Fourteenth 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

7 June 2022, Virtual Meeting

Meeting Minutes

Participants

Enrica Alteri (formerly European Medicines Agency), Yoshiko Atsuta (Japan Data Center for Hematopetic Cell Transplantation), Elodie Aubrun (Novartis), 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), Juhaeri Juhaeri (Sanofi), Laurie Lambert (Canadian Agency for Drugs and Technologies in Health), Jie Li (US Food and Drug Administration), Monica da Luz Carvalho Soares (Agência Nacional de Vigilância Sanitária, Brazil), Andrea Machlitt (Bayer), Manami Nomura (Pharmaceuticals and Medical Devices Agency, Japan), Takahiro Nonaka (Osaka Metropolitan University, Japan), Heather Rubino (Pfizer), Lembit Rägo (CIOMS), Anja Schiel (Norwegian Medicines Agency), David Shaw (University of Bern, Switzerland), Julia Wicherski (Bundesinstitut für Arzneimittel und Medizinprodukte, Germany), and David Wormser (Novartis).

Regrets

Laurent Azoulay (McGill University, Canada), Elodie Baumfeld Andre (Roche), Stella Blackburn (IQVIA), Mariette Boerstoel (AstraZeneca), 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), Michele Jonsson Funk (University of North Carolina, US), Cynthia de Luise (Pfizer), Miguel-Angel Mayer (Universitat Pompeu Fabra Barcelona, Spain), Mareike Millner (Maastricht University, Nertherlands), Monika Nothacker (Association of the Scientific Medical Societies, Germany), Daniela Rojas (Maastricht University, Netherlands), Andreas Rudkjoebing (World Medical Association), Julia Stingl (University of Aafchen, Germany), David Townend (Maastricht University, Netherlands), Rika Wakao (Pharmaceuticals and Medical Devices Agency, Japan), and Kristina Zint (Boehringer Ingelheim).

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 is at the final stage of editing and will be published soon.

- The CIOMS WG XIV on Artificial Intelligence in Pharmacovigilance held its 1st meeting with participants attending both in-person and virtually on 18-19 May 2022 in Geneva, Switzerland.
- The meeting agenda was adopted.
- Kateriina was rapporteur.

Progress updates and discussions on chapters

Chapter 1. Introduction.

- The introduction will be reviewed once the remaining chapters have been finalised.
- A paragraph summarising the key messages from each chapter will be added.
- The report uses the terms 'medical product' and 'medicinal product´, and the WG agreed to use 'medical product' throughout the report, as it encompasses the broadest meaning.
  [Post-meeting comment from Enrica: Sorry to insist, but if we use "medical product" because it has a broader meaning than medicinal, and then we exclude the devices, what is the term encompassing? It seems to me contradictory, and it contradicts definitions available elsewhere (EMA and FDA).]
- The term 'medical product' should be defined in the introduction and/or included in the glossary (if the report is to have one).
- Several jurisdictions currently use 'medicines' instead of 'drugs', and the report should follow this direction.

Including medical devices

- It was agreed to exclude a discussion on medical devices as this will not be the primary focus of the report. The WG does not possess specific expertise in this area to provide significant recommendations.
- Medical devices will be recognised as producing data and several of the principles discussed in the report could apply to any RWD / RWE, regardless of the source.
- The introduction will provide a list of medical products the report focuses on when providing principles and recommendations.

The definition of RWD

- Enrica suggested to not have the RWD definition sources in bold because they are not part of the definition. We should add a note about how RWD sometimes does not originate from routine clinical practice but from medical interventions, and not necessarily with the specific aim of collecting evidence on the medical intervention itself.
- Enrica has added comments to the chapter 1 draft and Sean will incorporate these.
- When defining RWD, we should use a term we think is correct and explain the reasons for the choice, taking into account the wider audience and not just experts.
- The WG will strive for the best possible definition as the field is constantly evolving. If necessary, explanations will be provided in the form of footnotes and/or glossary definitions.

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

- The chapter is in the process of being finalised.
- Sections will be added to address:

    - the scope and nature of inspections from a regulatory perspective;
    - transparency and disclosure of protocol; and
    - good pharmacoepidemiological and documentation practises.
- The section on 'Engaging with regulators' has been drafted. Thank you to Monica for adding the information on Brazilian Health Regulatory Agency (Anvisa).
- The chapter team would like to have a broader geographical spread regarding the guidelines and the acceptance criteria of RWD.
- Lembit agreed to contact the Australian regulatory authority for their input.
- There are sections of the chapter 2 draft that may be better placed in other parts of the report, e.g. the section on the external control arm could be moved to chapter 4 and the section on the STROBE checklist and GRADE framework to chapter 3. The Chapter 3 team will add the sections as an appendix and respective chapter teams are welcome to use them as they see fit.
- The conclusion and explanations on the terms used are being drafted.
- The WG members are invited to feedback the chapter draft.

Chapter 3: Real-world data and data sources

- Chapter 3 draft is nearly finalised and while some comments from WG members still need to be incorporated, the highlights of the chapter can already be used in the introduction of the report.
- Sanna provided the latest Google Docs link to chapter 3 and invited all to add comments to the online version of the chapter. [Post-meeting comment: this version turned out to be a wrong version of the chapter]. The team members provided comments using the document circulated by email; Juhaeri will review the draft chapter and send the revised document to Sanna and team members by email.
- The draft chapter includes a section on 'Healthcare databases' with a subsection on 'Real-world studies with ad-hoc data collection'. Solomon is welcome to propose suggestions on including the discussion on de novo data collection in Google Docs.

Chapter 4: Key scientific considerations in regulatory RWE generation

- Heather and Yoshiko have forwarded their newly drafted sections to Michele for feedback.
- Enrica felt that the discussions on estimand and the inclusion of ICH-E9 (R1) are too extensive. The ICH-E9 (R1) is a highly technical document; it could be cited as it contains principles that can be adapted to RWD. However, it remains essentially focused on clinical trials, and should be used only as an interesting concept that could potentially be adapted to RWD.
- The Chapter 4 team will continue progressing the draft.

Chapter 5. Ethics, governance, and related issues

- Chapter 5 is actively progressing and the draft is available on Google Docs. All WG members are urged to provide feedback so that the chapter team can proceed with the drafting.
- The following changes have been made:
    - The main questions at the start of the chapter have been slightly changed;
    - Several comments have been incorporated;
    - The section on the ethical arguments for the increasing use of RWD / RWE, including the efficacy-effectiveness gap (EEG), have been added;

  - David T. will add a section on data protection, while perspectives on legislation from Canada, Brazil, and the African Medicines Agency have already been incorporated.
  - A draft conclusion was added.
- The chapter team welcomes all suggestions on including the perspectives of different jurisdictions, in addition to those already mentioned, in order to create a more global approach to data protection legislation.
- David S. will send Lembit the questions so that he can forward them to his contacts in Australian Regulatory authority to include perspectives on the legislation on data protection.
- Enrica suggested including a more clearly focused mission statement in the context of the report. She elaborated on the chapter's added value in linking ethics and RWD / RWE, and suggested tackling the issues of data ownership and benefits to the research conducted.
- David S. added that instead of 'ownership of the data', he would prefer to use 'control over the processing of the data'.
- From an ethical perspective, is there additional benefit to using the data collected for other purposes?
- Lembit suggested referencing documents that have previously set the framework for research and ethics, e.g. the WMA Declaration of Helsinki, the Belmont report, and the CIOMS 2016 International ethical guidelines for health-related research involving humans.
- Given the increasing speed of data collection and the opportunities it creates, the report should focus on setting an ethical framework that would facilitate benefiting from RWD / RWE and prioritising the potentially valuable aspects over the restrictive settings that define boundaries and limitations.
- The chapter would benefit from providing recommendations.
- The position of the chapter within the report will be discussed at a later stage.

Executive summary and conclusion

- An Executive Summary will provide a brief and informative overview of the report and will be drafted as soon as the combined chapters document is available.
- Enrica volunteered to draft the Executive summary and WG members are welcome to join. The first draft will be circulated in late August or early September.
- The conclusion will be written in the light of the more mature chapters.

Public consultation

- The WG agreed to make the future draft report available for a six-week public consultation. This will also be an opportunity for the WG members to review the draft and provide their final comments. [Post-meeting comment from Enrica: We should publicise this opportunity in advance, so that organizations /individuals who want to comment can plan it ahead of time.]
- All comments received during the public consultation will be considered and the draft finalised for publication.

Editorial committee

- Jenni, Juhaeri and Sean have volunteered for the Editorial committee and more WG members are invited to join.

- Following the public consultation, the Editorial committee will be responsible for integrating the comments received into the report. If necessary, they will consult with chapter leads and the wider WG.

Scientific article

- David S., Juhaeri, Monica, and Sean have volunteered to write a scientific article to be published in a peer-reviewed, preferably open access journal. More volunteers are welcome.
- The article will help to raise awareness about the WG XIII's report publication.

Glossary

- Although previously the WG has not favoured including a glossary in the report, the chapter leads have listed several terms and definitions that would add value to the report, and to the wider field.
- Lembit encourages all to continue collecting the terms and definitions for a potential Glossary.

Agreed high-level timeline for completing the report

- By 22nd of June – The WG members to provide comments to the chapter leads via Google Docs or email.
- By 6th of July – Chapter leads to email updated chapters to Sanna.
- Early July – Sanna to combine and circulate the combined chapters.
- July-August – The WG to review the draft report, propose edits and comments.
- Late August / early September – The 15th CIOMS WG XIII meeting to be held.
  The WG to finalise the report content and issue a pre-warning / announcement via all WG networks about the approaching public consultation.
- October – Public consultation of the report. WG members to also review and provide comments in parallel.
- November – WG Editorial committee to address the comments received.
- End of 2022 – The report to be laid out and published, accompanied by a scientific publication in an open access scientific journal.

Future meetings and closing remarks

- [Post-meeting note: at the time of the 14th meeting, it was hoped that the 15th meeting might be held in-person in early September in Geneva, Switzerland. However, subsequent polling revealed that under 25% of the WG members would be able to travel to Switzerland at this time (probably due to pandemic travel policy restrictions), and therefore the 15th meeting will be held virtually.]
- Lembit concluded the meeting by thanking all WG members for their time and work.