



Fifteenth 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

9 September 2022, Virtual Meeting

Meeting Minutes

Participants

Enrica Alteri (formerly European Medicines Agency), Yoshiko Atsuta (Japan Data Center for Hematopoietic Cell Transplantation), Elodie Aubrun (Novartis), Mariette Boerstoeel (AstraZeneca), John Concato (US Food and Drug Administration), Gracy Crane (Roche), Sean Hennessy (University of Pennsylvania, US), Sanna Hill (CIOMS), Solomon Iyasu (Merck, Merck Sharp & Dohme Corp), Michele Jonsson Funk (University of North Carolina, US), Juhaeri Juhaeri (Sanofi), Jie Li (US Food and Drug Administration), Monica da Luz Carvalho Soares (Agência Nacional de Vigilância Sanitária, Brazil), Andrea Machlitt (Bayer), Takahiro Nonaka (Osaka Metropolitan University, Japan), Lembit Rägo (CIOMS), Anja Schiel (Norwegian Medicines Agency), David Shaw (University of Bern, Switzerland), David Townend (University of London, UK), Rika Wakao (Pharmaceuticals and Medical Devices Agency, Japan), Julia Wicherski (Bundesinstitut für Arzneimittel und Medizinprodukte, Germany), and Kristina Zint (Boehringer Ingelheim).

Regrets

Laurent Azoulay (McGill University, Canada), Elodie Baumfeld Andre (Roche), Stella Blackburn (IQVIA), Thomas Brookland (Roche), Wim Goettsch (Utrecht Centre for Pharmaceutical Policy, Netherlands), Britta Haenisch (Bundesinstitut für Arzneimittel und Medizinprodukte, Germany), Steffen Heß (Bundesinstitut für Arzneimittel und Medizinprodukte, Germany), Lu Hong (National Medical Products Administration, China), Alar Irs (State Agency of Medicines, Estonia), Laurie Lambert (Canadian Agency for Drugs and Technologies in Health), Cynthia de Luise (Pfizer), Miguel-Angel Mayer (Universitat Pompeu Fabra Barcelona, Spain), Mareike Millner (Maastricht University, Netherlands), Manami Nomura (Pharmaceuticals and Medical Devices Agency, Japan), Monika Nothacker (Association of the Scientific Medical Societies, Germany), Daniela Rojas (Maastricht University, Netherlands), Heather Rubino (Pfizer), Andreas Rudkjoebing (World Medical Association), Julia Stingl (University of Aachen, Germany), and David Wormser (Novartis).

Introduction

- Lembit welcomed the WG XIII members and chaired the meeting.
- On the 6th of September, CIOMS published the [Patient Involvement in the development, regulation and safe use of medicines report of the CIOMS Working Group XI](#).
- [Post meeting comment: on 15th of September, CIOMS published the [CIOMS Cumulative Glossary with a focus on Pharmacovigilance \(Version 2.0\)](#).]



- In later September, CIOMS is expecting to publish an ICH Cumulative Glossary.
- The two glossaries above will be different in scope although they will have links such as shared histories and dynamics. For pragmatic reasons, it will be easier to update the glossaries separately. In terms of their relevance to RWD and RWE, we anticipate fairly little overlaps.
- The meeting agenda was adopted.

Progress updates and discussion on chapters

Chapter 1. Introduction.

- Sean and Mariette: The definitions have been progressed, and there have been some fine-tuning throughout the chapter, but major edits will take place once other chapters have matured more.

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

- Elodie A: received comments with suggested improvements in wording and accepted these.
- Elodie wants to meet with the chapter team to discuss the team's own comments.

Chapter 3: Real-world data and data sources

- There were no changes to the chapter to date.
- Juhaeri thanked Sean for his suggestions to improve legibility and to clarify the chapter.
- There was also a question over whether the Chapter 3 should remain descriptive or be re-worked to be more prescriptive. After reflection, Juhaeri felt Chapter 3 works well as it is, especially because Chapter 4 is rich with recommendations.
- The European data sources mentioned – [DARWIN](#), [European Health Data Space](#), [Eu2P](#), and [IMI's PROTECT](#) – are considered sufficient now.

Chapter 4: Key scientific considerations in regulatory RWE generation

- Michele acknowledged comments received pointing out overlaps between Chapters 3 and 4, and now in the light of Juhaeri's comments above, she wondered whether the descriptive content within Chapter 4 is helpful (e.g. regarding choosing data sources). Juhaeri confirmed that some repetition is good but perhaps we can reduce it.
- Solomon made the point that as this chapter brings together many concepts touching on e.g. from 'different data sources' and 'evidence generation considerations' to 'fitness of data', it requires some repetition to make its arguments.
- Lembit added that some readers will only read select chapters and so it is helpful if chapters can function as stand-alone entities.

Chapter 5: Ethical and legal issues in using real-world data

- David T. has drafted a new text on data protection. He feels Chapter 5 is EU-centric in terms of its General Data Protection Regulation (GDPR) especially in terms of its examples, although the team has received some examples from different jurisdictions. David T. requests everyone to comment on whether the chapter reflects the common experience. Please indicate divergence.
- David S. has added a paragraph on the approach in Japan based on content provided by Yoshiko.



- Sean had commented that Chapter 5 was different in style from the other chapters, and David S. offered to consider this, although the different nature of the content may suit a different style.
- David T. has expanded the conclusion.

Discussion on representativeness and ethics

- Solomon mentioned the chapter left him feeling unsure about why we should be using RWD/RWE. He was concerned about the underlying assumptions that maybe in some parts the discussion questions the ethical underpinnings of RCTs and that it positions RWE as more ethical. We don't want to give this message. The ethical standards around RCTs have been worked out over many years and there are rules & regulations about what is ethical/unethical, over what the regulations/constraints/control systems are. Solomon was not sure whether RWE use is entirely/partially pushed by the idea that continuing on the RCT path being unethical.
- David S. responded that RCTs are not conducted in an unethical way but that some populations end up being excluded and this means RCTs do not give all the evidence we need. David S. will ensure this is expressed more clearly in the draft.
- John urged to keep at the back of our minds the concepts of validity, generalized ability, human subject protection, and general ethics.
- We need to take care over how the term 'Gold standard' is used, if it is to be used at all. It can mean different things in different contexts.
- There is an issue with the secondary use of already gathered data, i.e. the re-purposing of data, unless we are to invest into re-consenting. The practicality of this will be near-impossible. This invites a different relationship between citizens and trials – it suggests that any gathered data is fair game for an industrial purpose. The ethics of re-framing the environment from 'opting in' to at best 'opting out'. The majority of the citizens will need to believe this to be a fair deal, that they have fair access to the product, and that there are adequate safeguards. We need a business realism and not just an ethical stance.

Other topics

Glossary

- The current plan is to provide definitions in the body copy and/or footnotes, and decide at a later date whether we want a glossary in the report.
- Q: Does a group of informed readers test-read the draft report in advance of publication and feedback e.g. regarding inconsistencies in the use of terms?
[Post meeting comment: A: Only the editorial team and we will receive some feedback via the public consultation.]
- We would need to consider the CIOMS Cumulative Glossary and the ICH Cumulative Glossary for alignment. Glossaries are not created in a vacuum.
- The CIOMS WG XIII Chapter 1 has a new updated definition for RWD that is specific to what we want to write about and we have done this independently from a potential WG XIII glossary and consulting with other sources for the time being.



- If we end up using a lot of uncommon terms, we could re-consider having a small glossary in the WG XIII report, which in time can be included with the CIOMS Cumulative Glossary.
- Regardless of whether the WG XIII report has a glossary, when we use or adapt a term, we need to include references, and these can be to earlier existing documents too.
- The chapter leads are welcome to consider their chapters' glossary requirements.
- Even if the WG XIII report does not have a glossary, any definitions in the body copy and from footnotes can be taken into the CIOMS Cumulative Glossary.

Executive Summary

- Enrica presented a slide set in an effort to ascertain the type of text required.
- The target audience is expected consist of product developers, those working for public institutions; not the wider public.
- The Executive Summary should be self-contained, a mini-version of the report, like an abstract.
- It should allow the reader to navigate to a place in the report that they are interested in.

Given the options presented in the slide set, the WG chose an enhanced option 1. This is an ambitious report. We are getting to a new era with advanced tools, not tools in their infancy. We may capture the attention of non-specialist readers within industry or regulators too e.g. regarding future investment choices (Do we invest in more big trials or in sophisticated analytical tools? Who do we want to hire?).

This may have implications for other parties who are indirectly involved – electronic health records may need improving at hospital level / regional level / national level. Many are not research-friendly. It is difficult to get data out in a meaningful way.

Timeline

- Chapter teams to finalise their chapters by 7th of October.
- Sanna to combine chapters, work on formatting and references, by 7th-15th of October.
- Sanna to continue working on references, cross-references, flow, consistency, work with editorial team (e.g. remove redundancies, contradictions), finish by December, possibly even begin a six-week public consultation before the end of the year, and if not, then in the New Year.
- We will aim to publish by the summer.

Implementations team

- We would welcome a small group of volunteers to help promote the report by:
 - writing and placing articles into scientific journals;
 - seeking speaker opportunities at events;
 - putting together a webinar.

This can be discussed more at the next WG meeting.

Any other business

- Gracy shared [ICMRA statement on international collaboration to enable real-world evidence \(RWE\) for regulatory decision-making](#) for inclusion in the report.



- Lembit suggested perhaps adding it as an example if it could fit somewhere in the report or as an appendix.

Future meetings and closing remarks

- We can have a full WG meeting in advance of or after the public consultation. If this should be before Christmas, the meeting would be held virtually. March or April 2023 may be interesting for an in-person meeting, if the WG feels by consensus this to be preferable.
- We will have a full WG meeting before the report is published. Again, this may be held in-person if the WG feels by consensus this to be preferable.