



Eighth 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

6 May 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 Boerstoele (Alexion), Ulka Campbell* (Pfizer), 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), Sanna Hill (CIOMS), Alar Irs (State Agency of Medicines, Estonia), Akihiro Ishiguro (Pharmaceuticals and Medical Devices Agency, Japan), Michele Jonsson Funk (University of North Carolina), Juhaeri Juhaeri (Sanofi), Laurie Lambert (CADTH), Jie Li (US FDA), Takahiro Nonaka (Pharmaceuticals and Medical Devices Agency, Japan), Kateriina Rannula (CIOMS), Lembit Rägo (CIOMS), Julia Stingl (University of Aachen, Germany), and Julia Wicherski (Bundesinstitut für Arzneimittel und Medizinprodukte).

Regrets

Elodie Aubrun (Novartis), Thomas Brookland (Roche), Steffen Heß (Bundesinstitut für Arzneimittel und Medizinprodukte), Solomon Iyasu (Merck, Merck Sharp & Dohme Corp), Lu Hong (National Medical Products Administration, China), Andrea Machlitt (Bayer), Miguel-Angel Mayer (Universitat Pompeu Fabra Barcelona), Andreas Rudkjoebing (World Medical Association), David Townend (Maastricht University), David Wormser (Novartis), Anja Schiel (Norwegian Medicines Agency), and Kristina Zint (Boehringer Ingelheim).

Alternate not attending

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

* New member since last meeting.

Introduction

- Lembit welcomed the members and chaired the meeting.
- He made the following announcements:
 - CIOMS WG on Recommended Standards of Education and Training for Health Professionals Participating in Medicines Development was launched on 26-27 April;



- The report from the CIOMS WG on Clinical Research in Resource-Limited Settings was available for public consultation and is currently being finalised by the editorial team, and will soon be published;
- Another CIOMS WG will be launched before summer, tackling the topic of research ethics.
- Lembit welcomed the new WG member, Ulka Campell, the head of the Safety Surveillance research team at Pfizer.
- The meeting agenda was adopted.
- Kateriina was rapporteur.

Chapter teams' presentations

Chapter 1. Introduction

- Stella and Mariette gave an update on Chapter 1 and added that the introduction would be finalized when the rest of the chapters are ready.

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

- Elo informed the WG that the Chapter 2 team will continue addressing the feedback received from the WG members and will edit the chapter with an aim to preserve its alignment with the document's original objective. The team will share the updated chapter with the WG by the end of May.
- Akihiro has added a descriptive section on the PMDA activities to Chapter 2 and welcomes all feedback.

Chapter 3: Real world data and data sources

- Juhaeri gave an overview of the updated Chapter 3.

Social media

- Include high-level, neutral information on the potential usage of social media with its negative and positive sides;
- Social media is recognised to detect adverse events;
- Studies indicate that when analysing data retrieved from social media, the incidence of false-positive results is low, which is important to note in the chapter;
- The most significant limitation to using data retrieved from social media is that individuals characterize their health-related experiences differently depending on their cultural environment.
- Social media provides valuable information on the changes in quality of life;
- While social media is not a reliable source to detect signals, the data may be further evaluated with other, more credible data sources;
- Data from social media would be of interest to the centres of disease control, in the field of prevention and identification of possible outbreak areas, and the topic should be included.

Artificial intelligence

- Briefly mention artificial intelligence (AI) in Chapter 3 in relation to social media, but discuss it in more detail in Chapter 4 section discussing different elements of a study, e.g. cases where AI is



employed to define cancer events, using MRI images, etc. Juhaeri offered his assistance in further drafting the section.

- The use of AI is not limited to emerging data sources, e.g. social media, and has been employed in pharmacoepidemiologic studies using traditional data sources.
- The current most dominant application of AI is to structure unstructured data. Even in the case of structured data, e.g. in electronic health records, the severity, propensity score, etc. can be identified using AI.
- Machine learning can be utilised to ascertain diabetic ketoacidosis. Juhaeri will add a reference on it to Chapter 3.
- AI is beneficial in distinguishing between irrelevant information and valuable signals. Juhaeri will make the final edits to the chapter and forward it to Sanna to be circulated among the WG members with a final feedback request.

Chapter 4: Key scientific considerations in regulatory RWE generation

- Michele gave an overview of the updated Chapter 4.
- All case studies that could be used throughout the chapter are appreciated.
- Subheadings will be added to section 4.1. to help keep the reader oriented, and a user-friendly discussion on estimand is included, as the term is increasingly used.

Data sources and discussing “fit for purpose”.

- An overlap with Chapter 3 will be removed. Juhaeri is welcome to comment on topics that should be included in the section.
- Discussion on the use of a single database versus mixed-type data will be added.
- Juhaeri agreed to add a discussion on common data models e.g. Sentinel, PCORnet, etc. in Chapter 3.
- Jenni offered to provide a section describing Sentinel.
- When collecting data from different sources, it must be acknowledged that the data are transformed, and although they are in a common data model, there may be subtle differences, requiring caution with interpretation.
- Yoshiko added that when data are merged from multiple sites or countries, a potential threat of duplicates must be considered, e.g. not counting the same individual twice.
- The team concluded that heterogeneity is possible, and although data sources differ in terms of reliability, there are several that have been carefully curated, e.g. Sentinel.

Study design and sources of bias

- John will provide the latest version of the FDA figure representing different study designs.
- The section on “new user active comparator design, the prevalent new user design” will be moved up in the chapter. A section on more traditional case-control studies will be included.
- Laurent will add a section on basic study designs.
- The chapter would benefit from less detailed subheadings to integrate different sections and ensure flow.
- A section will be added that crosswalks the study designs and the sources of bias to highlight which ones are of particular concern in the different types of studies described in the previous section.
- Section on outcome definitions, selecting confounders or effect modifiers will be added.



Chapter 5: Ethics, governance, and related issues

- David shared key progress milestones on Chapter 5 via email:
 - Identification of key data protection issues and potential solutions for data sharing that possess a “data ethics” element;
 - Development of work on inclusion and diversity - including focus groups.
- David will summarise a draft in advance of the next meeting.

Case studies

- The main aim in including case studies is to provide clarity and insight into the topics included in the document.
- Following the discussion, the WG decided:
 - Include carefully chosen case studies (regulators will only be able to contribute case studies in the public domain);
 - Include case studies on both safety and effectiveness, but focusing on effectiveness studies;
 - Add case studies that are fully observational and non-interventional;
 - Not to include examples on each type of studies, prioritise submission-related case studies;
 - WG members from the regulatory agencies would be able to provide added value by giving feedback on the chosen case studies in terms of their specific context and characterisation;
 - The RCT duplicate results are important, but explicitly using concordance between the trials and the real-world study might be problematic;
 - WG members can suggest examples of unsuccessful submissions, but only if they choose to.
- Michelle proposed including the example of [Tocilizumab](#).
- Ulka offered to send references of case studies that relate to safety.
- Gracy shared a summary of [case studies](#) from the EMA by Cave et al.
- Sanna will share notes on case studies suggested by WG members at the very start of the WG work.

Glossary

- [CIOMS Cumulative Pharmacovigilance Glossary](#) has been published and is recommended for consulting as a starting point when choosing terms and definitions for the report’s glossary.
- Chapter leads will forward their suggested terms and definitions to Sanna, who will then share them with the entire WG.
- Stella volunteered for the future glossary team subgroup and offered her assistance to Chapter leads in determining the entries.



Future meetings and closing remarks

- Sanna will open a Doodle poll to help schedule the next meeting at the end of June. Following that, the team would gather in late August or in September.
- Lembit thanked all WG members for joining and for their time and effort in progressing the WG's agenda.