Eleventh 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

3 December 2021, Virtual Meeting

Meeting Minutes

Participants

Enrica Alteri (former EMA), Yoshiko Atsuta (Japan Data Center for Hematopetic Cell Transplantation), Laurent Azoulay (McGill University), Stella Blackburn (IQVIA), John Concato (US FDA), Gracy Crane (Roche), 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), Andrea Machlitt (Bayer), Kateriina Rannula (CIOMS), Heather Rubino* (Pfizer), Lembit Rägo (CIOMS), David Shaw* (University of Bern), David Townend (Maastricht University), Julia Wicherski (Bundesinstitut für Arzneimittel und Medizinprodukte), David Wormser (Novartis), and Kristina Zint (Boehringer Ingelheim).

Regrets

Elodie Aubrun (Novartis), Elodie Baumfeld Andre (Roche), Mariette Boerstoel (Alexion), Thomas Brookland (Roche), Wim Goettsch (Utrecht Centre for Pharmaceutical Policy), Britta Haenisch (Bundesinstitut für Arzneimittel und Medizinprodukte), Steffen Heß (Bundesinstitut für Arzneimittel und Medizinprodukte), Lu Hong (National Medical Products Administration, China), Solomon Iyasu (Merck, Merck Sharp & Dohme Corp), Cynthia de Luise (Pfizer), Monica da Luz Carvalho Soares (Agência Nacional de Vigilância Sanitária, Brazil), Miguel-Angel Mayer (Universitat Pompeu Fabra Barcelona), Mareike Millner (Maastricht University), Takahiro Nonaka (Pharmaceuticals and Medical Devices Agency, Japan), Monika Nothaker* (Association of the Scientific Medical Societies), Daniela Rojas (Maastricht University), Andreas Rudkjoebing (World Medical Association), Anja Schiel (Norwegian Medicines Agency), and Julia Stingl (University of Aachen, Germany).

* New members since last meeting

Introduction

- Lembit welcomed the WG members and chaired the meeting.
- Three new WG members joined the WG: Monika Nothacker from the Association of the Scientific Medical Societies in Germany, Heather Rubino, Pfizer, and David Shaw, University of Bern.
- The CIOMS Working Group XI: Patient Involvement in the Development, Regulation and Safe use of Medicines is preparing for its public consultation in early 2022.

- Lembit and David T. participated in a virtual Conference on the Ethical, Legal and Social Issues (ELSI) in the Use of Big Data & International Conference on China's Ethics Committee Development (ECD 2021). It was organised in Shanghai, China by CIOMS, Shanghai Ethics Committee for Clinical Research (SECCR), and Shanghai Clinical Research Center (SCRC) on 2 December 2021. The conference addressed the issues of data protection, research, related ethical dimensions and legal implications in different countries.
- The meeting agenda was adopted.
- Kateriina was rapporteur.

Progress updates and discussions on chapters

Chapter 1. Introduction

- The introduction will be reviewed in the light of the revised chapters following the meeting.

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

- The differences between regulatory decision-making and HTA activities should be described.
- We should emphasise the benefits of collaboration and the possibility of including RWE in the early stages of preparing an HTA submission.
- The chapter needs to be balanced in terms of information on HTA compared to regulators; the aim is to relatively reduce the HTA content.
- The section discussing the industry perspective will not be removed but will be made more compact.
- Lembit suggested placing sections that might affect the chapter balance to an appendix. This is yet to be decided by the chapter team.
- The references and content of the chapter will be updated following the recently published draft U.S. FDA Guidance for assessing EHR and medical claims data, U.S. FDA Guidance for Registries and the EMA guidance on registry-based studies.
- Several guidance documents relevant to the WG agenda are in preparation.
- The aim is to allay fears that RWE will replace RCTs and maintain an open dialogue on this topic.
- Michele suggested adding a brief summary of situations where there are significant limitations to trials and where we believe RWE can be used.
- The chapter includes two lists: one where RCTs have shortcomings or are impossible, and another where RWE could replace RCTs depending on the research question. Another kind of list could be created in which RWE is presented as a solution to the shortcomings of RCTs. Alar would appreciate Michele's feedback on the lists.
- The chapter 2 team urged the WG to add ideas and text directly to the Google Docs draft, allowing the chapter to progress more efficiently. The draft will then be reviewed, and any repetitions will be removed.
- Elo will review the chapter.
- The chapter 2 team agreed to convene before the next full WG meeting to discuss the structure and length of the draft's subsections.

Chapter 3: Real-world data and data sources

- Chapter 3 team will incorporate the comments received from the WG members.
- The concept of a registry database needs further clarification but caution is needed regarding the amount of detail added as other data sources have been explained only briefly.
- The aim is for the chapter to maintain its clear structure and, if possible, the current length.
- Michele suggested providing explanations of terms used, e.g. registry, claims, etc. and adding discussion on the importance of access to and discussion with people closest to data generation and processing.
- Juhaeri urged WG members to add information on European projects as the chapter 3 draft focuses too much on the US space. In past comments, suggestions were made by Anja and her contribution would be appreciated.
- Enrica offered to contribute on the European context including the DARWIN EU project and the EMA guidance on registry-based studies. Alar and Anja are welcome to contribute their expertise.
- The chapter 3 team requests that the WG members add text and/or links to the chapter directly to Google Docs, as this would make the work process faster and more efficient.
- Following Robertino's departure from the WG, there is no designated author for the section on emerging sources, and the chapter 3 team welcomes any suggestions for improving this section. Overall, the section is satisfactory.

Chapter 4: Key scientific considerations in regulatory RWE generation

- The chapter 4 team had convened in November and progressed the chapter in determining the structure and areas requiring contributions.
- The chapter 4 team will need to reconvene to produce a more mature draft.
- Michele will notify the WG when the chapter is revised and open for comments in Google Docs.

Chapter 5: Ethics, governance, and related issues

- David T. welcomed David Shaw, an ethicist from the University of Bern, to the chapter 5 team.
- The chapter is progressing, and having read the most recent combined chapters document, David has gained a clearer idea of the content needed for chapter 5, which has led to much of the first draft being rewritten.
- Chapter 5 team plans to hold another meeting in January and will try to present a more mature draft before the next full WG meeting.

General discussion

Addressing COVID-19

- All the issues related to COVID-19 will be grouped in a separate chapter to fully cover the impact of the pandemic. The chapter will be forward-looking in providing an opportunity to learn from experiences, should we face a similar situation in the future.
- The WG members outlined initial key considerations to be addressed in the chapter:
    - Include examples of how RWD has been beneficial in the context of a pandemic e.g. a case study in the appendix;

  - Outline the potential harms due to poor use of RWD / RWE;
  - Emphasise the importance of RWE given the rapid development of vaccines, for which long-term data are not available;
  - RWE is beneficial for monitoring the real-time safety of vaccines, as a vast amount of data is constantly received;
  - Data credibility, data collection, and further use of data are critical for communication and public reassurance (need to generate actionable evidence that is reliable and timely);
  - COVID-19 has created a focus and pressure to maximise the use of data. Although the transparency and availability of data is commendable, there are examples of the dangers of transparency (misinterpretation) and the misuse of data;
  - The pandemic has had a disruptive effect on epidemiology, e.g. impact on background rates;
  - Signal detection issues have and will occur due to the massive influx of data;
  - How to generate reliable yet timely evidence;
  - Pre-approval of vaccines and the shift from RCTs to RWE undermined confidence in vaccines among certain social groups.
- It is possible that COVID-19 has already influenced the writing of the existing chapters. We should decide which sections from the chapters can and should be included in the separate chapter and which aspects would be better left in their original place. Cross-references will link the information on similar topics.
- The final report should not be changed because of COVID-19.
- The WG agreed that at least one person from each of the chapter teams will work with the chapter addressing the pandemic. The WG members who have already volunteered are: Enrica, David S, Gracy, Heather, and Michele.
- Sanna will open a Doodle poll for January for the WG members to consider contributing to drafting a chapter addressing the pandemic.
- The team agreed that carefully selected and presented case studies would add value to discussions on COVID -19.

Glossary

- The CIOMS Cumulative Pharmacovigilance Glossary is available as a resource when considering the terms for the glossary. Relevant terms may be refined or redefined to specify their meaning in the report's context and objectives.
- Terms from the final CIOMS WG XIII report will be included to the CIOMS Cumulative Pharmacovigilance Glossary.
- Juhaeri will contribute a list of terms from chapter 3 and the chapter 2 team has provided its glossary items in the combined chapters document on Google Docs.
- Chapter leads are invited to continuously add to their glossary lists. Please give the term, a proposed definition, and a reference – you can adopt from an existing source, modify an existing definition, or formulate your own de novo wording.

Future meetings and closing remarks

- Sanna will open a Doodle poll to help schedule the next full WG meeting for late January or February.

- Sanna will upload the chapters separately on Google Docs to allow WG members to work with them at their convenience. [Post-meeting note: for the benefit of those who are unable to access Google Docs, Sanna will download, combine and email the chapters every month.]
- Sanna will send the most recent version of chapter 3 to Juhaeri for confirmation.
- The chapter leads for chapters 2-5 will send the reviewed drafts to Sanna.
- Michele suggested that each chapter lead also send instructions with requested comments and timeline.
- A combined chapters document will be created in January and the WG will have an opportunity to read and reflect on the combined chapters in preparation for the 12th WG meeting in late January or early February.
- The WG agreed to use "edit mode" when adding to the chapters in Google Docs.
- The WG had previously discussed the need for holding an in-person meeting in 2022. As several members' organisations have reinstated travel bans, the WG meetings will continue to be held online.
- Lembit concluded the meeting by thanking all WG members for joining and for their time and effort in progressing the WG's agenda.