# Seventeenth 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

**30 May 2023, Virtual Meeting**

## Meeting Minutes

### Participants

Enrica Alteri (formerly European Medicines Agency), Yoshiko Atsuta (Japan Data Center for Hematopetic Cell Transplantation), Mariette Boerstoel (formerly AstraZeneca), John Concato (US Food and Drug Administration), Gracy Crane (Roche), Andres Gomez-Caminero (Merck, Merck Sharp & Dohme Corp), Britta Haenisch (Bundesinstitut für Arzneimittel und Medizinprodukte, Germany), Sean Hennessy (University of Pennsylvania, US), Sanna Hill (CIOMS), Solomon Iyasu (formerly Merck, Merck Sharp & Dohme Corp), Juhaeri Juhaeri (Sanofi), Michele Jonsson Funk (University of North Carolina, US), Moriya Junji (PMDA), 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), Miguel-Angel Mayer (Universitat Pompeu Fabra Barcelona, Spain), Manami Nomura (Pharmaceuticals and Medical Devices Agency, Japan), Lembit Rägo (CIOMS), David Shaw (University of Bern, Switzerland), David Townend (University of London, UK), Shirley Wang (Harvard Medical School), Julia Wicherski (Bundesinstitut für Arzneimittel und Medizinprodukte, Germany), David Wormser (Novartis), and Kristina Zint (Boehringer Ingelheim).

### Regrets

Elodie Aubrun (Novartis), Laurent Azoulay (McGill University, Canada), Elodie Baumfeld Andre (Roche), Stella Blackburn (IQVIA), Thomas Brookland (Roche), Wim Goettsch (Utrecht Centre for Pharmaceutical Policy, Netherlands), Steffen Heß (Bundesinstitut für Arzneimittel und Medizinprodukte, Germany), Lu Hong (National Medical Products Administration, China), Alar Irs (State Agency of Medicines, Estonia), Cynthia de Luise (Pfizer), Takahiro Nonaka (Osaka Metropolitan University, Japan), Monika Nothacker (Association of the Scientific Medical Societies, Germany), Heather Rubino (Pfizer), Andreas Rudkjoebing (World Medical Association), Anja Schiel (Norwegian Medicines Agency), and Julia Stingl (University of Aafchen, Germany).

### Introduction

- Lembit gave some news regarding WG members:
    - We are pleased to welcome a new member: Shirley Wang, Associate Professor, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine Brigham and Women's Hospital, Harvard Medical School.

  - Solomon has retired from MSD, and although he continues to work with us, our new WG member at MSD is Andres Gomez-Caminero, VP, Epidemiology, Biostatistics and Research Decision Sciences.
  - Rika has left PMDA and she has been replaced at the CIOMS WG XIII by Moriya Junji, a deputy director of Advanced Science and Technology Division, at the Office of Research Promotion.
  - Stella has retired from IQVIA but continues to work with us.
- The CIOMS WG XII's report on *Benefit-Risk Balance for Medicinal Products* is at a similar stage of readiness as the WG XIII's report and will soon begin its Public Consultation.
- The CIOMS WG on *Severe Cutaneous Adverse Reactions to Drugs – SCARs* has a draft report expected to begin its Public Consultation in the autumn 2023.

## Progress updates and discussion on Abbreviations

- The Brazilian Health Regulatory Agency (ANVISA) title is to be written without the article.
- In terms of abbreviations, the Preface, the Executive summary, and the rest of the report all function as stand-alone units.

## Progress updates and discussion on new items

**Preface**

- We softened the phrase "This evidence has almost always taken the form of RCTs" by changing it to "has usually taken the form".
- To give historical accuracy, we added the underlined text to: "regulatory agencies have for many years accepted what we now call real-world evidence (RWE) derived from data".

**Executive summary**

- The Executive summary copies and brings together elements from the various chapters. There was a discussion about whether it was acceptable for readers to recognise the same phrasing as is used in the chapters themselves. It was agreed that this had been talked about upfront, done intentionally, and therefore is fine.
- The technical chapters are synthesised lightly. There is more content on the ethics chapter as it has elements that are novel to the field. This chapter highlights how we should not forget that the technical and regulatory advances come in an ethical frame.
- Feedback was received via email in advance of the meeting from Enrica, Kristina and Andrea on the Executive summary, and on the rest of the report thereafter, and the feedback was inserted into the master document ahead of the meeting.
- At line 184, we softened the phrase "(RCTs) were considered to be the only valid evidence for evaluating …" by changing it to "the preferred source of evidence".
- At lines 227-230, we discussed adding underlined text for completion to the effect of: "a continuous process that includes consideration of the therapeutic context, including the target population with a given disease or condition, the available therapies, the unmet medical need, and the outcomes of the main studies".

## Progress updates and discussion on chapters

- There was a suggestion to provide key points at the start of each chapter but if was felt this should have been planned for from the beginning. It takes time to do this properly. It was decided to not draft key points for the time being.

**Introduction**

- At line 430, we softened the phrase "the only valid evidence for evaluating …" by changing it to "the preferred source of evidence".
- Line 455, we added the underlined text for accuracy to: "Another limitation is that RCTs are designed with sufficient sample size to assess efficacy, and thus may not have enough statistical power to detect uncommon safety issues. To detect such safety issues in the real-world setting and address them appropriately, studies utilising real-world data (RWD) are needed. "
- It was agreed that some more content would be added on ethics. The Executive summary gives comparatively more content on ethics and currently the Introduction is not in proportion to this.
- In the Introduction, we should be explicit about how investigational products cannot generate RWD (relevant to the product, yes, but on the product no), and this is why until now, RWD has been almost exclusively related to safety issues. These days, RWD is being used increasingly for ameliorating how we can gather evidence on investigational products. However, some exceptions to this are: compassionate use / expanded access / investigational unapproved products.

Chapter 1. Uses of RWE in the regulatory process during the product lifecycle

- Line 684, we introduce a recommendation for one stakeholder but not for others: "We recommend that RWE be included in the effects table as well as data from RCTs." Should we have recommendations systematically for all stakeholders?
- At line 720, there is another isolated near-recommendation: "More transparent planning and use of RWD would be beneficial for improved coverage decisions".
- There are 40 instances of recommendations in the report.
- The sub-title "Pharma company / MAHs" was expanded to: "Pharma companies, MAHs, and other product developers". The reasons was because some organisations/companies – Sponsors or Applicants – never receive a Marketing Authorisation but they still conduct studies.

Chapter 2: Real-world data and data sources

- The OMOP CDM version 6.0 was changed to version 5.4 as version 6.0 is still under development and is currently not recommended. Link to be implemented.
- At line 1551, Miguel-Angel will propose text to replace this sentence in order to improve accuracy: "As in the case of ENCePP, in DARWIN EU system the databases are analysed separately without CDM". It is interesting to compare EnCePP and DARWIN EU.
- Miguel-Angel proposed sending some short sentences on the EHDEN project for consideration for addition into Chapter 2.
- The following sub-titles edits were made:
    - 2.1.1 "Pre-existing health care databases" became: "Health care databases"
    - 2.1.2 "RWD with ad-hoc data collection" became: "Ad-hoc data collection"
    - 2.1.3 "Sentinel systems" became: "Federated systems"

- 2.1.4 “Other traditional sources” became: “Other sources”

Chapter 3: Key scientific considerations in regulatory RWE generation

- We have defined RWD and RWE but in places we seem to use the terms interchangeably. This needs to be reviewed for correct usage. Two examples were given:
  - Line 2374: “When addressing the use of RWE it is important to realise that assessment of systematic error (bias) is a key element of any study that aims to evaluate a possible treatment effect of a medicinal product.”
  - Line 2384: “An underlying assumption of RWE studies is that there is no unmeasured confounding.”
- Not all RWD will lead to RWE.
- In the context of the pandemic, and in the US in particular with a focus on race/ethnicity/racism, there is an opportunity to highlight the handling of race and ethnicity in studies where we are trying to generate RWE and help elevate those data. Michele proposed adding a brief section on how important effect modifiers (biological sources of differences) should only be considered in safety and effectiveness studies if there is a strong underlying reason to do so. That sort of flawed logic in these sort of studies is still very common.
- At Line 2318, should the sub-title “Non-randomised single arm trials using external RWD controls” be changed to “Single arm trials using external RWD controls”?
- John will send an updated Figure 4.
- Solomon questioned if outcome definitions are covered sufficiently in the report and this content was not located during the meeting. [Post-meeting note: there is a section on outcome definitions in Chapter 3 starting at line 1942.]

Chapter 4: Ethical and legal issues in using real-world data

- We would expect a good amount of comments from the Public Consultation.
- At line 3441, the underlined were edited for clarity: “There is an urgent need for guidance from the regulators, and for regulators to come together to harmonise that guidance” to: “There is an urgent need for principles from the regulators, and for regulators to come together to harmonise the approach taken”.
- The Sub-title “Conclusion” may be better re-named as “Summary” in order to differentiate it from the Chapter 5 title: “Conclusions and future directions”.

Chapter 5: Conclusions and future directions

- This chapter will bring together the concluding remarks from all the chapters. At the moment, some chapters have conclusions and some don’t. We do not yet have the content from Chapter 3 on methods and so this is still work in progress. We also need to work on the style, remove the sub-headings (i.e. Ch. 1, Ch. 2, conclusion, recommendations etc.), and work on the transition sentences.
- This chapter will be completed in time for the Public Consultation.
- Michele will draft the Chapter 3 content towards this chapter.

## Progress updates and discussion on case studies

- Each case study should include a note about where the protocol was registered. This information can be added during the Public Consultation, if it is not available before.
- The case studies from PMDA have been approved for inclusion in the Public Consultation:
    - E. Cardiovascular risk of urate-lowering drugs: a study using the National Database of Health Insurance Claims and Specific Health Check-ups of Japan;
    - F. Nested case-control study utilising MID-NET® on thrombocytopenia associated with pegfilgrastim in patients treated with antineoplastic agents.
- The case study from Sanofi is waiting for legal clearance and so will not be included in the Public Consultation:
    - G. Cancer incidence among those initiating insulin therapy with glargine versus human NPH insulin.

## Public Consultation process

- Once the report has been made available for Public Consultation, CIOMS will liaise with its own stakeholder contacts (e.g. IFPMA, EFPIA and ISPOR), including regulatory networks (e.g. ICMRA), industry associations, and academic organisations.
- The WG members are requested to help raise awareness within their companies/organisations, partnerships, networks, and channels (e.g. socials media).

## Any other business

**Editorial Committee meeting**

- The next Editorial Committee meeting is scheduled for the 2nd of June 2023 and this meeting will need to be extended in view of the great amount of feedback received. All proposed new text, figures etc. should be sent in for before then.
- The next full WG meeting will be held in-person on the 4th and 5th of October 2023 in Geneva, Switzerland. The venue and other details will be confirmed soon.
- At this next WG meeting, we will be able to discuss implementation activities, such as organising a webinar to promote the WG XIII report and publishing a scientific article in an open access journal on the topic of the report.
- Recently, in the context of the Editorial Committee meetings, an abstract was submitted for the DIA RWE Conference in Baltimore US, scheduled for 16-17 October 2023, via David Martin, member of the Steering Committee. We have not heard back and so it seems we were perhaps too close to the deadline.
- Laurie is on the Committee at the DIA Annual Pharmacovigilance Meeting scheduled for January 2024 and could help to facilitate a topic/session there.