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Fifth meeting of the CIOMS Working Group XII:
Benefit-Risk Balance for Medicinal Products – Update of CIOMS IV
18 June 2021, virtual meeting, hosted by CIOMS

Meeting Minutes

Participants

Guacira Corrêa de Matos (Anvisa), Scott Evans (GWSPH, Chair of PRAC), Richard Forshee (US FDA CBER), Stewart Geary (Eisai), Takahiro Goto (WHO), Luther Gwaza (WHO), Sanna Hill (CIOMS), Vicky Hogan (Health Canada), Claudia Ianos (Pfizer), Sara Khosrovani (MEB), Mari Kihara (PMDA), Shahrul Mt-Isa (MSD), Kitami Noriaki (PMDA), Leo Plouffe (Bayer), George Quartey (Roche), Qun-Ying Yue (UMC), Lembit Rägo (CIOMS), Cheryl Renz (AbbVie), Tomas Salmonson (former Chair CHMP), Stephanie Storre (Swissmedic), Sabine Straus (MEB, Chair of PRAC), Stéphanie Tcherny-Lessenot (Sanofi), 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), Stephen Evans (LSHTM), Sergei Glagolev (Ministry of Health of Russia), Leila Lackey (US FDA CBER), Shanthi Pal (WHO), and Steffen Thirstrup (CORS).

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

Welcome and opening of the meeting

- Lembit welcomed the members and thanked everyone for joining.
- News from CIOMS WGs:
  1) The CIOMS Cumulative Pharmacovigilance Glossary 1.1 was published earlier in June 2021, with the most notable update being the inclusion of the vaccine safety terms and definitions;
  2) The CIOMS WG on Clinical Research in Resource-Limited Settings issued its report;
  3) A new CIOMS WG was launched in April on Recommended Standards of Education and Training for Health Professionals Participating in Medicines Development;
  4) A new CIOMS WG will be launched in early July on strengthening the governance of clinical research;
  5) The CIOMS quarterly Newsletter will be distributed before the end of June.
- Vicky summarised the major advances across the subgroups, as explained in more detail below.
- The agenda and the working mode were adopted.
- Sanna was rapporteur at the meeting.

Subgroup 1 presentation by Leo and Richard

- Subgroup 1 has been holding monthly meetings to advance its work and intends to continue in this manner. The subgroup also met with subgroups 2 and 3 regarding overlaps and content in

general, including e.g. the strengths and the limitations of the methods and when to use them. There was also a meeting with Hong regarding qualitative, semi-quantitative, and quantitative divisions for benefit-risk assessment (BRA).

- Stéphanie drafted sections on *Special Situations* and *From Early Development Through Late Life-Cycle*. The latter embodies the key theme of moving BRA considerations to the early part of the drug development cycle, so that those can be considered in the design of the entire research programme, enabling the development of appropriate evidence. The section will cover different stages and the types of BRA that are useful at each stage. Some of the considerations throughout the chapter will be on resource constraints (time, personnel, etc.), and how that factors into the way we approach BRA. We will focus on a patient-level, integrated, benefit-risk (B-R) approach. The team is still working on the terminology

- Claudia produced a plan for a section on *Study Design* and started drafting a section on *Pragmatic and Large Simple Trials*. The latter is currently being reviewed by the subgroup. It highlights practical elements and is a good interface to real-world evidence (RWE), in particular on the role of RWE in terms of methodological consideration to enhance BRA.

- Scott drafted a section on the newer methodological concepts: the patient-level BRA, including ideas shared to date, and highlighting the current shortcomings of the existing methods. This is currently being reviewed by the subgroup.

- Leo and Claudia agreed to start drafting a section on *Uncertainties*.

- Steven has been putting together an example on data visualisation using bar graphs. We will discuss how many visual examples we give and refer to, and will probably include forest plots and heat maps. All contributions are welcome.

- Claudia's case study on varenicline makes the key point that we cannot assess B-R in a vacuum. The smoking cessation medicine brought up questions about distinguishing between psychiatric adverse events of the drug and the symptoms of the underlying condition being treated.

- Panos provided a draft on gene therapy, which may be suitable for the appendix section. It is a stimulating subject but we probably have to shorten it.

- Stéphanie agreed to work on a case study on a novel oral anticoagulant therapy.

- Panos agreed to create a table outlining major international initiatives.

Subgroup 2 presentation by Hong and Cheryl

- Hong discussed the subgroup 2 updates in terms of a slide set from the 4th WG meeting.

- Chapter 2 will emphasise the structured framework and discuss additional quantitative analysis for complex problems.

- Subgroup 2 has progressed on the quantitative risk assessment aspects. Hong suggests including a wide range of quantitative analysis options to address different kinds of situations. The chapter will discuss how to consider the therapeutic context, the benefits, the risks, the uncertainties, and the trade-offs. Sometimes simple quantitative analysis, e.g. sensitivity analysis, can be very helpful e.g. in the case of uncertainty. BRA is a process, not one single analysis. It can serve as part of evidence, is problem-driven, and done on a case-by-case basis. It does not replace clinical judgement. Hong's two case studies give different situations and show the kind of analysis that may be helpful. She would like to check with subgroup 1 for more examples. The value of additional analysis is partly determined by data quality.

- Leo suggested that we clarify that we always come back to the structured framework. We start off with a structured framework based on statistical data, then we may see the need for additional data that we can generate, but those data are then reintegrated into the structured framework. Otherwise, it will give the impression that the structured frameworks do not work.

- Richard suggested communicating the concepts using a high-level conceptual flowchart that goes through the decision-making process. Hong suggested laying out the rotavirus case study in this way. Vicky added that when the flowchart gets to asking the question "is there any benefit

in in doing further analysis?", if yes, then that could dovetail with subgroup 1's various different quantitative methods and what they are best used for. Hong and Richard offered to work on some proposals.
- Hong mentioned some areas of overlap with subgroup 1 (life-cycle approach, role of patients, and quantitative BRA) and clarified that subgroup 1 will focus on the methodology aspects and subgroup 2 will focus on considerations on the structured B-R framework.
- Hong presented two case studies to demonstrate the quantitative analysis approach. The first shows how to use Monte Carlo simulation / a sensitivity analysis, to conduct post-market BRA, incorporating different data sources. The second uses Multi-Criteria Decision Analysis (MCDA) to help handle trade-offs within a B-R question.

Case study 1: Potential intussusception risk versus benefits of rotavirus vaccination in the United States (slide set provided separately).
- This is a good example of the post-licensure quantitative BRA for a vaccine.
- Rotavirus vaccines have a very clear benefit but can have a potential risk (severe consequence).
- When the vaccine was approved, there was no evidence in the US that intussusception was related to the vaccine, but the risk was captured in international data. In the case study, a mathematical model (Monte Carlo simulation and sensitivity analysis) was used to incorporate different sorts of data for the post-market B-R to evaluate the impact of uncertainty.
- The B-R endpoint for this analysis: the benefit endpoint is the prevention of rotavirus-associated deaths, hospitalisations, and emergency department visits, and the risk endpoint is the assessed deaths, hospitalisations and the emergency department visits due to vaccine-associated intussusception.
- The assessment integrates the B-R ratio for these three clinical outcomes: the deaths, hospitalisations, and emergency department visits, and calculates the B-R ratio.
- Key lessons from this case study:
  1. When there is uncertainty about a severe risk associated with a licenced product, a continuous evaluation of B-R post-market is important;
  2. Computational techniques can be used to inform decision making in the case of uncertainty.
  3. Probabilistic computational models can be used as a tool to incorporate different sorts of data on uncertainty. In this case, the model incorporated:
     - Post-market clinical trial data;
     - National immunisation surveys on vaccine coverage data;
     - Hospital emergency department discharge database (to calculate the baseline intussusception rate);
     - International vaccine-associated intussusception rate.
- In this case, Monte Carlo simulation and sensitivity analysis were used to evaluate the worst case scenario given the uncertainty about the data and/or about the assumptions made. Even under the worst case scenario, the benefits outweighed the risks and this helped the decision making.
- Vicky added that regarding the rotavirus vaccine case example, we can say it demonstrates probabilistic modelling via Monte Carlo analysis, the life-cycle approach (we cover the post-market BRA), and the flow of the structured framework. Hong pointed out that we do not have the evaluation at the pre-market stage, but she can look for this. (Vicky suggested that it might be nice to have an example that would show how at the pre-market stage there was a qualitative analysis, and then the post-market stage, show the same drug, the same event, using a quantitative analysis when we have more data available.)
- Vicky asked if Hong was considering using a case study on qualitative approaches too? Hong answered that as the plan is to not separate BRA along the lines of quantitative and qualitative

approaches, in principle, the BRA framework applies to every situation. The quantitative analysis only brings added value under complex situations.

Case study 2: Net clinical benefit of oral anticoagulants: a multiple criteria decision analysis (slide set provided separately).

- Hong presented the rationale behind this case study proposal to gage the interest of the WG.
- The oral anticoagulant case study demonstrates the MCDA quantitative analysis, the use of a value tree, and the assessment looked at individual patient needs.
- Would we show the oral anticoagulant case study without the MCDA quantitative analysis in the context of demonstrating when it is important to use additional analysis?

Subgroup 3 presentation by Tomas

- Tomas commended Leila for running subgroup 3 very well.
- The draft produced in August 2020 was succinct and looked to explain why the CIOMS WG XII is producing this report at this time. Overall, the subgroup feels it cannot do more until the other subgroups have shared their drafts.
- Subgroup 3 held meetings with subgroups 1 and 2, and received input on its draft.
- Major topics to include are: the changes since the CIOMS WG IV report; the arguments / drivers for the work we are doing; and emergency situations and vaccines.
- We have learned a lot from the COVID experience in terms of decision making under pressure, the role of vaccines, the take up of vaccines, links to transparency in the B-R work done.
- The B-R supports communication to other stakeholders (the public, government decision makers, HTA, clinicians, and patients).
- Subgroup 3 is also looking to discuss how we present information, visualisation (heatmaps etc.), and will need to balance this with the other subgroups.
- Subgroup 3 will also cover the important topic of risk management and its role in risk minimization and how well that can be done and what can be assumed in the context of BRA.

Patient preference and patient perspective

- Would it be helpful to incorporate patient preferences and perspectives in the different B-R case studies? It is becoming increasingly important and sometimes patients' preferences might be very different. What we feel is a severe risk, they might want to accept and vice versa.
- Scott's contribution fits in with this theme.
- When a patient preference study yields a very clear result, e.g. 95% of patients think X, it can be helpful, but if the result is much more nuanced, which is often the case, the patient preference studies can contribute a further element to the uncertainty, rather than make for a very clear discussion. Subgroup 1 will discuss using a case study to highlight this.
- Vicky felt that in the Chantix case study, one key point is the importance of the stakeholder involvement (key opinion leaders and healthcare professionals), and suggested that we consider patients as part of the advisory committee and the decision making process. Given that public meetings took place, where the public was asked to provide its input to the drug and its approval, this qualifies as patient input.
- It is uncontroversial to use patient-reported outcomes (for efficacy or safety data) and patient preference studies, but the role of patients in the decision making is more controversial. We should have a view on this.
- Including patient-level data in B-R is not currently routine. Perhaps we could look at that as a special area? Unless we have predetermined endpoints in clinical studies, we are not going to have patient-level data. It may be that we're not capturing or at least not analysing in the right way to get this endpoint. That could be an area to specifically target in the framework.
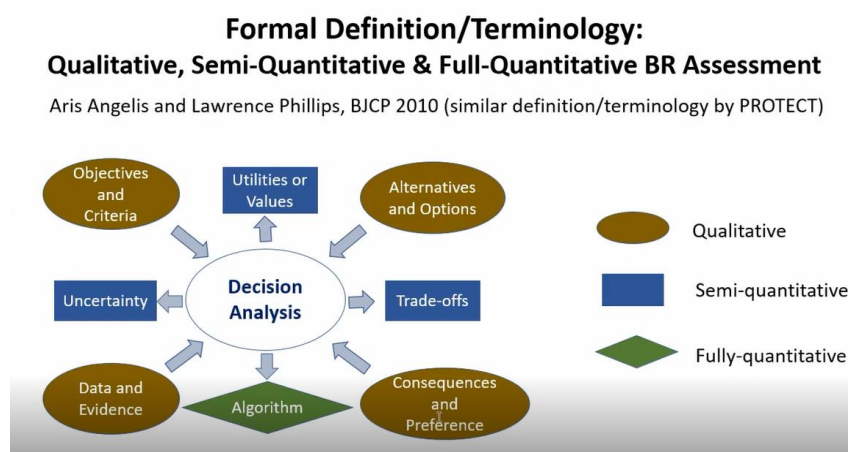
- We may need to push all the clinical teams to sometimes produce new data to help better inform BRA.

Updates on the global benefit-risk initiatives

- The ISPE's (International Society of Pharmacoepidemiology) BRACE group has been focusing on patient preference studies and aligning with IMI-Prefer. At present, nothing impacts full front with our overall B-R view.
- The American Statistical Association (ASA) has been focusing on B-R but has not made announcements recently.
- The Health and Safety Authority (HAS) B-R planning assessment task force has been focusing on several activities, including researching the statistical aspects of B-R, surveying some pharmaceutical companies to get a sense of the current B-R approaches in use, particularly structured approaches, and what some pharmaceutical companies think the future holds. They will use this to inform their BRA tools planning from early stages and throughout the life-cycle.
- Vicky suggested we acknowledge these groups in our field and offered to compile a summary of the different B-R WGs and task forces, and summarise their philosophies / concepts. Panos mentioned that ASA will provide CIOMS its output in due course. He suggested building this picture gradually.
- Richard supports the idea and suggested including ICH too.
- Leo pointed out that there are many different contexts / purposes for B-R, e.g. ours is the regulatory context and the US Preventive Task Force's is the clinical community. We would need to decide how we frame this.
- The history of different methods, including e.g. the multi-criteria decision analysis in Europe, Universal Methodology for Benefit-Risk Assessment (UMBRA), and Benefit-Risk Action Team (BRAT), are important to relate. Do we mention these as the building blocks for the benefit-based structure that many agencies use today? Or are they also important for future development? And do we foresee a development in this area? Or, are we not going to move beyond where we are today with a type of structured BRA that many regulators use?

Nomenclature and the WG XII glossary team

- Hong has been working on nomenclature with respect to the qualitative, quantitative and semi-quantitative approaches. She met with Subgroup 1 and has accepted to join the glossary team.
- The glossary team will be meeting for the first time after the 5th WG XII meeting.
- Hong presented a slide set (see slides for full content).
- She presented a definition for quantitative BRA by Aris Angelis and Lawrence Philips, BJCP 2010 depicted in terms of the diagram below:

Formal Definition/Terminology:
Qualitative, Semi-Quantitative & Full-Quantitative BR Assessment

Aris Angelis and Lawrence Phillips, BJCP 2010 (similar definition/terminology by PROTECT)

- Semi-quantitative: in the case of different B-R endpoints, where one is more important, we can collect more data on that aspect and conduct additional analysis about the value utility of those endpoints, and similarly about the trade-offs between different endpoints. We can focus what is important for our key decision-making issues.
- Quantitative: this amounts to a programme incorporating everything to give a performance score along the lines of a MCDA.
- Issues with the existing terminology (quantitative, semi-quantitative, qualitative): it is unclear, complicated, and sometimes counter-intuitive.
- There was support among the WG members for Hong's approach.
- Vicky felt using the term "basic" for "qualitative" would be too elusive and she recommended using a different term.

Addressing emergency approvals during pandemics

- The WG agreed to use the 2020 COVID-19 statement in a report appendix.
- We would not have much more to say on this subject - our decision making would not be very different in assessing the B-R for a vaccine during a pandemic.
- There are areas that we have not discussed elsewhere in the report yet e.g. emergency authorizations / conditional authorisations (regional differences).
- Perhaps we can do a case study because there are some new elements to the COVID scenario, e.g. vaccines monitored in a different way due to limited data and uncertainties, and with intensive monitoring (and other measures?) in place unlike before.
- Stéphanie reminded that the section on *Special Situations* is primarily about this topic and confirmed that the content is consistent with the statement.
- Scott said this is an opportunity to discuss the dynamic nature of B-R and highlight the context components. A structured B-R approach typically has some discussion about the context, and a part of that context is explaining the therapeutic alternatives and their B-R profiles. At the start of a pandemic (like COVID), early on, we have nothing, but a few months later, as medicines start getting approved, we start to accumulate options, and all of a sudden, the context changes. We get a hyper-speed evolution of the context. Maybe within the structured framework, when we discuss the context, we could make a point about the dynamic nature?
- Lembit added that collaboration between regulators internationally during a pandemic is very important. Regulators have probably done reasonably well, but e.g. in Europe, the health authorities have applied very different strategies: one declined the use of a vaccine for everybody, while another only allowed it in certain contexts and for subsections of patients. The regulatory background and information were the same but the countries took quite different programmatic measures. It does not give confidence in vaccines to the populations. Collaboration during a pandemic is crucial. Maybe it would be of value to point out some of these high-level issues even if we do not go into the specifics? We can use either a case study or the statement, if we are all still in agreement.
- We should all review the statement, and while doing this, we can contemplate whether ethics committees have contributed meaningfully to BRAs during emergencies.

Any other business

- Vicky encouraged all to place drafts on the shared resources for WG XII on the CIOMS website.
- A screenshot of the full WG was taken for communications (CIOMS Newsletter, website, PPT presentations, member organisations' promotions, etc.).

Closing remarks

- The WG is progressing well. Thank you to everyone.

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
<u>Leo</u>	Stewart	Takahiro
Panos	<u>Cheryl</u>	<u>Steffen</u>
Scott	Stéphanie	<u>Tomas</u>
Stephen	<u>Hong</u>	<u>Leila</u>
<u>Richard</u>	Sebastian	Sabine
Patrick	Julie	George
Qun-Ying	Sergei	Shanthi
Stéphanie	Kitami	
Luther	Mariko	
Claudia	Mari	

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