Twelfth 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

4 February 2022, Virtual Meeting

Meeting Minutes

Participants

Enrica Alteri (former EMA), Yoshiko Atsuta (Japan Data Center for Hematopetic Cell Transplantation), Elodie Aubrun (Novartis), Laurent Azoulay (McGill University), Stella Blackburn (IQVIA), Mariette Boerstoel (AstraZeneca), John Concato (US FDA), Gracy Crane (Roche), Wim Goettsch (Utrecht Centre for Pharmaceutical Policy), Sean Hennessy (University of Pennsylvania), Sanna Hill (CIOMS), Alar Irs (State Agency of Medicines, Estonia), Solomon Iyasu (Merck, Merck Sharp & Dohme Corp), Michele Jonsson Funk (University of North Carolina), Juhaeri Juhaeri (Sanofi), Laurie Lambert (CADTH), Monica da Luz Carvalho Soares (Agência Nacional de Vigilância Sanitária, Brazil), Andrea Machlitt (Bayer), Kateriina Rannula (CIOMS), Heather Rubino (Pfizer), Lembit Rägo (CIOMS), Anja Schiel (Norwegian Medicines Agency), David Shaw (University of Bern), Julia Wicherski (Bundesinstitut für Arzneimittel und Medizinprodukte), and Kristina Zint (Boehringer Ingelheim).

Regrets

Elodie Baumfeld Andre (Roche), Thomas Brookland (Roche), Britta Haenisch (Bundesinstitut für Arzneimittel und Medizinprodukte), Steffen Heß (Bundesinstitut für Arzneimittel und Medizinprodukte), Lu Hong (National Medical Products Administration, China), Akihiro Ishiguro (Pharmaceuticals and Medical Devices Agency, Japan), Jie Li (US FDA), Cynthia de Luise (Pfizer), Miguel-Angel Mayer (Universitat Pompeu Fabra Barcelona), Mareike Millner (Maastricht University), Takahiro Nonaka (Pharmaceuticals and Medical Devices Agency, Japan), Monika Nothacker (Association of the Scientific Medical Societies), Daniela Rojas (Maastricht University), Andreas Rudkjoebing (World Medical Association), Julia Stingl (University of Aachen, Germany), David Townend (Maastricht University), and David Wormser (Novartis).

Introduction

- Lembit welcomed the WG members and chaired the meeting.
- The CIOMS Working Group XI: Patient Involvement in the Development, Regulation and Safe Use of Medicines draft report will be available for public consultation in February 2022.
- A new CIOMS WG will be launched soon on artificial intelligence in pharmacovigilance.
- The meeting agenda was adopted.
- Kateriina was rapporteur.

Progress updates and discussions on chapters

Chapter 1. Introduction

- There have been no major revisions to the draft and the team has been addressing the comments from the WG.
- The Chapter 1 team agreed to update the definitions for RWE / RWD, reviewing a publication comparing different potential definitions, and using the CIOMS Cumulative Pharmacovigilance Glossary.
- There is no consensus on a standard definition, but the majority of the definitions, including the one used in IMI-GetReal, define RWD / RWE as data not collected in conventional randomised clinical trials (RCTs).
- The definitions of RWD / RWE should not only focus on the type of studies but also on the purpose for which the data are collected.
- John suggested focusing on the purposes of this document by stating the framework and/or approach of the definition throughout the report. He shared an article addressing the definitions with the WG.
- It would be useful to clarify in the definition what elements contribute to something not being understood as RWD. Randomisation alone is not the defining characteristic. It has to do with how the data are collected. The definition should take into account how much control can be exercised over the potential sources of bias.
- In the section "Regulatory potential of RWE and current controversies and challenges", an example of preventive treatments is added to the previous example of vaccines.
- As Chapter 1 serves as an introduction to the report, we should also add a concluding chapter, renumber the chapters and add the introduction and a conclusion without numbers. Would an executive summary add value to the report?
- Will we include forward-looking statements addressing the development of the field?
- How should the references be included - all at the end of the report or separately after each chapter?
- The WG is invited to review the introduction in light of the development of the team members' respective chapters and suggest changes if needed.
- Chapter teams are invited to add a brief description of their chapter to the section in the introduction where the framework of the report is presented.

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

- The team held several meetings to review the sections of the chapter and fill in any gaps.
- The focus of the chapter is on regulatory decision-making, while the HTA topics will be revisited at a later stage.
- Members of the WG are invited to contribute by commenting or editing to make the chapter more comprehensive and expand the scope in terms of the regulatory geography.

Chapter 3: Real-world data and data sources

- WG members' comments to the Chapter 3 draft have been constructive and have not changed the overall direction of the chapter.
- Michele suggested adding discussion on the importance of access to and discussion with parties closest to data generation and processing to ensure appropriate use of the data elements. The discussion is most relevant regarding the employment of pre-existing data sources and is added to section 3.1.1. Healthcare databases.

Definitions of the terms

- As suggested by Kristina, a definition for the registry database has been provided. How detailed should we be, and should we define all databases, including claims, medical records, etc.?
- It was agreed to not provide detailed definitions, while elaboration of the term "registry" is justified due to its dual nature and various possible definitions. The remaining terms could be included in the glossary of the report.
- The presentation of terms should be done in a similar way throughout the report.

Data linkage and data fusion

- Information on linking the US claims databases and the National Death Index (NDI) was added to the draft. The linkage can be direct or in the form of a comparison/connecting, depending on the settings, registriers and databases being attempted to link. There are several databases or registries outside of public awareness, e.g. data linked to driving licences that contain eye health data.
- There are several issues to consider when directly linking data including confidentiality and ethical issues. Data fusion is a method that can use the estimated value of other data sources.
- An example of data fusion is using data from the cancer registry to determine the incidence per population, and then using data from the transplant registry to investigate whether the mortality rate of survivors is higher compared to the general population if they are long-term survivors after, for example, cancer or transplantation. Different data sources are used, but not exactly via data linkage.
- The aspects of direct data linkage and data fusion will be included in the draft. The concept of tokenisation should also be considered.
- For each database, the quality and trustworthiness of the data needs to be assessed, and this concept needs to be included in the draft. In Chapter 3, quality is discussed in all sections, e.g. in relation to the validity and limitations of databases in healthcare. Quality has a dual character that should be taken into account in the discussion.
- Laurie is invited to add a brief section on quality of data.

Including registry guidance

- US FDA registry guidance uses, "reliability", "relevance", "accuracy", "completeness", "provenance", and "traceability" instead of the term "quality", which may be relevant for the Chapter 3 draft.

- US FDA has recently published four guidance documents on RWD / RWE. In 2022, two more guidance documents will be published that are also relevant for the WG report (on externally controlled trials, and on trials and clinical practice settings).
- John shared a summary of recent US FDA guidance on RWD / RWE relevant for Chapter 3 draft.
- It was agreed that the draft will include all relevant guidance documents in order to be as exhaustive as possible and to provide readers with knowledge of the regulatory guidance documents available at the time of writing the report. WG members are invited to share relevant documents.
- Quality considerations for assessing databases are addressed in Chapter 4.
- Section 1.1.2 "Real world studies with ad hoc data collection" was complemented with a paragraph regarding the limitations of RWD sources with ad hoc data collection. All feedback is welcome.
- Information on Data Analysis and Real World Interrogation Network (DARWIN EU) was added to section 1.1.4 "Sentinel system".
- Juhaeri will send the draft of the chapter to Sanna for uploading to Google Docs. The WG is invited to provide feedback.

Chapter 4: Key scientific considerations in regulatory RWE generation

- Michele presented the updated Chapter 4 draft.
- The Chapter 4 team will continue addressing the comments on the draft, whereas there have been no major changes to the content.
- The WG members are welcome to comment on the scope of the information provided on bias, as there are documents such as the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which are referenced and provide a detailed description of the topic.
- The aim is to discuss to the most important forms of bias and their relevance for the WG report.
- The team suggested including confounding bias, information bias and selection bias with appropriate examples. The aim is to strengthen the text and not remove too much.
- Kateriina will send out a Doodle poll to help schedule the next meeting of the team for Chapter 4 in February.

Chapter 5: Ethics, governance, and related issues

- The chapter is currently too focused on Europe and would benefit from contributions from the perspective of different jurisdictions, e.g. the US, Canada, Japan, etc. to present a more global approach on legislation regarding data protection. Examples would illustrate and add value to the chapter.
- David S. will confirm with David T. if he would like to compile the answers to the questions on different jurisdictions beforehand.
- Experts from outside the WG could be approached with a request for input on the Chapter 5 draft.
- Monica will send David S. materials regarding the data protection legislation in Brazil.
- Yoshiko will send David S. materials on the relevant legislation regarding Japan.
- Laurie will forward a request from Davit S. to an ethics expert in CADTH who may be able to provide data for Canada.

- David S. will contact a law professor to discuss his possible contribution regarding the legislation in the US.
- The Chapter 5 team is planning to convene prior the next full WG meeting and Sanna will send out a Doodle poll to help schedule the meeting.

Addressing COVID-19

- Following a separate meeting regarding the inclusion of content on the COVID-19 pandemic, the WG agreed to not create a separate chapter on this and instead include a brief subsection in the introduction. Examples and case studies will be appended.
- The COVID-19 pandemic has accelerated certain processes involving RWD / RWE and has created a focus and pressure to maximise the use of data, nevertheless, the processes are not methodologically different from those used in the past.
- Heather agreed to draft a short paragraph on what could be included in the subsection in Chapter 1 and send it to the Chapter 1 team.

Glossary

- The WG agreed to include a glossary as a separate section to the report.
- The CIOMS Cumulative Pharmacovigilance Glossary is available as a resource when considering the terms for the glossary. Other relevant sources will also be considered.
- Relevant terms may be refined or redefined to specify their meaning in the report's context and objectives. Some terms need to be updated to correspond to the present situation.
- Chapter leads are invited to discuss with their teams and add to their glossary lists. Please provide the term, a proposed definition, and a reference – you can adopt an existing source, modify an existing definition, or formulate your own de novo wording.
- The terms and definitions will be made available to the WG before the next WG meeting.
- The Chapter 2 team has provided its terms for the glossary and they are available on Google Docs.

Future meetings and closing remarks

- We will schedule the next two-hour WG meeting for early April.
- Lembit concluded the meeting by thanking all WG members for joining and for their time and effort in progressing the WG's agenda.