



Sixth virtual meeting of the CIOMS Working Group XIII Defining Intent, and Guiding Harmonization and Ethics Standards for Real-World Data and Real-World Evidence in Regulatory Decision-Making

26 February 2021, Virtual Meeting

Meeting Minutes

Participants

Enrica Alteri (former EMA), Yoshiko Atsuta (Japan Data Center for Hematopoietic Cell Transplantation), Laurent Azoulay (McGill University), Elodie Baumfeld Andre (Roche), Stella Blackburn (IQVIA), Mariette Boerstoeel (Alexion), John Concato (US FDA), Gracy Crane (Roche), Monica da Luz Carvalho Soares (Agência Nacional de Vigilância Sanitária, Brazil), Wim Goettsch (Utrecht Centre for Pharmaceutical Policy), Britta Haenisch (Bundesinstitut für Arzneimittel und Medizinprodukte), Sean Hennessy (University of Pennsylvania), Steffen Heß (Bundesinstitut für Arzneimittel und Medizinprodukte), Sanna Hill (CIOMS), Alar Irs (State Agency of Medicines, Estonia), Akihiro Ishiguro (Pharmaceuticals and Medical Devices Agency, Japan), Solomon Iyasu (Merck, Merck Sharp & Dohme Corp), Michele Jonsson Funk (University of North Carolina), Juhaeri Juhaeri (Sanofi), Laurie Lambert (CADTH), Jie Li (US FDA), Andrea Machlitt (Bayer), Takahiro Nonaka (Pharmaceuticals and Medical Devices Agency, Japan), Kateriina Rannula (CIOMS), Lembit Rägo (CIOMS), Anja Schiel (Norwegian Medicines Agency), David Townend (Maastricht University), Julia Wicherski* (Bundesinstitut für Arzneimittel und Medizinprodukte), David Wormser (Novartis), and Kristina Zint (Boehringer Ingelheim).

Regrets

Elodie Aubrun (Novartis), Thomas Brookland (Roche), Lu Hong (National Medical Products Administration, China), Miguel-Angel Mayer (Universitat Pompeu Fabra Barcelona), and Andreas Rudkjoebing (World Medical Association).

Alternate not attending

Daisaku Sato (Pharmaceuticals and Medical Devices Agency, Japan).

* New members since last meeting.

Introduction

- Lembit welcomed the members and chaired the meeting.
- He updated the group about a new CIOMS Working Group that has been launched on Severe Cutaneous Adverse Reactions (SCARs).
- Lembit also made the following announcements:
 - Robertino has left Gilead and our WG, and we are expecting a replacement member soon;



- Three new alternates have joined the WG: Gracy Crane, Roche; Takahiro Nonaka, PMDA; and Julia Wicherski, BfArM. Kinue Nishioka, PMDA, is no longer with our WG.
- A new editorial guidance document is being finalized and will be shared as soon as it is available.
- The meeting agenda was adopted.
- Kateriina was rapporteur at the meeting.

Chapter teams' presentations

Chapter 1. Introduction

- Sean presented the chapter draft and the notes below reflect only the WG's discussion points.
- The group discussed including/excluding product names in case examples in the report:
 - Lembit said it is the WG's decision how to present information;
 - Readers have appreciated specific examples in past CIOMS publications;
 - As a precautionary measure, companies could be asked for their consent for using their product as an example;
 - The document should focus on the underlying principles and it would seem unfair to choose one product example over another similar product;
 - It is not a matter of endorsement;
 - If the information is in the public domain we can use it;
 - The readers would benefit from the possibility of searching for additional information;
 - The WG agreed to include examples throughout the report.
- Sean asked the WG's opinion on the document's overall tone/viewpoint towards RWE, suspecting that we may need to add an appropriate level of caution.
- Mariette agreed that more critical aspects could be added.
- Alar suggested: 1) describing the current acceptance of RWD, including stating the differences between regions, considering the regulatory aspects; and 2) describing scientific issues with what can/cannot be achieved in a specific type of study or dataset.
- Wim felt the general tone of the document to be quite neutral but that the acceptance of the document would benefit from reflecting the existing scepticism towards RWE.
- Stella agreed the document should have a balance between using randomized controlled trials (RCTs) and RWE, as so far in practice, the emphasis has been on RCT. Perhaps it is the WG's aim to present the alternative approach?
- At the early stages, randomized data is beneficial in demonstrating whether a drug has efficacy, but at a later stage, that data increasingly loses its value as it does not provide information on the specifics of a drug's effectiveness. Stella was in favour of conditional approvals and then confirming a drug's true place with more RWD over time.
- In the case of ultra-rare diseases, it is not possible to use RCT.
- The introduction can be finalized once the rest of the document is ready.

Chapter 2. Uses of RWE in the regulatory process during the product life cycle

- Alar presented the chapter draft and the notes below reflect only the WG's discussion points.
- There was a discussion about HTA and payers' roles:
 - Wim suggested clarifying the HTA and payers' roles, and focusing on their different perspectives on RWD.



- Enrica felt it would be helpful for Wim to advise what should be highlighted from the payer's perspective as they do not have the same viewpoint as the HTA.
- Wim added that HTA organizations are in essence technical organizations providing technical assessment and have a more positive approach towards using RWD. It varies within the countries: Germany and France might have more a conservative view compared to the UK, Sweden or Norway.
- Lembit confirmed that the intent is to provide global coverage.
- Alar commented that the information is sufficient regarding the US and Europe, but that the chapter would benefit from information on other regions.
- Regarding subsection 2.4, Akihiro offered to create a descriptive section on the PMDA activities for the next WG meeting.
- Alar asked whether information on agencies, involving both HTA and the traditional drug regulation, e.g. the Norwegian agency, should be added to Chapter 2. He asked whether Anja would agree writing a short paragraph describing the process in general with some examples of its usefulness. Anja accepted and said she would exchange with Alar to specify the angle and length of the text.
- Solomon asked whether any team members would be involved in a new Duke Margolis work stream that would tackle the topics of evidentiary requirements for the HTA and offered sending information about the working group being launched.
- Alar recommended describing the current acceptance of data from real-world settings, including descriptions of how developers approach agencies. This would be beneficial and interesting for the readers.
- Mariette suggested also highlighting that Japan has historically been a frontrunner in its approach to RWE approval.
- The group would like to expand the topic of RWE usage over the product lifecycle, and describe the widely accepted uses and the more controversial ones.
- The chapter team requested additional examples on the pre-and post-approval phases and received the following suggestions:
 - Jenni offered an example for the post-approval phase, and although another example on the pre-approval phase is not in the public domain, if no other examples are found, she can help with summarizing the main principles to serve as an alternative approach.
 - Solomon offered an example to the post-approval section regarding one of the zoster vaccines. Solomon commented on the use cases in the pre-approval phase, which may not be something that we do for approval but which inform clinical development decisions, e.g. the biomarker studies that are conducted to understand the prognostic value of specific biomarkers, for example, in cancer therapy, to inform populations, patient selection or target population. He asked whether this would be considered under the pre-approval use of RWD.
 - Kristina agreed, and Solomon offered to share the publications related to biomarkers, their problems and prognostic value for survival or other disease progression markers.
 - John referred to the observational study reference shared by Michele and suggested to use the methodology of the example to describe good practices.
 - Michele agreed and added that describing the study design and unsuccessful methods used in the examples helps to differentiate between the successful and unsuccessful approaches.



- Kristina added that a figure is being created, which will provide a more comprehensive view of all the opportunities along the life cycle.
- Elo said the use case section will discuss the connection between specific diagnostic observations and the measurement data within the drug development process, and will outline the implication of inaccurate laboratory information on study results, and potentially to some extent on regulation.
- On the subject of repurposing of drugs, the following points were made:
 - Alar asked whether the topic should be addressed in Chapter 2 or perhaps in the methods section of the report.
 - Lembit supported adding the topic of repurposing drugs and using RWD into the report.
 - Jenni agreed and shared a recent example regarding finding a treatment for COVID-19 using an observational study.
- Monica offered to share an article on the drug development process, including the topic of artificial intelligence (AI) and machine learning (ML).
- Jenni commented that from the FDA perspective, the engagement with regulators is more viewed as a process and suggested to describe the situation as process-oriented instead of analysing the individual cases.

Chapter 3: Real world data and data sources

- Juhaeri presented the Chapter 3 draft and the notes below reflect only the WG's discussion points.
- Michele enquired whether it would be beneficial to discuss emerging pooled data sources in Chapter 3 as there are several potential challenges involved. She gave an example of collecting data on patients diagnosed with COVID-19 across multiple health systems. The concerning issues relate to how complete the data is, which is difficult to assess, especially if the process by which the data is pooled is not transparent.
- Juhaeri agreed that the topic should be included in Chapter 3, and according to Laurie's suggestion, it should be linked to COVID-19. He agreed to Michele's proposal to raise the data gathering issues in Chapter 2, whereas the challenges it creates from the methods perspective would be further elaborated on in Chapter 4.
- Gracy commented on ad hoc data collections, saying that they are potentially used where quality of life information is needed. Several studies have been conducted where quality of life information has been gathered, e.g. for patients with brain metastases. Otherwise, these patients would typically be excluded from clinical trials.
- Solomon mentioned a Task Force paper that would be beneficial regarding the before-mentioned issues and offered to try to locate and share it.
- Mariette suggested including Sentinel in the subsection "Other traditional sources".
- Juhaeri agreed that data pooling should be addressed in Chapter 3, and further discussions on the wording and which techniques to include would follow.
- Jenni suggested including AI and ML into the section "Emerging data sources", and Juhaeri agreed.



Chapter 4: Key scientific considerations in regulatory RWE generation

- Michele introduced the Chapter 4 draft and the notes below reflect only the WG's discussion points.
- Chapter 4 team agreed to edit the text to remove possible overlaps and shorten the chapters for the sake of the report's proportionality.
- Michele suggested expanding on the topic of external control arms as some issues may not be well understood.
- Andrea commented that a section in 4.5 addressing transparency reporting was inspired by what is recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Society for Pharmacoepidemiology (ISPE), Duke-Margolis and personal experience. She welcomes input on what is considered best practice for study registration.
- Gracy added that as she is involved in the ISPOR/ISPE work stream, as well as the RWE transparency initiative, she would like to raise two considerations: 1) an opportunity to register the types of studies; 2) a Duke-Margolis website has been created, which is only a testing site at the moment but would be useful in the future. She continued that the second initiative led by Shirley Wang in the ISPOR/ISPE work stream relates to the harmonisation of protocols. Every sponsor and every academic have their own protocols and there is a need to harmonise core elements. It is a work-in-progress document.
- Stella commented that the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study registry was created at the request of ISPE many years ago and opened up to any pharmacovigilance or pharmacoepidemiologic study, as it was designed to be a pharmacoepidemiologic equivalent of ClinicalTrials.gov.
- She asked whether by "harmonising protocols", Gracy meant "harmonising the sections", which should be included within the protocol, and added that a mandatory form exists, issued by the EMA. Gracy agreed on the terminology suggested and offered to share the ISPOR/ISPE notes discussing harmonising the protocol sections.
- Michele added that there are potentially multiple sites for registering protocols, and perhaps it would be beneficial to be clear on the motivation for the new effort initiated, especially if there is a distinct purpose for that different from the ENCePP site.
- Gracy suggested including a small informative table, clarifying the location of studies.
- She added that the ultimate goal is to increase the trust and reliability to be able to upload a protocol at a given location. It would be beneficial so that the regulators could investigate it and know that it is a pre-specified analysis.
- John commented on the pre-specified analysis as represented in point 2, "post a study protocol and analysis", saying that one of the issues is that unlike in the case of a clinical trial, where the data has to be collected going forward, the data already exists, so to state in Chapter 4 that the data was not searched several times to find the preferred associations would pose a challenge.
- Gracy agreed that it is one of the issues currently under discussion but has remained without a definite solution.
- Andrea commented that it would already be an achievement if the protocol were to be registered before presenting the data elsewhere. If the WG were able to provide a recommendation on which registry to use and which elements to register, that would be an advancement. She suggested presenting the current situations and offering future possibilities.



Chapter 5: Ethics, governance and related issues

- David presented his thoughts on the chapter and the notes below reflect only the WG's discussion points.
- WG members are welcome to join the Chapter 5 team. If necessary, it would be possible to include a person from outside the group too. [Post-meeting comment: Yoshiko and Gracy volunteered to join the team].
- Solomon commented that David's presentation approached ethics in a valuable and comprehensive manner. Ethics is often only discussed in terms of privacy, confidentiality and data governance, and autonomy issues.
- Enrica added that David's perspective on ethics introduces a new dimension to the WG. The challenge lies in connecting Chapter 5 to the rest of the report. She suggested cross-referencing to strengthen the connection, e.g. when data is discussed, reference should be made to the section in Chapter 5 addressing data governance.
- Lembit agreed with Enrica and added that ethics is a rapidly evolving field, and without doubt, the usage of RWD and RWE will increase, and there should be a long-term vision on how to implement that data. The data governance issue is one of the crucial topics of the chapter as the enormously increasing amount of data is being collected. The chapter offers an opportunity to present a visionary approach to addressing ethics.
- David added that one of the major problems is that medical data is viewed as special data, different from all the rest of data, and an area that needs to have enormous protection. The question of how to encourage people not to be fearful of allowing their data to be used in medical research remains. He expressed hope that people would be as enthusiastic about joining research as they are about joining with e.g. Google, where personal data is not protected.
- Anja commented that as in Europe there is a social healthcare system, it should perhaps be voiced that citizens also have a responsibility to contribute with their data, under the guarantee that data handling would be explicitly explained to them. It often happens that the most beneficial intentions to use data are stopped, whereas some initiatives with debatable integrity can access almost all aspects of personal data, which is naively presented to them.
- Michele added two ways of connecting ethical considerations with the specifics of RWD and RWE:
 - RWD and RWE have the potential for addressing some of the inherently inequitable access to randomised trials, as participants are not a random sample, and as trials underrepresent many of the people who might benefit the most from the treatments but are excluded.
 - There is a problem accessing secondary data because the infrastructure for collecting those data is not evenly distributed around the world. The places where we can quickly generate more information from these types of data are populations with financial resources.
- Solomon voiced some of the issues/questions around the topic of a public good:
 - The idea of possessing the right to science and the right to knowledge
 - Who has the right to science?
 - Can an individual give up their data because there is a societal right to science and knowledge?



- How does this operate within a society?
- Lembit added that individual rights are emphasised, whereas the obligation to give is not addressed at all. Anyone could contribute with the data they have because nowadays in several countries, there are electronic health records and members of society could contribute by allowing, through good governance, access to their data.
- David agreed that this aspect would have to be explored. We would need to approach the members of society who want to participate with their data but who are frightened because they have experienced misuse in the political or medical system. Perhaps the mistrust is due to the narrative created; and in order to change the narrative, the scientific community would need to explain their actions openly?
- He continued by bringing the example of trusting one's doctor and having a similar attitude towards science.
- Lembit added that more understandable data governance principles should be created to promote trust towards research and science in general.
- Anja commented that technology and data are dangerous combinations because many people live in the illusion of having complete control over their data.

CIOMS WG XIII report glossary

- Lembit mentioned that a glossary should be created and approved by all the chapter teams. The choice of sources is the WG's decision. If necessary, the WG members are welcome to provide a new definition instead of using an existing one.
- The CIOMS Cumulative Pharmacovigilance Glossary, currently under development, includes all terms from previous CIOMS pharmacovigilance reports, and the document will soon be published on the CIOMS website. It will be a living document, and the terms from the current report, once finished, will also be added.

Future meetings and closing remarks

- Lembit thanked all the WG members for the beneficial discussions and for everyone's efforts in drafting the chapters, and concluded by expressing hope to return to the topics during future WG meetings.
- Sanna asked the chapter teams to send her the most recent version of their chapters.
- Next WG meeting is set for April 1st, and Sanna will create Doodle polls to continue scheduling the monthly meetings thereafter.
- Regarding simultaneous editing software, CIOMS has not identified a single platform that would be acceptable for all team members and organisations involved. Therefore, CIOMS recommends that the individual teams use software that suits their needs, ideally with CIOMS able access too.
- CIOMS provides a password-protected area on the CIOMS website for sharing documents, and everyone is encouraged to share their chapters there so that the other chapter teams can follow their progress.