the one of the regulators and authorities and continued by asking whether there have been discussions about the communication plan with other stakeholders who are involved in launching the vaccine.
- Stephanie responded that there has not been a major change and all the traditional communication channels are used, perhaps some more communication outside the traditional channels was observed.
- Cheryl added that just learning to work virtually has been a major learning experience. She expressed her interest in observing how various companies and agencies will balance the office-based versus virtual working situations.
- Lembit concluded the discussion by thanking everybody for their commitment and the progress made and added that if any kind of help would be required, the secretariat would be more than willing to be of assistance.

Next steps

All members of the working group provide Vicky with comments on the proposal of structured approach during the next 4 weeks, after which she agreed to prepare a second draft which will be discussed with co-leads during the next zoom conference organized by Sanna.

Action items and conclusions

- All subgroups continue working according to their plans.

Chairwoman: Vicky
Co-Chair: Patrick
Co-Chair: Scott

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

Subgroup 1	**Subgroup 2**	**Subgroup 3**
Methods Including integrated B-R methodologies / patient level	**SDA** Structured descriptive assessment	**Benefit-risk landscape**
Shahrul Leo Panos Scott Stephen Richard Patrick Qun-Ying Stéphanie T Luther	Sherry Stewart Cheryl Stephanie S Stéphanie T Sebastian Julie Sergei Hong Kitami Mariko	Guacira Takahiro Steffen Tomas Leila Sabine George Shanthi

Vicky is currently not attached to a subgroup.