Fourth meeting of the CIOMS Working Group XII:
Benefit-Risk Balance for Medicinal Products – Update of CIOMS IV
2-3 March 2021, 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), Takahiro Goto (WHO), Claudia Ianos (Pfizer)*, Shahrul Mt-Isa (MSD), 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), 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), Sebastian Vulcu (BI), Julie Williams (MHRA), Hong Yang (US FDA CBER), and Xi Sherry Zhang (Gilead).

Day 1 only
Steffen Thirstrup (CORS) and Mariko Tsukuda (PMDA).

Apologies: Patrick Caubel (Pfizer), Sergei Glagolev (Ministry of Health of Russia), Shanthi Pal (WHO), and Hervé Le Louët (CIOMS).

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

* New to the working group since previous meeting.

DAY 1

Welcome and opening of the meeting

- Lembit welcomed the members and thanked everyone for joining the meeting.
- He informed the group about new CIOMS WGs on the following subjects:
  1) Severe Cutaneous Adverse Reactions of Drugs – SCARS;
  2) Educating medical professionals and e.g. staff at pharmaceutical companies with the necessary skillset to help strengthen drug development. This WG will be a joint effort between CIOMS and one of its constituency organisations, International Federation of Associations of Pharmaceutical Physicians and Pharmaceutical Medicine.
- Vicky acknowledged that everybody has been very busy and she is encouraged by the progress. The co-chairs and subgroups have not touched base recently while smaller groups have been working at their own speeds. She appreciates the level of effort invested.
- The agenda and the working mode were adopted.

- Sanna was rapporteur at the meeting.

Subgroup 1 presentation: Methods by Leo

- An alignment meeting between Subgroups 1 and 2 was held in Q4 2020.
- Subgroup 1 met in Q1 2021 for an update from its working pairs/trios and the chapter outline was revised.
- The subgroup 1 documents are available at the CIOMS website for WG XII, under password-protection, and the discussion below covers the discussion points only.
- Due to work with the Pfizer-BioNTech vaccine, Patrick has been busy and has invited his colleague, Claudia Ianos, to contribute to subgroup 1 in his place for the time being.

Methodological considerations

- Panos questioned the benefit-risk (B-R) endpoints in a trial protocol: will this make the statistical analysis complicated? Will such endpoints be exploratory or are we looking to have them side-by-side, or even replacing, some of the standard endpoints?
- Scott answered that this would not be as a replacement to the standard processes that are beneficial and an important part of B-R analysis. Whether this is done in stages or from the beginning, the vision is to elevate the B-R endpoints on equal footing with the other types of endpoints. One way to describe some of the issues is that the arithmetic that we use in aggregating data and understanding the data in clinical trials is not aligned with the way patients experience the outcomes. We analyse the outcomes of the trial patients, and we would like to switch this around, so that we use the outcomes to analyse what happens to the patients. This allows us to glean things that we would not otherwise.
- Panos appreciated the rationale but said regulators will want to see the traditional approaches to compare with other treatments. At this stage, do we know if it will affect the sample size? Will we require bigger trials?
- Scott said the answer depends on which endpoints we want a size for, and arguments could be made one way or another for how to do that. We have had cases where theoretically it could go either way, but we have also had cases where some of the methods have been able to recognise finer gradations of response, which brings in more sensitivity than is often evaluated for efficacy endpoints. It may be a reasonable starting place to say: 1) bring it in as an exploratory endpoint and move it up the scale (would like to see it on equal footing with efficacy and safety); 2) particularly in late-phase trials, we might still look at efficacy as a primary, but also have safety endpoints and B-R endpoints. We will tailor to the setting.
- Stephen added that he does not think these considerations would make the analysis more complicated. In answer to the sample size, if you have made your sample size solely for efficacy, then that is one thing, but if you take the sample size to assess risk and benefit balance, that may increase the sample size.
- Richard made two points: 1) Some simulation work could be done to better understand what some of the sample size implications are; 2) understanding the correlation between the benefit and the risk among patients in a trial would be useful in any B-R assessment (BRA). Even if it is imprecise, it is more than we currently have.
- Regarding how we refer to the "proactive approach", the following responses were given:
    - Patient-level BRA – preferred by Hong as it is clear
    - Joint benefit-risk assessment – Hong felt it was not clear e.g. what is "joint"?
    - Patient-level analysis – Hong feels it is not clear that benefit and risk are brought together.
    - Other:
        - Claudia suggested "Integrated BRA", to underscore the inclusiveness and coordination required for BRA, or "consolidated BRA".
        - Vicky, Stéphanie T-L, Leila, and Steffen would like to have "patient" in the title.

    - Steffen added that if you have “joint” or “consolidated” but not “patient”, it is not clear what is joint or consolidated.
    - Leila added that it could be “participant” or “individual” but the definition will be important. She felt people may think we are looking to identify if there is one hypothetical individual who could stand to have benefit exceed risk, and once we find at least one person who satisfies that, then we are fine with the product, but that is not what we are proposing.
- Richard added that some of the main points are to start the BRA earlier in the process, with early consultation with regulatory agencies, and certainly before reaching phase 3 clinical trials.

Visualisation

- Panos mentioned some examples from the IMI project. Could we start by looking at them?
- Cheryl added that there may be a way to also showcase various quantitative analysis methodologies to perhaps link some of the visualisations with the quantitative methodologies. Certain visualisations are directly linked to certain quantitative analysis (e.g. waterfall approach).
- Panos reflected back to the first meeting when Scott shared some of the visualisations and suggested we look at that again. Leo added that there were e.g. heat maps of B-R.
- Richard agrees and added that he often uses visualisation as a key part of communicating the results of a complex analysis, and so the point about linking the quantitative analysis with the visualisation is part of communicating with a range of stakeholders.
- Stephen was in favour of using a few examples that link to general principles, feeling it would be more helpful than a comprehensive list. Sensible presentations of data for various statistical methods, will come up with the same answer if you assemble the data in the right way.
- Regarding the patient perspective in the context of the CIOMS XI report, and communicating graphically with patients, is there something we should be integrating or using? Panos said it could be informative to see what has been used in studies, i.e. examples of how information has been presented to patients, and what people think about them.
- Leo mentioned that a forest plot with a confidence interval worked great in a science setting but many times for patients it shows that we do not know what we are talking about with all the uncertainty. So a helpful scientific concept becomes counter-productive in the lay public setting.
- Stéphanie T-L agreed it is important to link to the methods but we can also link to different steps in the B-R process: what we do when planning, analysing, and sharing results. Possibly not in this part but we can link these also to the content.

Subgroup 2 presentation: Structured descriptive assessment by Cheryl and Hong

- The Subgroup 2 materials are available at the CIOMS website for WG XII, under password-protection.
- Vicky thanked subgroups 1 and 2 for having worked through the potential overlaps, as this will save a lot of time, and she encouraged them to continue working in collaboration.
- Hong requested clarification from subgroup 1 on “the lifecycle approach to BRA”, as subgroup 2 will focus on the purpose of BRA at different stages. At the early stage, the purpose may be to identify e.g. the medical need and the more meaningful clinical endpoint for the patient. Subgroup 1 will be more focused on updating B-R throughout the life cycle, gradually gaining more new information as we go through the life cycle. The purpose and application will be how to support decision making at different phases of development. Subgroup 2 will support the message about starting earlier.
- Cheryl thanked the subgroup 2 members whose drafts ended up with subgroup 1.

Case studies

Case study 1 Dengvaxia

- Hong included this to show how sometimes the clinical trial data cannot immediately give enough information to make a B-R judgement. When data does not represent the real-world setting, additional analysis is needed to find the real-world B-R, to be more informative and clear.
- Vicky confirmed that we would like to have this sort of case study in the report, but as Hong presented a shortened version, Vicky questioned how Hong reached her conclusions and the use of quantitative methodology.
- Hong confirmed that the detailed version of the case study will summarise the model and how to assess the benefit for a group that has prior Dengue infection, and the risk for a group that has never had an infection.
- Leo felt there was an argument in favour of qualitative judgement. He is aware of several cases involving qualitative assessment of B-R, including approvals of the FDA and EMA, where the statistical colleagues wanted to test how robust the multi-criteria decision analysis (MCDA) method would be, and the conclusion was that it was a lot of additional work that did not add anything more to the conclusion of the qualitative assessment. It would be useful to see why and when we need quantitative analysis as opposed to qualitative.
- Hong had left out some of the detail in order to condense the information for the slides but she explained the full detail.
- Stephen found the study interesting academically but an extraordinarily unusual situation, and as such, he felt it was an unsuitable example for the CIOMS report. His opinion was based on:
  1) the controversy in the Philippines that followed the use of the vaccine;
  2) the complexity of the situation: a simple test for the prior infection does not exist, and using the vaccine in a place with a lot of prior infection may be reasonable, but as it is so complex, it is difficult to put in the report. He does not know of any other vaccine in which those who have not had a prior infection, get vaccine-enhanced disease, and those have had prior infection, do not.
- Hong confirmed that the purpose of this case study was to demonstrate the need for quantitative analysis with information from the real-world setting that may change the BRA.
- Stephen recommended considering intussusception with the Rota virus vaccines. This would allow a comparison between RotaShield and RotaTeq, and a comparison of different BRAs in countries with different prevalences and severities of Rota virus infection and associated mortality rates.
- Hong asked if Stephen knows of a quantitative analysis for these vaccines. Stephen was unsure if anything has been published. He recalled a meeting at the Centers for Disease Control and Prevention (CDC), where the issues were discussed. He felt it would be easy to go back to the trial data and the reports. They contained good estimations of intussusception risk and the vaccine showed high efficacy at preventing Rota virus infection.

Case study 2 Sotagliflozin

- This drug was not approved by the FDA as the risks outweigh the benefits.
- Hong's concern was that in this example the quantitative approach has limitations, and so therefore the example itself has limitations. Is this acceptable?
- Stephen finds this is an interesting example to use for B-R but it shows the problems with EMA's effects tables. HbA1C is a surrogate variable, and not a good surrogate for a lot of important diseases, and so would not give the best, complete picture.
- Leo asked whether other health authorities might have approved the drug, as it is always interesting to look at different perspectives in B-R. Stéphanie T-L confirmed it was approved in Europe with restrictions. Leo asked for thoughts on how we could reflect this and whether we

need to reflect it. Lembit supported this type of controversial example, as it would be interesting and helpful, but it will need a carefully designed explanatory note.

- Shahrul questioned the purpose of the case studies. Hong responded that the two case studies demonstrate the different quantitative analysis approaches used in BRA. She added that the Sotagliflozin case uses a quantitative approach to integrate different B-R endpoints to assess a net benefit. For Shahrul this was not clear in the case as presented.
- Scott said this case study focuses on the composite nature of an endpoint, and although it raised the issue of evaluation of B-R in the context of surrogate outcomes, he wondered if some discussion of surrogate outcomes would be worthwhile, as this is a particularly important issue. Even under the accelerated approval path followed by the FDA, in which you can gain approval using a surrogate marker, there are meant to be post-marketing studies to confirm the surrogacy and that there are indeed effects on a clinical outcome. In many ways, there are accumulating examples of "surrogates" that did not hold up.
- Leila said she believes the composite only looks at one of the "quadrants" of B-R (benefit without risk). It could be interesting to see if we can calculate the other three quadrants.
- Stephen suggested considering use of the "Win Ratio" when using composite endpoints and provided a link to an article, The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities.

- Cheryl added that the main framework to be presented in the subgroup 2 chapter will highlight that the basis of BRAs is really about key benefits and key risks.
- George asked why the qualitative approach does not involve the measurement of uncertainty as well. BRA, whether qualitative or quantitative, should take into account uncertainties surrounding the benefit and uncertainties surrounding the risks.
- Hong's understanding is that the "data and evidence" (under the qualitative approach) includes statistical analysis, which confuses the differences between quantitative and qualitative analysis. She understands that the uncertainty included in the blue rectangle means further analysis of uncertainty, e.g. you can do sensitivity analysis to incorporate the uncertainties, to work out the impact of changes on the B-R.
- Leo felt the presentation was provocative, thorough, and captured the ambiguity in the system between the quantitative, the semi-quantitative, and the qualitative approaches.
- He feels we could make significant advances if we could better align on definitions - we could potentially propose a new BRA framework.
- Leo mentioned the U.S. Preventive Services Task Force that makes some specific clinical recommendations based on what seems to be a quantitative B-R approach. Should we explore that further, and other similar groups, e.g. the Oxford Collaboration, outside the regulatory settings, that provide clear clinical guidance? There exist some very prescriptive recommendations based on quantitative analysis, and this could help further our discussion.

Case studies – general points for the full WG

- There were many discussions about case studies and ideas about what to include in the report:
  - one case study on a vaccine (even if the BRA can be challenging), and other product groups e.g. a medicine-device combination product;
  - all three types of methodologies: quantitative, semi-quantitative, and qualitative;
  - demonstrate how uncertainty and the B-R balance can change over time;
  - possibly a negative outcome.
- Case examples should not be too long and complex.
- Case studies can be written by colleagues outside this WG and every author's contribution will be acknowledged. Please make sure the information is given to Sanna.

- Tomas agreed we should use the examples to illustrate points, not to show that one side can be right and one side can be wrong, or to show the complexity of a composite endpoint (unless this is the point being made). We are not putting forward examples to show that EU and FDA came to different conclusions; they are there to demonstrate how things can be displayed, how a subjective assessment can be conveyed to other stakeholders or other readers.
- Vicky asked all to consider "why am I presenting this example?" What is the purpose of the case, and what is it intended to illustrate that is important in the concepts presented in the chapter.
- In order to avoid case studies being overly complex we should only include those benefits and risks in a product review that are relevant to the discussion, and note that other benefits and risks exist with the particular drug.

Subgroup 3 presentation: Introductory chapter: benefit-risk landscape by Leila, Sabine and Sara

- Leila said that subgroup 3 has not been as productive.
- Sabine presented a case example on Nerlynx nilotinib and suggested giving the WG members time to review it, saying she would welcome comments at a later time.
- She had experienced difficulties with fitting the case study into the template. Vicky replied that although the template may require effort on behalf of the authors, especially to avoid duplication, the readers will benefit from being able to find the information they are searching for.
- Leila had 1) some general observations about the report, 2) what to include and exclude related to the life cycle, and 3) questions about the multi-disciplinary team.

B-R analysis throughout the product life cycle

- Leila felt that quantitative methods could be challenging to apply in the post-market setting, when we do not have controlled trials or randomisation. Have subgroups 1 and 2 given thought to how the approach or methods might be applied in that setting, since that is within our charge?
- Hong thinks this is one of the aspects discussed under the chapter on Special Situations, e.g. RWE for assessing B-R in rare diseases.
- Leila finds this very uncommon. She was rather thinking about scenarios where all we have are event reports of a serious risk and we do not have information about the likelihood of that risk and what is supposed to be done in those situations. The CIOMS IV report did a good job of addressing these scenarios. It is a situation where structured BRA techniques and quantitative BRA become a lot harder to do because of the evidence gap. She wonders how such situations would be addressed since theoretically we are developing something to be applied across the entire life cycle of products.
- Leo agreed this is an excellent point and acknowledged it has not been considered by subgroup 1, but it can be taken on. He confirmed the query: in the context of the current active surveillance with spontaneous reports flowing in, if there is a serious event, e.g. hepatotoxicity, that was not picked up before, and we have limited data, other than broad clinical use, how would that be approached? Leila agreed. It is difficult to say how many times this represents the challenge in B-R decision point, but if we are trying to do something that is applicable in all situations and all phases of a product's life cycle, we should not underserve certain situations.
- Stéphanie T-L commented that subgroup 1 wanted to address this issue under the life cycle approach, discussing the heterogeneity of data, and different levels of evidence, and she agrees there is an issue with having information from evidence reports on new risks. Is there consensus on how we want to address this? She would like to use RWD to enrich the B-R but others may say we cannot combine these types of evidence.
- Vicky thanked all three subgroups and looks forward to the discussions the next day.

DAY 2

Welcome and opening of the second day

Lembit welcomed all and expressed his hope for starting to make more rapid progress with drafting the chapters. He understands many WG members are under pressure but feels we have a momentum and we need to use it.

Standalone chapter: Special Situations by Stéphanie T-L

- The Special Situations presentation is available at the CIOMS website for WG XII, under password-protection, and the discussion below covers the discussion points only.
- Vicky appreciated the systematic approach for covering each situation and she invited the WG to suggest additional special situations to Stéphanie's list.
- Leila said the list of "special situations" applies to approximately half of FDA/CDER novel drug approval decisions. Sabine added that many topics are not really "*special*".
- Leila felt this could be a venue for discussing examples.
- Vicky summarised that if these cases, once considered to be outside the norm are now becoming more mainstream, and not so special, maybe a comment to that effect needs to be made within the chapter.
- She added that several countries have approved Covid drugs on interim orders, and they are not necessarily conditional approvals, but they have been fast-tracked through the review process, and there are a lot of post-market commitments associated with them. Leila added that in the US that would be considered as "emergency use".
- Leo supports the content. He is involved with a range of therapies (gene therapy, cell therapy, and allogeneic cell therapy) and drug-device combination products, which are becoming increasingly prevalent. Gene therapy and cell therapy are being used for more chronic disease states. They used to be monogenic, orphan, drug conditions, but they are in other areas now. In Leo's opinion, they are for the future and so he was not thinking of covering them here, feeling they may need their own separate chapter.
- Stephen supports having a chapter in which a list of special situations is included, although they will change over time. The fundamental principle is the lack of information on benefits and harms. The question is where there is such uncertainty over the magnitude of benefits and harms that you need to consider their balance in a different way. One needs to identify the key possible harm that would change dramatically the risk and benefit balance. This has not always been made explicit. He would rather see the special situations as an appendix and the general principles around situations where there is uncertainty. We are back to the known unknowns and the unknown unknowns. Particularly if we do quantitative work, we need to identify when to carry out sensitivity analysis: if there is a harm at this level, then the risk and benefit balance would change. For example, Hydroxychloroquine ended up being authorized for emergency use and there was a question about the benefits (entirely uncertain at that point); there were no randomized trials suggesting it.
- Tomas questioned what makes these situations so special. We see many applications these days with quite a high degree of uncertainty. It is a matter of magnitude of uncertainties in different situations that needs to be balanced versus unmet needs, potential values, severity of disease etc. They need to be special from a BRA perspective.
- Tomas likes the first three types of special situations:
  - emergency use – it is interesting to link to the Covid pandemic situation;
  - rare disease products – very common, especially in the advanced therapy medicinal products (ATMPs) space;
  - legacy products – timely;

    - special populations – this can be covered in the above bullets in particular;
    - conditional approvals – this is different and brings us to regulatory/legal structures: "conditional" in the EU is different from "accelerated" in the US. This is about handling the post-approval commitments and a structure for early approval in some situations. Should we focus on this?
- Panos said there are some advanced therapies and gene therapies where there are increasing requirements to report efficacy and safety information over a very long period of time. Stéphanie T-L agreed that this should be partly covered under conditional approvals and we can highlight a specific example. Tomas did not feel that just because we have a long follow up, that the consequence of uncertainties and the way we address the uncertainties, e.g. in gene therapy, whether that makes it special. Panos responded that for most, this is a one-off treatment: you apply the treatment and the risk is quite specific. Because they use viral vectors to enter the gene, you have potential issues with leukemia, which have happened in recent times. This is a different scenario, but as it is not so common, and maybe it could be an example? Some companies have approached CIOMS to come up with a guideline on safety monitoring for e.g. gene therapy. Tomas feels the interesting discussion then is, and this is on the EMA and FDA sides, the different approaches towards some gene therapies, e.g. for childhood diseases where there is no treatment versus e.g. heamophilia. When there is an alternative treatment, when you are perhaps replacing factor concentrates, people ask for longer time for follow up to ensure you are not exposing patients to uncertainty or to safety events etc. From that perspective, it can be a good example that we need to bring in these new, novel therapies into our normal way of thinking about B-R.
- Sabine commented that the list of special situations mixes up issues relating to medicine, population, and regulatory status. She agreed with Stephen that the fundamental issue is lack of certainty or information. She likes the topic, and agrees with Leila that it is a good venue for examples, but maybe we need to give more thought to what we would like to highlight. Sabine is not sure what legacy products are here and why they are special. The lack of certainty or information is the binding topic for all, if we focus on that, it might be easier to decide which scenarios to pursue.
- Leila agrees that uncertainty seems to be a common thread – which aspect of the B-R problem is uncertain and why. We could also include in this, and it is alluded to with conditional approval (which means accelerated approval for FDA), the use of surrogate endpoints, or intermediate endpoints, instead of clinical outcomes. That also would apply to the gene therapy questions. Another area which is also uncertainty in some aspects, but not quite, is when you need to combine different sources of data that are not easily combinable – this would cover what she was talking about yesterday with the post-market situations, where you might have passive reporting of safety issues and your elements of benefit come from controlled trial settings. That could be another class of specific situations to cover.
- Hong commented that "combining different sources of data" could be the problem in any of the special cases. In the case of emergencies, we cannot wait for clinical trial data, in rare diseases, we do not have a big enough sample size, and you need to base on RWD and consider the history of the disease. Regarding legacy products, she is not sure if it is a special situation, as that B-R is already used widely. We are not able to conduct B-R for every legacy product, so we need to identify a threshold situation.
- Stéphanie T-L replied that for legacy products, when you have had a product on the market for decades and you need to question the B-R, and you need to go back to the evidence, and here we lack good clinical trials, we have only the various sources of post-marketing and no clear information on comparators.
- With regard to the emergency situation we are now in, Lembit said there have been a lot of attempts at repurposing of drugs. Should we write about this? Some claim that when

repurposing drugs, we know more about the B-R, but so far, the experience of repurposing has not been great.

- Hong responded that repurposing is slightly different from the other scenarios. The other scenarios are about uncertainty about benefits, but with repurposing, it is about uncertainty about the safety because we have used the drug for other purposes.
- Tomas agrees that repurposing is interesting and warrants being part of this special situations group because it presents specific challenges when it comes to a number of types of biases etc, not only publication biases.
- Leo reflected that because drugs are now available via the internet etc, there is a potential for rapid proliferation of use for the new purpose before any adequate evidence has been generated. Hydroxychloroquine is an example of having limited pre-clinical data and use proliferation. If you do it with an experimental drug, few people have access to it, but if you repurpose an approved drug, there is a risk that it becomes standard of care in some environments without any adequate evidence.
- In the context of legacy products, Vicky recalled when around 15 years ago, the use of Albumin as a plasma expander in severe trauma patients was causing hypovolemic shock, and they went back to look at the BRA of the product after it had been on the market for 50-60 years. There were no clinical trials and no data available to rebalance the B-R. This was a concern and before the time of regulators using RWE. Vicky suggested keeping the topic and perhaps using the Albumin example?
- The special situations group is a big, mixed bag, they all are special in some way, and we need to focus the effort of writing up each one of these topics. Think about how they are the same. Could we have introductory remarks about how they all have different levels of uncertainty; they all have potential issues with access to data sources that can be used to review the BRA? Then you can develop what is unique about each situation.
- Claudia said in the context of legacy products, the B-R and their evolution becomes very important when new therapies are approved. New therapies are not always compared with older therapies. Even if a new and better therapy becomes available, it does not mean that an older therapy is no longer of clinical value. Over time, some older products no longer get the attention and the therapeutic utility they would have and they are even removed from guidelines. How do we manage their benefit in a situation when clinical guidelines no longer recommend them and the medical community no longer considers them of use?
- Ying suggested including a pharmacogenomic population under special populations. There is a similarity with rare diseases. Vicky thinks this is worthy of mention.
- Lembit suggested there may be value in presenting this topic in the form of a table, listing all the situations and major challenges linked to them, to give a quick overview. The challenges can be quite different in different cases. Hong suggested including key considerations for each item. Vicky appreciates the systematic review as it allows the divergent situations to come across less as a mixed bag.
- Vicky supports including all the topics mentioned – we can always remove content afterwards.

Plenary discussion on options for moving forward chaired by Vicky

- It was decided that we could return to a more normal way of functioning and start holding more regular meetings. We need to stay connected, keep the momentum going, and start drafting our respective chapters.
- The WG discussed several options for future work approaches and the following was decided:
    - Three-four meetings per year of two- or three-hours maximum;
    - Email conversation was confirmed as a good way for Vicky to check in with the subgroups between WG meetings;
    - Stephen said being able to review the recording afterwards would help him;

- Hong requested setting up a Microsoft Teams space for the CIOMS group, as it is used successfully at FDA, but Stephen disagreed.
- Sanna is available to help convene meetings, if logistical support can help.

- Vicky will be polling the subgroups for agenda topics but the following were already noted:
  - Case studies - co-leads to expand on why the chosen case study is a good fit for the chapter;
  - Glossary terms and definitions;
  - Evaluating our advancement of concepts underpinning BRA (life cycle approach, start B-R earlier, include patient considerations) in the light of the other conceptual views on BRA from ISPOR, ISPE, and ASA, etc.

Target objectives for the next three to six months chaired by Vicky

- Subgroup 1 intends to consolidate its work further and circulate it. Leo envisages polling some of the topics discussed on Day 1. The subgroup will continue working in pairs and trios. Claudia joining will ease progress. Leo anticipates having more time for the WG work and returning to a more normal working format over the next three months.
- Subgroup 2 now has a roadmap and will work within subgroup 2 to share out the writing tasks. They already have a first draft and will now revisit it. Hong confirmed they will continue working on the Sotagliflozin case study. She would appreciate clear direction from subgroup 1 on the Dengvaxia case study and some considerations on the terminology and scope on the quantitative BRA section, before starting further work on these.
  - Vicky – it is hard for all of the WG members to provide direction on the case studies to be used in a particular chapter because it depends on what we are trying to illustrate. Vicky recommended that Hong write what the case studies are going to demonstrate and why they are relevant to the chapter. Vicky added that there are no bad case studies, only some that are more illustrative than others.
  - Cheryl said one of the bigger challenges for subgroup 2 is that their centre piece - the CIOMS structured framework - is going to require rounds of vetting within subgroup 2 and more widely. Many other elements will interface with it (life cycle, patient perspective, methodology, opportunities), and the case studies could be illustrative of how that framework can be put to use.
  - Hong's other question was about the quantitative section terminology. She believes we can put forward qualitative, quantitative, and semi-quantitative approaches. Semi-quantitative is interesting, more feasible and helpful. The guideline needs to mention also the semi-quantitative approach – there has not been much discussion about this. Vicky confirmed the semi-quantitative approach needs to be equally weighted alongside the qualitative and quantitative approaches.
  - Leo confirmed that subgroup 1 will cover methods that would be considered in the semi-quantitative space. They may touch on the quantitative, although his personal bias is against this – otherwise it means we only need one regulatory agency for the world, as there would only be one answer for every question. Methods that are recognised and quantitative can help inform qualitative judgement on the situation. The intent is to try methodologically to cover selected examples (not a full compendium).
- Subgroup 3 – Leila asked if it would be helpful for subgroup 3 to write their introduction chapter. Lembit answered this can be different for each group. Sometimes, you can have something broad prepared and then finish it when we know what the chapters will contain. Sanna added that the historical aspects will not change. Leila proposed to discuss with subgroup 3 which parts can be drafted sooner and will come up with an approach for those.

Glossaries

- Lembit asked all to keep in mind the terms and definitions they would like to include in the report glossary.
- Panos proposed leading a small team to work on the WG XII report glossary. With other CIOMS reports, the chapter leads have tended to keep an eye on the terms and definitions with view to what could be included in the report glossary. The glossary team could then review against what already exists or what new has appeared. It may be best to form the group once the chapters have written a little more. If new or modified terms and/definitions are needed, a case can be made to the whole WG XII, and if all agree, they can be adopted into the WG XII report glossary, and in time to the CIOMS Cumulative Pharmacovigilance Glossary.
- Panos advised we would probably need a member from the methods area as the CIOMS Cumulative Pharmacovigilance Glossary does not include terminology on the quantitative and semi-quantitative methods. Vicky suggested that at least one person could join from each subgroup as well as herself.
- Lembit added that times move on and different lenses can reveal different definitions. Panos gave an example, when the CIOMS WG IX report was being written, there was no definition for the term "burden" and so the group created one in terms of a health system, and at the moment, this is perhaps the only such definition.
- The CIOMS Cumulative Pharmacovigilance Glossary will be published over the coming week or two. It brings together terms and definitions from just under 10 past CIOMS reports. The WG XII is welcome to make use of the definitions. Lembit added that it will be a living document, such that we add the terms from each new published CIOMS pharmacovigilance report, and there will be an advisory board to consider suggestions and edits as we go forward.
- Stephen added that the team that worked on the CIOMS WG X report on meta-analysis put a great deal of energy into the glossary. This would be a good starting point for the WG XII report glossary as many of the terms in meta-analysis are about measures of effect. We would want to be careful about having an alternative definition that was not importantly different from the CIOMS WG X report definitions because it would be best to keep consistency unless there is a good reason to change.

How to set out citations and references presented by Sanna

- The CIOMS reports follow the WHO editorial style guideline and we have recently finished compiling a guideline for CIOMS reports themselves. Sanna will share this. Among other things, it includes how to set out references in Vancouver style. The Imperial College London provides good advice. It will be easier if we all use the same approach, saving time at the end.
- Following discussions over different softwares, we have arrived at the conclusion that it is easiest for us to work with Word's own endnotes, because not everyone has access to the same softwares and are trained with using them.
- The CIOMS secretariat will help if there are problems but would be grateful for receiving as much detail as possible.

Any other business

- Leila informed the group that the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has convened a Good Practices Task Force to look at Quantitative benefit risk assessment (qBRA) in December 2020 and is expected to run for around two years. Leila will be participating and will keep the CIOMS WG XII updated. It could be a useful reference to cite if it publishes before our report is finished.
- ISPOR publishes the Value in Health journal and works in pharmacoeconomics (evaluations of benefit-cost and B-R) and research in scientific work related to patient preference and has published a number of papers on the topic, there have been prior publications from ISPOR

related to B-R, two reports related to Multiple Criteria Decision Analysis (MCDA), reviews, which some WG XII members may be familiar with.

- The ISPOR Task Force would be expected to produce a manuscript, made available for review / open comment, with final revision before publication.
- Vicky related that in Canada, the Common Drug Review, who has health economists on staff, and once the health assessment of a particular new product is complete by the scientific community, the economists take over and carry out a cost-benefit analysis to determine whether the drug gets on the formulary list within all the provinces of Canada. There seems to be a lot of commonality.
- Vicky would welcome Leila giving a summary following her first meeting(s) at the ISPOR Task Force on qBRA on the conceptual thinking.
- Leo mentioned the International Society for Pharmaceutical Engineering (ISPE)'s special interest group, Benefit-Risk Assessment, Communication and Evaluation (BRACE), which is also producing documentation on quantitative B-R. Maybe in one of our upcoming meetings we can have a conversation about where we want to be placed. While several of us may have some challenges about quantitative methods, there continues to be a lot of them. When people refer to quantitative B-R, do they really mean quantitative, as in it generates the one correct answer, or quantitative methods to better inform a judgement-based B-R. It would be important for us to discuss and find our joint position. We can cover the methods but the question is how do you use the methods. We have increasingly advanced mathematical and statistical models being applied, but if they get represented as quantitative B-R, where does that leave us?
- The American Statistical Association is also working in this area.
- Stephen was concerned about some of the quantitative methods being used for more than guidelines. He is in favour of quantitative B-R methods being used to illustrate the data, to illustrate the issues, and other things, but the idea that the number than comes out of any quantitative B-R modelling should be used to make the decision is a mistake.
- Hong agrees and that is why she thinks the most useful for those approaches is help discussion and deliberation instead of generating a number to make decisions. Eventually, the decisions still are based on judgement.
- Vicky has seen political / shortage and other extenuating circumstances taken into consideration when deciding what to do with B-R analysis results. An example was the approval in Canada of the use of Technical Grade Ethanol (TGE) in hand sanitizer products at the start of the COVID pandemic when there was a shortage of pharmaceutical grade hand sanitizer products available. We should include some narrative in the guidance as to why we might choose to go in a particular direction notwithstanding the results received from the analysis undertaken. This could possibly go in subgroup 3's chapter?

Closing remarks

- Lembit thanked all for joining, despite the difficult times, for their contribution and continued commitment. We are making progress and hopefully we can start progressing faster.
- Vicky appreciates the work accomplished in challenging times. She thanked everyone for continuing to stay focused and motivated.

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	Takahiro
Panos	Cheryl	Steffen
Scott	Stéphanie T-L	Tomas
Stephen	Hong	Leila
Richard	Sebastian	Sabine
Patrick	Julie	George
Qun-Ying	Sergei	Shanthi
Stéphanie T-L	Kitami	
Luther	Mariko	
Claudia		

Vicky is currently not attached to a subgroup.

Glossary team: Panos, Vicky, Stephen, and Lembit