Sixteenth 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

5 December 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), Britta Haenisch (Bundesinstitut für Arzneimittel und Medizinprodukte, Germany), 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), Lembit Rägo (CIOMS), Heather Rubino (Pfizer), Anja Schiel (Norwegian Medicines Agency), David Shaw (University of Bern, Switzerland), David Wormser (Novartis), and Kristina Zint (Boehringer Ingelheim).

Regrets

Laurent Azoulay (McGill University, Canada), Elodie Baumfeld Andre (Roche), Stella Blackburn (IQVIA), Mariette Boerstoel (AstraZeneca), Thomas Brookland (Roche), Gracy Crane (Roche), Wim Goettsch (Utrecht Centre for Pharmaceutical Policy, Netherlands), Steffen Heß (Bundesinstitut für Arzneimittel und Medizinprodukte, Germany), Sean Hennessy (University of Pennsylvania, US), 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), Andrea Machlitt (Bayer), Miguel-Angel Mayer (Universitat Pompeu Fabra Barcelona, Spain), Mareike Millner (Maastricht University, Nertherlands), Manami Nomura (Pharmaceuticals and Medical Devices Agency, Japan), Takahiro Nonaka (Osaka Metropolitan University, Japan), 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 (University of London, UK), Rika Wakao (Pharmaceuticals and Medical Devices Agency, Japan), and Julia Wicherski (Bundesinstitut für Arzneimittel und Medizinprodukte, Germany).

Introduction

- On 15th of September, CIOMS published the CIOMS Cumulative Glossary with a focus on Pharmacovigilance (Version 2.0).
- On 26th of September, CIOMS published the Glossary of ICH terms and definitions.

Progress updates and discussion on chapters

Some chapter teams needed longer than previously anticipated to finish their work due to busy workloads and illness.

Chapter 1. Introduction.

- This chapter is being fine-tuned as the other chapters mature.

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

- This chapter was finished in November.

Chapter 3: Real-world data and data sources

- This chapter was finished in September.

Chapter 4: Key scientific considerations in regulatory RWE generation

- Michele and the Chapter 4 team delivered an extremely thorough chapter that is roughly 80-90% finished, and Michele now has a high workload that prevents her from taking the chapter to its completion. Others from the Chapter 4 team have not been able to volunteer to lead the team.
- Initially the Editorial Committee members Juhaeri and Sean were going to finish the chapter, with help from Yoshiko who has been with Chapter 4 from the start, but this is not ideal as Juhaeri and Sean are new to the chapter.
- The new plan is for Juhaeri and Sean to review Chapter 4 over the holidays (December – January) and share a revised version in January for John to review in turn. Solomon and Yoshiko can help if needed e.g. by providing commentary in places. John, Solomon and Yoshiko were in the original Chapter 4 team.
- The type of work needed includes fleshing out a few bullets, condensing text in places, and perhaps moving text to an appendix, if appropriate.

Chapter 5: Ethical and legal issues in using real-world data

- Some WG members made more language edits to the chapter, which have been addressed by David S.
- David T. is working on the terminology and will complete this by Friday 9th of December. If there are any further delays, David S. will help to complete the chapter.

Other topics

Mismatch in charge v. draft

In the original Concept Note, the charge we were given was to provide instructions on how RWE is to be used in regulatory decision making, whereas our draft does not go into a great amount of detail in answering this question. For example, the five FDA papers detail the timing, the drug development, the type of disease, etc, and we do not provide that degree of depth in our draft.

Discussion

- At this stage, we could add a justificatory paragraph about why we have diverged.
- This topic is going to continue to evolve and each case will be specific. The only way would be to cite examples.

- This is a sensitive issue and we can only give information as far as the WG members are willing do so. Lembit invited the regulators to give their views:
    - Britta (representing both a regulatory agency and academia): This is difficult. It is on a use case-basis. You need to carry out special analysis on this kind of data. You cannot have an overall toolbox. As part of the Horizon Europe project, we will develop new methods for RWD analysis e.g. including Artificial Intelligence methods. This is work-in-progress in most cases.
    - John: The topic is not too sensitive. The questions are about the fitness of the use of the data, the adequacy of the study design, the appropriateness of the conduct of the study itself. We cannot provide an exact "How to" guide. We should explain what we did and why we did it. Regulators are willing to consider RWD but often the data is unavailable.
    - Enrica: We should ask if our draft is adding value. Enrica feels it is. It gives a landscape of things to consider when addressing the use of RWD for regulatory decision making. It is a systematic approach of what you need to do and think about. One differentiator for our report is the ethical standards we provide.
- Juhaeri – There is no mismatch. The Concept Note mentions "harmonisation and ethics standards for RWE in regulatory decision making" but this does not mean we have to have a clear prescription. What we have is good enough. The key is to have more granular guidance on methods, regulatory perspective, databases, etc. Our draft is very detailed. For safety (and more), RWD has been used for a long time, e.g. ISPE provided guidance since 2004.
- Heather – The target moved as a result of lots of conversations with the right people around the table, and what we have written is more important.
- Anja – As Guido Rasi, Former Director of the EMA, said: regulation follows the science, not the other way round. The science is not yet there, hence we cannot give regulatory conclusions or advice or full guidance. From experience in the EMA context, examples can be tricky. We put them in because we don't have real guidance; and they can be misinterpreted and misused afterwards. It would be better to keep to the principles without explicitly putting something forward as the gold standard, because this is how people tend to read examples. If the science has not progressed to the extent where we can give firm guidance, that is a simple thing we can state in the report, it's not a problem that we don't have the material to come up with the conclusive guidance. We shouldn't be afraid of stating that we are not yet there. This is maybe coming too early for that. We may need to update at a later date when the science has caught up.

World Evidence-Based Healthcare Day

- CADTH held a webinar on RWE where Laurie and Anja presented; and Anja provided a brief overview to the WG.
- CADTH's Chief Scientist, Nicole Mittmann, moderated the session with content on:
    - National Institute for Health and Care Excellence (NICE);
    - Aetion Evidence Platform;
    - International Society for Pharmacoeconomics and Outcomes Research's (ISPOR) RWE Group;
    - RWE demonstration done with NICE and Integrated Scientific Advice (ISA) in the US;

    - Patient Preference data;
    - Laurie talked about the International Collaboration Programme at CADTH.
- There was interest in the CIOMS WG XIII draft report Public Consultation. Laurie offered the CADTH Symposium on 16-18 May 2023 as a place to promote the Public Consultation, if the timing were to be right.

Implementation phase

- CIOMS encourages its WG members to present at e.g. DIA meetings even before concluding the drafting process.
- Just before the WG publishes its report, we usually form an implementation subgroup of volunteers. The deliverables of this group would typically include:
    - Scientific article to be published in a scientific journal,
    - Webinar – hosted alone or in partnership with another organisation,
    - Slide set for the WG to use – going forward, when a slide set is compiled, it will be shared with the WG for review and comment in advance of its use. This will ensure transparency, efficiency and consistency.

Case studies

- Several CIOMS reports have had 2-3-page long case studies in appendices and they are usually much appreciated by readers. Placed in the appendices, several chapters can make cross-reference to them where appropriate.
- The following case studies are planned:
    - **Academic perspective: Miguel-Angel:** The European Health Data Evidence Network (EHDEN) of the Innovative Medicines Initiative and the H2020. Using the standards of OMOP-OHDSI, the idea is to make large-scale analysis of health data around Europe and worldwide to generate insights and evidence from Real World Health Data to support healthcare organizations and the pharmaceutical industry in understanding diseases, treatments and new therapeutics.
    - **Industry perspective: Elodie and Gracy**: Numerous case studies from Roche where we have used RWE to support regulatory decision making in the context of new license applications or supplemental/line extension applications - both trying to support decisions around safety but also efficacy, and across therapeutic areas e.g. oncology but also neuroscience for example.
    - **Regulatory perspective: Enrica**: Following a quick search, it seems all publicly reported EMA case studies are already included in the report however Enrica will have another look. Case studies from other regions are welcome too.
    - Others are welcome to contribute case studies. Please get in touch.
- Sanna will put together a template for the Editorial Committee's review, and this will then be provided to the case study writers to ease their writing task.
- [Post-meeting note: in light of Anja's comments about the risk of case studies being misinterpreted, we could add a note with the case studies to always refer to the principles provided.]
- Many comments were made with reference to the case studies:

- There are many publications in this area and any case study needs to be chosen well.
- The pandemic has initiated many studies that are still ongoing, and although interim results may have been presented at conferences, a peer-reviewed publication process may not have been completed yet.