



**First meeting of the CIOMS Working Group XII:  
Benefit-Risk Balance for Medicinal Products – Update of CIOMS IV  
17-18 September 2019, Geneva  
Best Western Chavannes De Bogis  
Chemin des Champs-Blancs 70B, 1279 Chavannes-de-Bogis**

## Meeting Minutes

### Participants

Ezaki Asami (PMDA), Patrick Caubel (Pfizer), Guacira Corrêa de Matos (Anvisa), Scott Evans (George Washington University, Milken Institute School of Public Health (GWSPH)), Stephen Evans (LSHTM), Richard Forshee (US FDA CBER), Sergei Glagolev (Roszdravnadzor – Regulatory Authority of Russian Federation), Takahiro Goto (WHO), Vicky Hogan (Health Canada), Leila Lackey (US FDA CBER), Shahrul Mt-Isa (MSD), Leo Plouffe (Bayer), Cheryl Renz (AbbVie), Tomas Salmonson (former Chair CHMP), Stephanie Storre (Swissmedic), Sabine Straus (MEB – Chair of PRAC), Steffen Thirstrup (Copenhagen Centre for Regulatory Science (CORS)), Mariko Tsukuda (PMDA), Sebastian Vulcu (BI), Julie Williams (MHRA), Hong Yang (US FDA CBER), Xi Sherry Zhang (Gilead), Sanna Hill, Hervé Le Louët and Lembit Rägo (CIOMS), and Panos Tsintis (CIOMS Senior Adviser).

Note: Tomas Salmonson (former Chair CHMP) joined after midday day 1; Stewart Geary (Eisai) attended day 2 only.

Apologies: George Quartey (Roche).

Alternates did not attend: Karen Kaplan (MSD), Hussein Laljee (Gilead), and Qun-Ying Yue (UMC) (*replaced Ola Caster*).

## DAY 1

### Welcome and opening of the meeting

- Hervé le Louët, CIOMS President, welcomed the participants.
- Lembit Rägo, CIOMS Secretary General, added his words of welcome and opened the meeting as Chairman for the two days.
- Sue Le Roux, CIOMS Administrative Assistant, explained logistics for the two-day meeting.
- Sanna Hill, CIOMS Medical Writer, was introduced as support for the working group.
- Tour de Table: all participants introduced themselves to the group.
- Lembit presented the CIOMS organisation and current activities.
- Panos Tsintis was appointed as Rapporteur for the meeting
- The meeting agenda was adopted

### Objectives for the meeting

- Feedback on the original CIOMS IV guidance published in 1998
- Identify key goals to focus on in the new guidance
- Develop CIOMS WG XII “business plan” (to be reflected in the Minutes)
- Identify other initiatives to interact with
- Consider completing the working group with more members
- Elect chair persons for this first meeting of the working group (WG)
- Set up subgroups to address main topics
- Draft a Table of Contents for the new guidance
- Agree on the next meeting details

### General viewpoints regarding WGXII expectations

- There is a general impression that the original CIOMS IV guidance was forward-looking with some core aspects still applicable today and is only now reaching implementation in many countries.
- Although some aspects of CIOMS IV are still relevant today, the examples used are now dated and benefit-risk professionals are still struggling in many of the areas covered, eg how to carry out weighing of benefits and risks correctly is still an issue.
- Interventions and up-to-date real-life examples can be of value to illustrate some of the challenges and support the benefit-risk framework as it applies today.
- There have been examples where the pharmacovigilance and risk management systems failed to detect or manage safety problems. Such examples could also be mentioned in the new guidance to explain why the new guidance is needed.
- Requirements may be different in low-income, middle-income and high-income countries.

### Regulatory perspectives

The regulators would like to discuss how to:

- Clarify the benefits of conducting qualitative assessments and quantitative assessments, with guidance on when to choose which, how to select variables, weigh such variables, and choose a methodology for benefit-risk (B-R) assessment.
- Address sensitivity analysis and certainty analysis, as these are often lacking.
- Acknowledge that quantitative tools are useful but always only a component of an overall qualitative decision that will also incorporate factors that cannot be quantified.
- Handle assessing data from clinical trials conducted on small populations, which alone may not show risks. Subscribe to the same approach, set up registry, and compare results?
- Acknowledge the very way in which diagnostic tests are carried out can impact results.
- Leverage and prioritise the abundance of available data sources eg electronic healthcare records
- Incorporate patient views, eg willingness to take risks where no adequate treatment exists
- Weigh patient preferences in a formal way, as they are integral to decision-making but there are no widely accepted quantitative means to factor them in at present.
- Handle missing factors in decision-making eg it is not always possible to carry out quantitative analysis and sometimes pragmatic decisions have to be based on available evidence
- Comparing old and new medications can be problematic as the former often have limited quantitative data. There is often a concern that older medications may bring less benefits and higher risks.
- Integrate pre-approval and post-approval data, including data from outside clinical trials, eg real-world evidence - RWE (data from healthcare services or spontaneous reports)
- Conduct post-marketing benefit-risk assessments after conditional approval and/or accelerated approval, eg with breakthrough products, including following up with periodic assessments
- Consider off-label usage for different indications than were approved

**Commented [SH1]:** Comment from Stephen Evans: I wasn't sure what was meant by "Certainty Analysis". If it means "quantifying or estimating uncertainty" then I think I understand.

- Continue evaluating and improving the benefit-risk balance in the post-marketing setting, including evaluating the effectiveness of risk-minimisation measures
- Communicate risks to all stakeholders – patients, industry and healthcare professionals – in a balanced, consistent and easy-to-understand way.
- Decide on thresholds / triggers for regulatory action
- Decide on when to use, and when not to use, quantitative methods of benefit-risk assessment
- Share experiences with risk management approaches
- Decide when to reject a marketing application or remove a product from the market
- Address benefit-risk throughout the full product life-cycle.
- Publish the CIOMS XII guidance: Alongside the pdf publication format, suggest publishing also in popular electronic formats compatible with use on eg smartphones.

#### Industry perspectives

Adding to the perspectives above, the industry representatives would like to discuss how to:

- Safeguard against using poor quality data.
- Use structured approaches to convey the totality of the benefit-risk balance. The CIOMS IV guideline focused separately on benefits and then on risks.
- Expand the therapeutic context to cover both benefit and risk (not weighted heavily on benefits as compared with risks) to show where a new product will impact the treatment paradigm.
- Consider patient perspectives on benefit-risk using appropriate methodologies.
- Present visually the outcomes of benefit-risk assessments
- Acknowledge pressure from social media, as today everyone can access data, although it is not necessarily reliable from a legal, medical, regulatory or business decision-making perspective.
- How to use RWE in benefit-risk assessment.
- Address long latency potential risks, eg gene therapy or stem cell therapy, where risks may not materialise over the first years while we are following patients. How to factor in these in the benefit-risk assessment?
- Define concepts like disability in the context of post-marketing monitoring in the spirit of reporting adverse events and having a follow up.
- Capture the long-term consequences of risks, eg risk of exposure during pregnancy and risks from contraceptives.

#### Academic perspectives

Adding to the perspectives above, the academics would like to discuss how to:

- Include patient perspectives in everything done, partly in order to reduce secrecy.
- Integrate a multi-variant approach that accommodates both benefits and risks in individual patients – these are not necessarily independent.
- A possible breakdown in the analysis could assess four sub-groups: Efficacy with no ADRs; Efficacy with ADRs; no efficacy no ADRs; no efficacy with ADRs.
- Communicate quantitative methods in an easy-to-understand manner so that patients too can understand.
- Synthesise global benefit-risk information in an appropriate way to ensure capture of important aspects of the effects on patients.
- Explain the necessity to combine information within-patient in order to see certain effects. Outcomes can be correlated and particularly important in a benefit-risk situation.
- Explain the cumulative nature of outcomes – often see studies on multiple safety outcomes and multiple efficacy outcomes, but rarely see the cumulative nature of different outcomes on individual patients, because this is not noted.
- Use graphical summaries to show signals in a more digestible way.

**Commented [SH2]:** Comment from Stephen Evans: "multivariate" better than "multivariant".

**Commented [SH3]:** Comment from Stephen Evans: I thought the graphics were B-R summaries rather than signals.

- Safeguard against selecting and combining inappropriate populations for statistical analysis. For instance, the current approach is to use separate populations for assessing safety and efficacy, this does not allow assessment of benefit-risk in individual patients.
- Safeguard against downstream consequences. Related eg: randomised trial of treatments A and B, where later patients change from treatment A to C, have a serious adverse event caused by the downstream consequences of A but which is incorrectly attributed to C.
- Improve in the CIOMS guidance the discussion on absolute risk versus relative risk, giving greater attention to the considerations of time.
- Explain balancing clinically relevant outcomes.
- Address issues with surrogate endpoints.
- Capture all key signals. Explain the concept of *Using Outcomes to Analyze Patients Rather than Patients to Analyze Outcomes: A Step Toward Pragmatism in Benefit:Risk Evaluation*.<sup>1</sup>  
The purpose of especially later phase clinical trials is to measure the outcomes to see how the patients are doing, not the other way round.
- Increase transparency eg by recommending protocols for designing trials, eg establish predefined benefit-risk evaluation outcomes, much like for efficacy outcomes and safety outcomes.
- Consider an ITT approach for the benefit-risk analysis.

#### Working Group discussions inspired by the perspectives above

##### Methodologies

- Explore new methodologies in order to address the new risks surrounding the uncertainties with biological drugs. (Where chemical drugs are concerned, comparatively, we have some experience with appropriate benefit-risk assessments models.)
- Agree it would be great to have knowledge upfront when heading to clinical trials. Would like to define key methodologies, eg quantitative methodologies, for systematic use globally, such that all give explanations of why the particular methodology was chosen, what were the assumptions made, why the analysis was undertaken in a certain way, towards standardising.
- List prerequisites for different methodologies, advantages and disadvantages.
- FDA CBER work has not gone as far as putting weights on outcomes, although they have built some sophisticated quantitative benefit-risk assessment models, but stopped at presenting estimates of positive and negative outcomes and the uncertainties and sensitivities around those, which are taken to advisory committees where experts apply judgements in a more qualitative way. Do not have support for putting on weights, although there is much discussion on putting values on weights.
- Cannot expect to recommend one solution globally.

##### Data

- Include a table showing the types of data needed to implement the different methodologies.
- Need comparative data, as benefit-risk evaluation cannot be done in isolation.
- Suggest how to use clinical data and post-market data for comparative benefit-risk assessment.

##### Generalisability

- Consider the generalisability and the pragmatic use of a benefit-risk analysis using data from a trial conducted in a narrow population, with limited concurrent drug use, limited flexibility on how they are applied and how they are used, under uncommon circumstances. What does it mean in terms of benefit-risk implications to the wider population?

<sup>1</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28435515>

#### Time

- Where benefits and risks are observable early, interventions are possible.
- The benefit-risk balance can change over time. Will risk get worse; will efficacy get better?
- Consider time, eg with smoking cessation drugs: harms appear early and benefits later.

#### Communication

- The process of applying a method can be as important as the result of the method, so when communicating / transferring, the process also needs transferring to the other stakeholder: why a methodology was selected, all the uncertainties, all the assumptions.
- Communication tends to focus on risks and less on benefits because regulators' role is to be neutral, not endorse a product, and this will not change.
- But, with reference to the above point, there are other means of communicating eg educational material in the RMP that can include advice to the physician on patient selection to optimise benefit as well as manage risks.

#### Patients

- Enhance how benefit-risk information is communicated to patients, who are increasingly involved in benefit-risk decision making and choosing their therapies.
- Leverage the working group members who also participate in the CIOMS XI working group on Patient Involvement.

#### Off-label usage

- Complex needs and complex settings may result in exceptional cases.
- WHO essential medicines list contains some medicines that are off-label, and so perhaps some benefit-risk assessment had been done even if not by the industry or regulator?
- There is no generally accepted definition for off-label use.
- The WG would need to decide whether to address this topic, in which case it should be covered fully or acknowledge the practice and explain why it is not covered by the WG.

#### Examples

- The existing guidance communicates well using examples.
- Where content is to be kept, new current-day examples are needed to update the old ones.
- Need case studies demonstrating successful outcomes and unsuccessful outcomes.
- Regarding the subject of approval, it would be helpful to find an example showing patient input as part of the assessment phase and the decision-making.
- Examples of when patient preference overrules submissions and/or approvals.

#### Identify other initiatives for CIOMS WG XII to interact with

The vast number of initiatives worldwide speaks volumes about how the benefit-risk world is moving forward. The WG will need to create links with peer initiatives and avoid redundancies. Ideally, this would reflect the global audience.

- FDA guidance
- FDA's benefit-risk assessment meetings online including videos
- FDA's benefit-risk guidance in PDUFA VI, whose implementation plan has been published, and a discussion document from a public meeting in May 2019 that lays out some of initial thinking regarding the content of the guidance, is still under development. The draft guidance is intended to be published in 2020.

- On the patient-side, there is the FDA Patient-Focused Drug Development, Voice Implication Initiative, with 24 disease-specific workshops where patients share their perspectives.
- On the quantitative side, CBER's Science of Patient Input Initiative programme looks at cutting-edge means of trying to get generalisable information about patient preference.
- American Statistical Association Task Force - focused on benefit-risk assessment planning throughout the life-cycle of products. In the near-term, will do a survey at medical product firms, not just on medicines but also on vaccines, devices etc focusing on getting a snapshot of the current approaches of the benefit-risk assessment within the companies. There is also a literature review planned and there will be a best practice document to come. The survey will launch in 2019, with a cross-functional spectrum among the people included in the survey. Topic: guide for companies and regulators on how to approach benefit-risk decisions.
- Task group of the American Psychiatric Association: Benefit-Risk Association Tool Suite working group. This has just started. After the survey and benefit-risk assessment planning for industry and regulatory firms from the American Statistical Association Task Force is available, this working group will develop a suite of tools to allow for inter-reacting on benefit-risk assessments between regulators and industry to communication about the key benefits, key data, and key evidence.
- Health Canada recently published a guidance document on the qualitative aspects of benefit-risk assessment entitled: *Format and content for post-market drug benefit-risk assessment in Canada, Guidance document*.
- The CTMP (Cell Therapy Management Program) is working on an algorithm to look into benefits and risks but this may be a personal initiative. They have information on the uncertainties of benefits and the uncertainties of risks by Mary Philips.
- The Addis software suite received funding from the IMI (Innovative Medicines Initiative).
- IMI PREFER – this is important for patient preference protective benefit-risk assessment. It is critical because the patient preference needs to be aligned with what is intended for benefit-risk assessment.
- IMI ADVANCE could also be relevant as vaccines' benefit-risk assessment can be different. This would be time-sensitive.
- The UK Medical Research Council is expected to publish new guidance on study design in April 2020, including specifying up-front what the benefit-risk measure will be and what methodologies are to be used at the end – this should be indicated in the protocols and proposals for the task.
- ICH guidance, in particular the M4ER2 guidance, entitled *The CTD – Efficacy Guidance for Industry*, which sets the stage for work on the CTD (Common Technical Document) for submissions and clinical overviews, contains a particular section 2.5.6 on *Benefits and Risks Conclusions*, and this has some useful material that could be used as a key background.
- ICH E2C(R2) Guidance on Periodic Benefit Risk Evaluation Reports (PBRERs) with some relevant concepts for assessment of benefit-risk during post-marketing may also be useful.
- The Benefit Risk Assessment, Communication, and Evaluation (BRACE) Special Interest Group (SIG) at ISPE (International Society for Pharmacoepidemiology) will be helpful especially for practical examples.
- Effects tables used routinely in the EU (the working group received a brief history of the origins of the Effects Tables and gave their views about the advantages and disadvantages.)
- CIOMS Working Group XI: Patient Involvement in Development and Safe Use of Medicines.
- [Added at a later date: Duke-Margolis Meeting on Benefit-Risk:  
<https://healthpolicy.duke.edu/events/benefit-risk-framework-public-workshop>  
Discussion Document:  
[https://healthpolicy.duke.edu/sites/default/files/atoms/files/discussion\\_guide\\_b-r\\_assessment\\_may16\\_0.pdf](https://healthpolicy.duke.edu/sites/default/files/atoms/files/discussion_guide_b-r_assessment_may16_0.pdf)]

#### [Suggested new members to invite to CIOMS WG XII](#)

- IMI PREFER – it would be good to have someone affiliated in the XII working group.
- Bennett Levitan, who is involved with BRACE and also on PREFER, as well as his superior, Jesse Berlin, who was involved in CIOMS X.
- Alexandra Freeman, Executive Director of the Winton Centre for Risk and Evidence Communication, who specialises in risk communication. She is involved at ISPE on preparing a document on risk communication.
- On patient preference inclusion, it may be helpful to find someone on patient preference methodology. Would Bennett Levitan be able to cover this, or someone more academic on benefit-risk patient preference methodology? Suggest F. Reed Johnson at Duke University.
- RTI International (formerly Research Triangle Institute), a consulting firm based in North Carolina, USA.

#### [Breakout Groups to evaluate existing guidance](#)

The breakout session objective was to review the existing guidance and suggest what to keep, remove, and change.

[Breakout Group 1](#) Guacira, Mariko, Patrick, Richard, Sabine, Sherry, Stephanie, and Stephen  
New concepts have emerged since the first CIOMS guideline was published, ie the focus on patient input and preference; the need for an integrated approach to benefit and risk evaluation; and the need to continue evaluating during the full product life-cycle.

It would be better to move from the whole option analysis to an overall risk management approach instead. The guideline sections should be rearranged as follows: start with a chapter on benefit-risk; explain how to integrate benefit and risk evaluations; breakout into subsequent sections; and add pieces on how to conduct an integrated approach. It would be best to delete the options section as this covers topics from CIOMS guidelines X and XI; although it would be helpful to mention how to handle options, ie review what other options are available, the criteria for selecting options, but not give emphasis on the analysis of options. New sections to add would include uncertainties and new therapies (eg gene therapies); the integration of benefit-risk assessment; and patient input and preferences. The guideline should keep benefit and risk sections but enhance them based on new concepts, and include risk minimisation content from other CIOMS guidances (CIOMS IX).

In the appendices, it may be helpful to include how the guideline relates to other sectors involved in benefit-risk assessment and how their approaches might compare to ours. It would be useful to include a case study of a drug with lots of uncertainty; a drug where the benefit-risk assessments were done by various different groups and the drug was taken off the market including the process that was followed; some non-therapeutic products eg nutraceuticals and non-drug products, and how their benefit-risk assessments might be conducted with examples.

Comments arising from the subsequent discussion

- Patient participation in the design and the setting of the outcomes to be studied are more important than patient participation in benefit-risk decision making.
- Every regulatory intervention should be evaluated: what we are doing, how to assess that, etc.

[Breakout Group 2](#) Hong, Julie, Leo, Scott, Sebastian, Stewart, Takahiro, and Vicky

The existing guidance focuses on general principles of benefit-risk assessment but the new guidance will need to move towards integrated benefit-risk assessment through the life-cycle approach. We need to establish principles for benefit-risk assessment that are applicable at all stages of the process. The pre-market and the post-market phases will run into each other and are hard to separate. We need to change the title and vision of the guide to reduce the emphasis on safety

signals. Since the existing guidance was published, a large amount of work has been done in the area of signals, and we can rely on other sources for this, and in the new guidance, we should focus more on the benefit-risk balance. The guidance should discuss integration and a cohesive whole, reflect the concept about “using outcomes to analyze patients”, and not the other way round.

The principle of benefit-risk assessment will depend on the region where the product is to be used, its disease incidence, population characterisation, healthcare resources – all of this will feed into the benefit-risk assessment. The context also ties into how risk mitigation measures can optimise the benefit-risk balance of a product. There needs to be a greater focus on uncertainty with a more transparent discussion, including patient perspectives. There are likely to be correlations between benefits and risks within individual patients, and this could be related to personalised medicine. The timing of the observability of benefits and risks can affect the benefit-risk equation. Issues can be quickly addressed and this can help to make the balance more favourable.

In contrast to the recommendations of Group 1, Group 2 feels the options analysis section should be retained, although it could be included in a different way. It is important to discuss alternatives, eg delaying a decision or denying a drug, and we need to be clear on the options and the consequences, including trying to anticipate unintended consequences related to a decision.

[Breakout Group 3](#) Asami, Cheryl, Leila, Sergei, Shahrul, Steffen, and Tomas

Discussion started with considerations about the stakeholders, with agreement on the approach of CIOMS guidance IV. However, the scope could be expanded to cover the full life-cycle, and this should be reflected already in the title of the guidance. The life-cycle is taken to start at the moment of the initial application at the time of licencing.

The scope is to be extended also regarding the data to be used. Any type of data is welcome to support an initial application or on-market status, including preclinical data, clinical data, and real-world data.

An assessment should be linked to a particular indication, also taking into consideration that results may vary according to geographical differences and healthcare setting differences, eg some products can be approved in some areas as a third line therapy, but in other areas, as a second line and a third line therapy, based on availability differences.

One key consideration is how to present assessment components. Group 3 envisaged calling the approach the “Structured Descriptive Assessment”, which is to have several key components, based on initiatives and frameworks, to be used by regulators and industry working together. Some of these components will be therapeutic context, key benefits, key risks, so that we arrive at a sense of totality, encompassing uncertainties and risk management recommendations; arriving at a conclusion that encapsulates trade-offs, weighing times, uncertainties, indication, etc.

It is important to clarify ownership of the final decision that is communicated to stakeholders, especially as it may be the result of a variety of influences, such as focus groups, patient groups, and quantitative methodologies.

The guidance is to cover thoroughly:

- Quantitative assessment – highlight the key methodologies, their key applications, explain when to use them, when to not use them, and what data sources are needed.
- Qualitative methodologies – describe how to form a focus group, carry out a survey, collect and use information.



It would be helpful to have a section focusing on the conduct and application of patient preference information.

There will be unique points to consider for special circumstances, eg legacy products, rare diseases, special populations (eg paediatric populations and the cognitively impaired), conditional approvals and urgent situations (eg where new findings prompt new assessments to possibly remove a product from the market), changing landscape (eg when treating symptoms advances to treating for a cure).

The new guidance should not address communicating the benefit-risk information to patients and healthcare providers, because although this is highly important, it involves related legal and regulatory issues.

Comments arising from the subsequent discussion:

- At times, added safety measures can help to mitigate against uncertainties such that the benefit-risk balance becomes favourable.
- Class reviews are a difficult area.
- Company confidentiality – regulators have details from all companies, and some feel that the public should have access to all the data, but most companies prefer to keep it confidential.
- Forward planning:
  - Planning for assessments needs to include information about how to conduct the structured assessment, with details about additional qualitative, quantitative and preference methods, and what information has to be collected during the whole life-cycle of the product, not just for the registration trials.
  - It may be good practice to establish regulatory protocols in advance for filing in a repository similar to [clinicaltrials.gov](https://clinicaltrials.gov) on benefit-risk assessments to be carried out by sponsors.
  - It would be helpful to specify in advance how to carry out an assessment during an emergency, eg an Ebola epidemic, regarding assessing a candidate drug and/or vaccine under pressure from politicians and the media; or for instance a safety crisis involving an authorised product.

## DAY 2

### Objectives for the day

- Decide on the guidance vision and scope
- Draft Business Plan and Table of Contents
- Nominate chair and co-chairs, as well as subgroup leads
- Agree place and provisional time for the next face-to-face meeting

### Discussion

- Answer the why, what, and how, as this reflects how guides are used.
- Provide examples of where benefit-risk assessments have succeeded and failed.
- The guidance will require a glossary. Previous CIOMS guidances can help for this and interaction with CIOMS XI on Patient Involvement is advised.
- It was felt that readers would benefit most from a new, stand-alone guidance, rather than an edit of the existing guidance or an extra resource alongside it.
- ICH, FDA, and other regulatory frameworks can serve as a foundation for the new guidance, with high-level references. This may be especially helpful for readers in less advantaged settings.

### [Breakout Groups to scope the new guidance](#)

The breakout session objective was to discuss the scope, high-level content, general principles, and examples for the new guidance.

#### [Group 1](#) Guacira, Mariko, Patrick, Richard, Sabine, Sherry, and Stephen

Group 1 discussed the guideline scope and how to differentiate from previous guides. They discussed shifting away from discussing benefits in one section and risks in another, moving rather to looking at a joint distribution of benefits and risks, from the early design stages, and clinical trials, all the way to later stages of the product use (ie pre-approval, peri-approval, post-approval). They discussed many aspects of the new guidance but concentrated on one visual representation, originally developed by Norton, using a heat map showing for each patient the benefits, risks, both, neither, and whether they left the study, comparing drug and placebo. This enables combining information on the benefits and risks, in a joint distribution, mirroring the reality of how patients experience symptoms simultaneously in a multi-variant way. This would affect how real-world evidence is generated and discussed. The heat map makes many simplified assumptions, views benefits and risks as binary, but achieves a visually communicated balance. Choosing an approach like this would fundamentally affect the CIOMS XII guidance intended document structure discussed to date.

Comments arising from the subsequent discussion:

- This approach seems a little futuristic as no one in the industry (outside academia) designs trials like this at the moment or analyses data like this. There would be a need to keep in parallel a more traditional approach for those who need to apply in the usual way in the short/medium-term.
- There seems to be value for presenting results of a clinical trial in this way but it is less clear what would be the benefit for post-approval. Reminds of an E9 Estimand-style approach.
- FDA collects data in a way that would allow them to create this type of visual, and it would not need to be created by the industry, but would other regulators have data for this use?
- Regarding methodologies on the whole, it would be important to work on the weights, in order to make it more objective, as this will influence the outcome.
- We fail to assess the benefits in the same way we assess risks.

#### [Group 2](#) Hong, Julie, Leo, Scott, Sebastian, Stephanie, Stewart, Takahiro, and Vicky

The new guidance should be a self-contained, standalone document enabling benefit-risk assessments by different stakeholders throughout the product life-cycle (pre-approval, possibly including in clinical development phase, peri-approval, post-approval and post-marketing commitments). Benefit-risk assessment should be an integrated approach and avoid any silo perspectives. This approach should be kept in mind when planning for future evaluation designs, data collection and analysis, not only regarding efficacy and safety end points, but also benefit-risk end points, and where possible, capturing within-patient outcome data. The individual patient-level outcome assessment should be the basis of the integrated benefit-risk evaluation. It is also important to measure the impact of effectiveness of risk minimisation measures (link to CIOMS IX). Patient preferences must be evaluated and guide the focus of the assessment on the main, relevant risks for patients. Uncertainties will include both those that can be quantified eg statistical uncertainties, and also uncertainties that cannot be quantified easily, due to limited data or lack of data, in terms of benefit-risk and risk minimization. We need to link how uncertainties impact the decision, patient preferences, and views around uncertainties. All of this must be linked in an integrated approach.

Comments arising from the subsequent discussion:

- Do we really want to address the benefit-risk decision making at every stage of a product life-cycle, even during the clinical development stage, or are there stages where we simply want to get one step further with continuing the study?
- The primary focus of the guidance should be at the first application for approval and then through the life-cycle. Earlier evaluations are often only for internal decision-making processes, and the clinical trial approval process is very different globally. The guidance could point out where elements could be used earlier in the life/cycle.
- In earlier discussions, we spoke about developing a universally applicable approach, with components that can be applied at any stage, eg at trial design, at the time of registration, etc.

[Group 3](#) Asami, Cheryl, Leila, Sergei, Shahrul, Steffen, and Tomas

Put into historical context why there is a need to update the CIOMS IV guidance now, mentioning the myriad data sources, multiple types of uncertainties, regulatory initiatives moving the field forward, and new therapies emerging, such as gene therapies with complex clinical trials. The general purpose of the new guidance is to enhance consistency and transparency in decision-making, and in communication, and to explain how to apply these at different junctures in the product life-cycle. Another anchor in the guidance will be indication. The guidance will put forward a “structured descriptive assessment”, which will give information on risk minimisation, and integrated conclusions, aligning with existing frameworks, in a simple pragmatic way. The “structured descriptive assessment” will be applicable at various junctures during a product life-cycle – early development, trial design, registration – explaining how to carry out the assessment, when to implement it and how to document it. There will be a section on quantitative benefit-risk methodology, giving three of the most applicable methodologies, with examples to explain when to use these and when not to use these, and what data sources to use. The guidance will also cover benefit-risk preference information / patient preference information, giving specialized methodologies and techniques, with information on how to use these. We will also cover key points to consider under special circumstances: rare diseases, special populations (pediatric populations), legacy products, conditional approvals, and off-label use.

Comments arising from the subsequent discussion:

- It would be helpful to offer to train staff at organizations (CBER offers two courses on risk assessment).
- Capacity building is important.
- If we could find multiple, well-conducted, reliable, generalizable preference studies, it would be good to address these under the “structured descriptive assessment” approach.
- Regarding patient involvement, is it important to remember that patients do not necessarily have information on long-term disease progression.
- Regarding surveys, it is important to keep in mind that snap reactions are not the same as considered opinions. “Deliberative polling” is an approach to collecting input involving briefing before obtaining considered opinions.
- The working group discussed other new methods too and considered including these in the appendix (eg HD methodologies and HDA methodologies).
- Under benefit-risk monitoring, it would be possible to also include studying how health benefits or risks vary depending on the practical aspects of using devices (wearables, apps, inhalers), encompassing the many aspects that come together to deliver health. This could include also data collection (eg via software) to intercept eg missed doses. This can have relevance also to compliance aspects.

### [Roles within the CIOMS XII Working Group](#)

Chairwoman: Vicky (regulator)

Co-chair: Patrick (industry)

Co-chair: Scott (academia)

Subgroups and leaders (leaders' names are underlined)

Subgroup 1	Subgroup 2	Subgroup 3
<u>Methods</u> Including integrated benefit-risk methodologies / patient level	<u>SDA</u> Structured descriptive assessment	<u>Benefit-risk landscape</u>
Shahrul	Sherry	Guacira
<u>Leo</u>	Stewart	Takahiro
Panos	<u>Cheryl</u>	<u>Steffen</u>
Scott	Stephanie	<u>Tomas</u>
Stephen	Sebastian	<u>Leila</u>
<u>Richard</u>	Julie	Sabine
Patrick	Sergei	<i>George subgroup tbc</i>
Qun-Ying	<u>Hong</u>	
	Ezaki	
	Mariko	

Vicky is currently not attached to a subgroup.

### [Table of Contents for the new guidance](#)

#### I. INTRODUCTION

Background (from CIOMS IV as applicable)

Benefit-risk landscape

- New complex products (eg gene therapy)
- New data sources (eg real-world evidence)
  - Importance of evidence-based assessment
- New clinical trial complexity
- Regulatory approaches / benefit-risk frameworks and initiatives (e.g. FDA, EMA, ICH...)

Highlight new approaches / key changes from CIOMS IV (why it was changed)

Purpose

- General purposes:
  - Benefit-risk decision-making
  - Integrated approach
  - Benefit-risk communication, transparency
  - Patient-centred approach
  - etc
- Life-cycle approach with focus on registration / approval and on-market
- Indication basis
- Transforming benefit-risk: patient level / benefit-risk integrated approach

- Out of scope (eg economic, etc.)

## II. STRUCTURED DESCRIPTIVE BR ASSESSMENT (ICH-based)

### General principles

- Ownership of benefit-risk decision / assessment

### Components

- Therapeutic context
  - Include unmet need
- Key benefits and key risks
  - Clarify key risks vs. P important risks vs. key risks; risk sources
- Key evidence
  - Benefit-risk integration / composites
  - Absolute vs relative risk
- Risk minimization / options
- Uncertainties
  - Includes aspects beyond statistical uncertainty
- Benefit-risk conclusion/characterization: reasons/rationales for benefit-risk decision
  - Context with indication
  - Addresses uncertainties
  - Incorporates various information sources including patient preferences
  - Provide an example of what good looks like [FDA to provide example(s)]
  - etc.

### Applications

- Design of clinical trials / planning?
- Approvals
- On market

## III. IMPLEMENTATION

### Planning?

### Steps to use the framework / components

### Training

### Points to consider

### Uses (internal decision-making)

## IV. BENEFIT RISK METHODOLOGY CONSIDERATIONS

[May structure this section based on type of question to address.]

### Qualitative methods (e.g. Delphi, systems models, surveys)

When to use qualitative method (type of question to address)

Types/categories of method(s) to address a question

Data source

*Do above for 3-5 key questions*

### Quantitative methods

When to use quantitative method (type of question to address)

Types /categories of method(s) to address a question

Data source

*Do above for 3-5 key questions*

### Points to consider

- Constraints (time, resource, etc.)
- Patient level benefit-risk integrated approach
- Patient preference
- Use of real-world data

**Special situations**

Rare disease products

Legacy products

Special populations (e.g. paediatrics)

Conditional approvals

Use of real-world data

Urgent / emergent situations (e.g. Ebola)

Risk minimization effectiveness / unintended consequences

~~Off Label Use (?)~~

**Annexes**

Glossary

Case examples

- Some ideas:
  - Tysabri? often used
  - Valproate
  - Gardasil (MCDA)
  - Product approved with different risk minimization measures (eg REMS (ETASU) vs. none/education only)

[Next meeting](#)

The next CIOMS XII working group meeting will be in New Jersey, USA, hosted by Pfizer, on Wednesday 29 and Thursday 30 April 2020.