Sixth meeting of the CIOMS Working Group XII:
Benefit-Risk Balance for Medicinal Products – Update of CIOMS IV
21 September 2021, virtual meeting, hosted by CIOMS

Meeting Minutes

Participants

Patrick Caubel (Pfizer), Guacira Corrêa de Matos (Anvisa), Scott Evans (GWSPH), Richard Forshee (US FDA CBER), Stewart Geary (Eisai), Luther Gwaza (WHO), Sanna Hill (CIOMS), Vicky Hogan (Health Canada), Claudia Ianos (Pfizer), Sara Khosrovani (MEB), Leila Lackey (US FDA CBER), Shahrul Mt-Isa (MSD), Leo Plouffe (Bayer), George Quartey (Roche), Tomas Salmonson (former Chair CHMP), Sabine Straus (MEB, Chair of PRAC), Steffen Thirstrup (CORS), Sebastian Vulcu (BI), Julie Williams (MHRA), Hong Yang (US FDA CBER), and Xi Sherry Zhang (Gilead).

Apologies: Stephen Evans (LSHTM), Sergei Glagolev (Ministry of Health of Russia), Mari Kihara (PMDA), Wataru Kuga (PMDA), Kitami Noriaki (PMDA), Shanthi Pal (WHO), Lembit Rägo (CIOMS), Cheryl Renz (AbbVie), Stéphanie Tcherny-Lessenot (Sanofi), Panos Tsintis (CIOMS Senior Adviser), and Qun-Ying Yue (UMC).

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

Welcome and opening of the meeting

- Vicky kindly chaired the meeting in the absence of Lembit. She commended the WG for maintaining a continuous momentum despite the ongoing pandemic.
- The agenda was adopted.
- Sanna was rapporteur at the meeting.

Presentation on Covid-19 mRNA vaccine benefit-risk assessment by Patrick

- Patrick's slides are confidential.
- The presentation focused on:
    - Importance of the spike protein;
    - Encapsulated mRNA;
    - Vaccine development journey;
    - Safety and efficacy information;
    - Administration of several leading vaccines;
    - Adverse events of special interest (AESI);
    - Vaccine Adverse Event Reporting System (VAERS);
    - Vaccine Safety Datalink (VSD);
    - Outcome events in 21-day risk interval after either dose of any mRNA vaccine;
    - Covid-19 vaccine in adults: Benefit-risk (B-R) discussion.

- Patrick touched on topics such as spontaneous reporting from multiple sources, spontaneous reporting v. social media reporting, biases, using electronic health records, extrapolation between what has been identified between clinical development and observed in real life, and vaccine hesitancy.

Comments

- Richard felt some of the data has been misinterpreted by some in the public.
- Following Patrick's VSD rapid cycle analysis, Richard added that the FDA also conducted sequential analysis using its Medicare data on adults aged 65 years and older. Four adverse events (AEs) passed the statistical threshold (pulmonary embolism, acute myocardial infarction, immune thrombocytopenia, and disseminated intravascular coagulation), and the FDA is investigating them with self-controlled methods; it does not think this indicates a causal relationship. The public statement is here.
- The level of safety scrutiny for these vaccines is unprecedented. We have never had this number of systems, proactively looked for this number of AEs, and so in many ways, it is incredible that so few credible signals have come up.
- Death can be an expected outcome, not necessarily an adverse reaction (AR), and when you are vaccinating a large population, especially with older age groups, natural deaths will happen.
- Vicky was interested in returning to the question of whether there is a return on investment for monitoring social media to follow risks on products in the market. Patrick said Pfizer has been monitoring this since before the Covid-19 vaccine and will need to complete its analysis and will then publish its findings.

Progress updates on chapter drafts and case studies

Subgroup 1 on methods, presentation by Leo and Richard, slides available online

- The subgroup is making good progress: drafting sections, circulating them within the team for comment, identifying gaps and assessing them for relevance, agreeing who will author them, refining its plan and setting objectives for the autumn.
- The team has drafted approximately 43 pages and has aligned with the other subgroups.
- Going forward, some section may need to be re-ordered and/or integrated, and reconciled with other sections.
- Leo asked to know if the other subgroups intend to also cover the following subjects:
    - Opportunities in analyses of existing data;
    - Uncertainty;
    - Statistical approaches.
- Leo asked about if we are to cover the formal guidelines of major regulatory agencies and reach out to select groups to summarize their methodological approaches (e.g. the Cochrane Collaboration and U.S. Preventive Services Task Force). This discussion is related more thoroughly under the subgroup 3 progress update.
- Hong envisages subgroups 1 and 2 will need to collaborate on the *Patient input* section. In the subgroup 1 draft this is entitled: *Facilitating patient healthcare professional interface*. Leo confirmed that subgroup 1 intends to address this from the methods perspective. In Scott's description, the patient-level benefit-risk assessment (BRA) includes patient insights and patient preferences approaches. The broader subject would be addressed by subgroup 2 and the two sections can cross-reference each other.
- The silos thinking around the quantitative, semi-quantitative, and qualitative approaches may need to be echoed throughout the report. It will be a major contribution of the WG XII report to the field. We will need to decide as a WG where this will be placed within the report, although Leo did not think that the main part would be in the methods section.

Subgroup 2 on structured benefit-risk approach/framework, presentation by Hong, slides available online

- There has not been much engagement within the subgroup 2 team due to the pandemic.
- The subgroup 2 co-lead, Cheryl, is about to begin her retirement and was unable to attend the meeting. AbbVie is looking to appoint a replacement as soon as possible and the new person's role in the WG will need to be confirmed upon their arrival. Cheryl wishes to continue following the progress of the WG.
- Vicky requested scheduling a meeting to discuss the subgroup 2 resourcing.
- Cheryl was involved in two subgroup 2 chapters and had not yet provided her drafts:
    - Ch 2: *Components of Structured Benefit-Risk Framework* (large part of the chapter);
    - Ch 4: *Role of the Patient in Structured Benefit-Risk Assessment* (overlaps with sbgrp 1).
- There was no update regarding Ch. 3: *The Lifecycle Approach to Benefit-Risk Assessment*.
- Hong gave an update on Ch 5: *Quantitative Benefit-Risk Analysis*, for which she has completed two case studies:
    - How to inform benefit-risk of rotavirus vaccine with emergence of risk of intussusception? (completed)
    - Benefit-Risk of Oral Anticoagulants (in progress, expect to complete by next meeting)
- Hong provided a refresher on the formal definition/terminology for qualitative, semi-quantitative & full-quantitative BRA by Aris Angelis and Lawrence Phillips, BJCP 2010 (similar definition/terminology by PROTECT) and the scope of the discussion.
- She presented a draft diagram to convey the proposed approach:

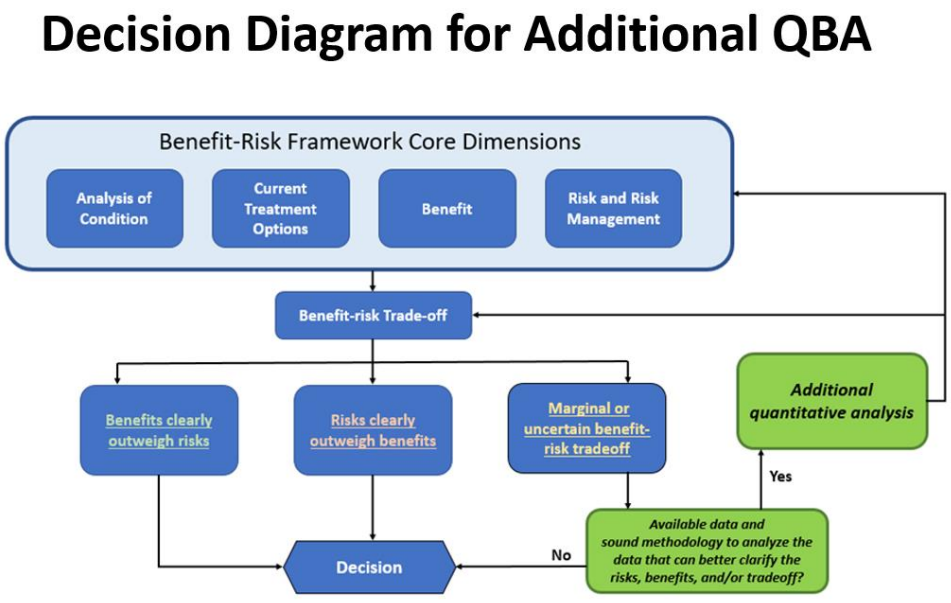

Figure. Decision tree for additional quantitative analysis in benefit-risk assessment for medical products

- Everyone is invited to feedback on the above approach, and once comments have been received, Hong and her team will draft text to accompany it.
- Subgroup 2 will present the above approach and subgroup 1 will provide more details about the additional quantitative analysis.

Subgroup 3 on benefit-risk landscape, presentation by Leila and Sara

- Leila summarised the subgroup 3's outline:
    - Key changes from the CIOMS WG IV report;

- The structured approach;
- A shift from a post-market focus to a lifecycle focus;
- Risk management throughout the lifecycle – drafted by Sabine and Sara.
  Sarah elaborated on the new paragraphs on risk management measures throughout the lifecycle and an example on checkpoint inhibitors.
- Leila suggested placing Hong's *Decision Diagram for additional QBA* in the introductory chapter, feeling it may be helpful for the reader to have a preview of what is going to come later. Similarly, it may be helpful to preview some of the methods and the associated pros and cons.

- Vicky proposed including a section under subgroup 3 on the different methodologies / protocols / approaches in the field.
  - There are many groups working in this space including scientific organisations and regulators.
  - This section would highlight the common features e.g. assessing / reassessing throughout the lifecycle of a product, the patient-centric approach, and transparency. There may be other features to discover.
  - The section would also highlight the diversity e.g. the different processes and the best stages / frequencies for re-evaluating.
  - Typically, the different groups agree to use the methods that make sense in the circumstances and apply them according to the particular features of the product in question and the capabilities of the organisation.
  - We would like to know each group's mandate, so we can know what differentiates us, and where they are in their drafting process.
  - Leo added that some on the initiatives focus on the core subject of the CIOMS WG XII report (e.g. ICH and IMI PROTECT), but there are also others that support e.g. the Health Technology Assessment (HTA) side (e.g. ICER, NICE, and CADTH), or the end-result B-R for the patient delivery. Subgroup 1 will acknowledge HTAs in its draft. All suggestions should specify where their initiative fits in.
  - As we build our list of other groups to consider, Leila suggested that we not reach out to organisations that focus on the economic side and cost effectiveness, as this will open the task to a far wider remit.
  - All WG members are requested to email their suggestions to Vicky and Sanna for compilation towards a comprehensive list. Vicky will present this at the next WG meeting and the WG can then decide which groups to acknowledge as major contributors and where in the report we should do this.
  - Richard expressed his support for this approach.
  - Below is a table of the groups mentioned to date:

Initiative	**Comments**
U.S. Preventive Services Task Force	• Doing significant work in this area. • Vicky's first attempt at contacting the group was not answered.
ICH M4E(R2) *Revision of M4E guideline on enhancing the format and structure of benefit-risk information*	Embraces the concepts of lifecycle approach, transparency and consistency, forethought to elements of predictability, and the use of structured approach.
Cochrane Collaboration	• Vicky was not sure if the Cochrane Collaboration has developed a methodology but it is worth researching. • Its systematic review methodology is extremely well developed.
IMI PROTECT Benefit-Risk group + EMA's Benefit-risk	• Vicky was on the expert advisory panel at the outset in 2019 and on the B-R Work Package. • This took a different approach, looking in-depth at decision

methodology project	theory, with experts from the London School of Economics and different European universities, and came up with a methodology.
UMBRA	
UN Global Pulse Group	The Data Innovation Risk, Harms and Benefits Assessment Tool was published in 2020 and currently under public consultation.
ASA/DIA taskforce on benefit-risk assessment planning	• Aligned with our WG. • Developing a template similar to the ASAP/PSAP templates (programme-wide safety analysis). • Hong and Cheryl have been involved. • Have conducted some interviews in industry / global experts to ascertain how B-R is used. • Some public presentations and a book chapter drafted.
ISPOR taskforce developing a best practices report on quantitative benefit risk assessment	• Possibly does not meet criteria but good for awareness. • The report is focused on quantitative (specifically, quantitative preferences and multi-criteria decision analysis) but they do not advocate that approach for all cases. • The introduction to the paper is essentially: assuming you have determined that quantitative is needed, here is how to do it. • Anticipated publication: 2022-23.
BRACE Benefit Risk Assessment, Communication and Evaluation	BRACE is a special interest group under the International Society for Pharmacoepidemiology. It focuses on the intersection of Pharmacoepidemiology and benefit-risk assessment. It is well in alignment with the CIOMS WG XII. Its activities include development, review and implementation of new BR and Pharmacoepidemiology tools/methods, development and sharing applied examples, research findings and information on best practices and promoting harmonization.
Regulators have their own methodologies	• FDA's structured BRA framework • Health Canada's document on BRA (not as structured, starting to be outdated)

Review the CIOMS WG XII COVID statement

- Richard and Vicky gave some reflections:
    - The pandemic time has been challenging because events have been moving so fast.
    - We have needed to make decisions on a timeline such as we would not normally do – there was a series of interim orders in Canada, which enabled expediting the review process for the COVID vaccines and some of the COVID treatments.
    - Sometimes we had to make decisions without as much data as in normal times.
    - We have maintained strong engagement with our advisory committees. This was important for transparency and getting public feedback. Sometimes our advisory committees pushed us in directions that perhaps we would not have been originally planning to go.
    - Staff have remained entirely science-based in their decision making.
    - We focused our attention on the post-market monitoring and surveillance of the COVID vaccines and COVID products, and increased our risk communications.
    - The interim orders in Canada ended in July and the COVID products that had been put on the market were reassessed in light of new information that had come forth during the pandemic.
    - Vicky believes Canada has followed the spirit of the CIOMS statement.
    - Now almost two years later, most of the major pharmaceutical companies that have been working in the space of COVID treatments, as well as the regulators that

participate in this WG, have delivered on our philosophy for how to move forward in the light of uncertainty.
    - History has yet to be written.

Nomenclature and report glossary

- The glossary team held two meetings: 8 July and 16 September, and the result was a merged list of terms submitted by the three subgroups. More terms are welcome.

Subgroup 1	Subgroup 2	Subgroup 3
Desirability of outcome ranking (DOOR)	Additional quantitative analysis for benefit-risk assessment	Advanced therapies
Effects Table	Anticipated adverse events	Basket Trials
Large simple trials (LSTs)	Benefit-risk evidence	Benefit-Risk (B/R) assessment
Learning system	Benefit-risk framework	Electronic Healthcare Record
Marginal analysis	Benefit-risk metrics	Individual Case Safety Report – ICSR
Partial credit analyses	Benefit-risk structured approach	MCDA
PBRER (currently mentioned under PSUR – elevate?)	Outcome measure	PRO – Patient Reported Outcome
Pragmatic clinical trials (PCTs)	Patient experience data	QoL – Quality of Life
Signal validation	Patient preference	Structured descriptive benefit-risk frameworks
Value tree	Real-word evidence	Umbrella Trial (not mentioned, but closely related to the above)
	Therapeutic context	

- We will consider the terms and existing definitions with view to potentially drafting some new definitions where necessary.
- We will continue discussions on the criteria for including terms in the WG XII glossary, e.g. subgroup 1 has many terms directly related to quantitative methodologies and methods that are not focused on pharmacovigilance or BRA. We are inclined to exclude “textbook” terms e.g. multi criteria decision analysis or a t-test. Feedback is welcome.
- The next step will be to divide the terms among the subgroups for drafting definitions, and by the next WG meeting, the glossary team will aim to present the proposed draft definitions.

Closing remarks

- Thank you for everyone’s participation.
- We made good progress despite the virtual nature of the meeting.
- Vicky would like to progress to sharing integrated, structured, detailed drafts from subgroups 1 and 2 by the end of November, so that all can have visibility of the work, in particular subgroup 3, and give meaningful feedback. This will enable all three subgroups to advance and mature their drafts in time for our next meeting in early April. This was supported by the WG.

WG structure

Chairwoman: Vicky
Co-Chair: Patrick (currently less active in this capacity)
Co-Chair: Scott

Subgroups and co-leaders (co-leaders' names are underlined)

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

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