



**Third 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**

**19 August 2020, Virtual Meeting**

## **Minutes**

### **Participants**

Yoshiko **Atsuta** (Japan Data Center for Hematopoietic Cell Transplantation), Elodie **Aubrun** (Novartis), Laurent **Azoulay** (McGill University), Elodie **Baumfeld Andre** (Roche), Michele **Jonsson Funk** (University of North Carolina), Sean **Hennessy** (University of Pennsylvania), Steffen **Heß** (Bundesinstitut für Arzneimittel und Medizinprodukte), Sanna **Hill** (CIOMS), Alar **Irs** (State Agency of Medicines, Estonia), Akihiro **Ishiguro** (Pharmaceuticals and Medical Devices Agency, Japan), Solomon **Iyasu** (Merck, Merck Sharp & Dohme Corp), Juhaeri **Juhaeri** (Sanofi), Andrea **Machlitt** (Bayer), Robertino **Mera** (Gilead), Lembit **Rägo** (CIOMS), and David **Wormser** (Novartis).

### **Regrets**

Enrica **Alteri** (former EMA), Stella **Blackburn** (IQVIA), Thomas **Brookland** (Roche), Monika **da Luz Carvalho Soares** (Agência Nacional de Vigilância Sanitária), Elisa **Gomez-Reino** (Alexion), Britta **Haenisch** (Bundesinstitut für Arzneimittel und Medizinprodukte), Lu Hong (National Medical Products Administration, China), Miguel-Angel **Mayer** (Universitat Pompeu Fabra Barcelona), Andreas **Rudkjoebing** (World Medical Association), and Kristina **Zint** (Boehringer Ingelheim).

### **Alternates**

Kinue **Nishioka** and Daisaku **Sato** (Pharmaceuticals and Medical Devices Agency, Japan).

### **Introduction**

- Lembit Rägo, Secretary General, CIOMS, welcomed the WG members and chaired the meeting.
- Prior to the meeting, the three subgroups proposed their overviews for the working group report; one new subgroup merged the content into a single overview, and a draft common outline was distributed to the full WG for their consideration.
- The meeting objective was to finalise the merged overview.

### **Discussion**

#### **Merged overview**

- Alar presented the merged overview by walking through the draft common outline.
- The weightings of the different sections are expected to become apparent with the first draft and can then be adjusted as work progresses.
- We may choose to focus on where existing documents have left gaps.

- CIOMS WG timelines can depend on the WG dynamics but we will aim for a preliminary draft by the end of 2020.

### **Health Technology Agencies (HTAs)**

- Covering this subject in detail would require inviting substantially more specialists to the WG.
- Lembit is currently seeking two HTA professionals with regulatory backgrounds to join the WG.
- We can expect to touch on certain commonalities with HTA but we cannot cover its specific needs. We can include challenges and opportunities identified.
- Andrea proposed striving for sufficiently rigorous criteria in conducting studies so that results could satisfy multiple industry participants. Just as safety issues need to be reported, it would be helpful if effectiveness data could also be shared. For example, such data could be used to extend an indication to a subpopulation that had not been included previously. At the moment, extra information is disregarded or not considered robust enough.

### **Ethical issues**

- Covering this subject would require inviting more specialists to the WG.
- The WG member, Andreas Rudkjoebing from the World Medical Association, is a specialist in related ethical aspects but lately his time seems to have been taken with Covid-19 commitments.
- Lembit will also approach appropriate ethicists who CIOMS has worked with in the past.
- Ethical issues can be drafted at a later time and addressed in a separate chapter or an appendix.
- Some existing documents in the field and fora can be referenced, even if we do not add more content of our own, and we can explain some of the shortcomings and challenges that have not been addressed to date. We may be able to make some recommendations of our own.
- Regarding randomised controlled clinical trials, the ethical framework is more established and probably easier to deal with, but there are issues with the use of non-randomised healthcare data. In addition, in Europe, there seems to be over-regulation especially around personal data protection. In terms of RWD, the majority of the ethical aspects concern:
  - The ownership of the data;
  - Who can benefit from the data;
  - How the benefits can be shared with owners of the data;
  - Can the benefits ever be shared with the owners of the data?
- Robertino feels we ought to address the sale and possession of tokenised healthcare data, which is particularly topical in the US. This refers to using anonymised, longitudinal healthcare data from all sources. Tokenised data is very helpful for investigators but many patients are unaware of the practice.
- The issue of tokenised healthcare data combines both ethical and legal issues, and would need to be discussed in the context of different healthcare systems and regulatory systems.

### **Safety testing**

- Safety testing should be mentioned concisely, providing references where helpful, but the focus of the report should be mostly on efficacy testing.
- Juhaeri mentioned there is a thin line between safety and effectiveness and it can depend on which drug is in question. When talking about insulin, malignancy may be a safety issue, but when talking about oncology products, the same malignancy may be a matter of effectiveness.
- Andrea added that sometimes outcomes become safety events and vice versa. To be able to discuss benefit-risk balance, we need to emphasise both sides of the equation. In the post-marketing space, RWD on safety is largely accepted, whereas during development, in the context of synthetic control arms, RWD on safety assessment may still be questioned.

- Juhaeri said we should be as inclusive as possible and acknowledge spontaneous reporting, e.g. FDA Adverse Event Reporting System (FAERS) and WHO's VigiBase, and even channels such as social media, even if we do not discuss them at length.
- Lembit agreed as these spontaneous reporting systems were until recently the major sources of signals. They need to be given due reference. Perhaps RWD can be integrated with spontaneous reporting to build a whole picture.

### **Covid-19**

- It was suggested that Covid-19 be covered by way of a case study in an annex, e.g. on the Surgisphere paper retraction and/or the Lancet retraction, to demonstrate the use/misuse of data. Solomon offered to be part of a team on data quality and integrity issues, perhaps centered around the *New England Journal of Medicine* position paper.
- Robertino mentioned close collaboration between the FDA and pharmaceutical companies working on multiple sources of RWD. The project, named "Accelerator Covid-19", involves bringing together seven different datasets from various US states, conforming to the same protocols. It provides advice on involving multiple data sources, carrying out sensitivity analysis, and reporting on the lessons learned. Robertino is close to the project and will ask informally for permission in the hope that we could advance in parallel.

### **Distributed networks**

- Laurent suggested including the topic of distributed networks, e.g. Sentinel in the US and Canadian Network for Observational Drug Effect Studies (CNODES), which were set up at the request of regulatory agencies to address mainly safety questions. This topic ties in with issues such as dealing with multiple datasets, concepts of replication, statistical power, ethics, access to data, data harmonisation, and data quality.
- Solomon agreed. Most of the Big Data analytics will be dependent on having multiple datasets that may be heterogeneous, i.e. from different data environments, and putting them into a common data model to be able to analyse them at the site (like Sentinel and CNODES do), and the aggregated data is analysed for decision making. Heterogeneity is a big aspect of the evaluation. See also Observational Medical Outcomes Partnership (OMOP) data model.
- Michele suggested that the National COVID Cohort Collaborative (N3C) initiative, which pulls data from across multiple US health systems and transforms that into the OMOP common data model, could form another Covid-19 case story. This is a National Institutes of Health (NIH) initiative but the data is open and available to researchers across industry and academia.
- Elo reflected that many of these initiatives, e.g. Sentinel, started with a focus on safety but are all evolving towards addressing efficacy.
- Lembit suggested dedicating an appendix to working with diverse datasets as this is an interesting, current hot topic.
- Solomon was involved with Sentinel at its inception and related that there were different data holders from different systems, and the key hurdle with bringing them together was around the governance of the distributed data. The rules, structure and policy had to be worked out before concerns over quality issues etc could be discussed. Distributed data systems and analysis is going to be so integral to the future that he feels it has to be part of the main chapter.
- Andrea added that EMA connects into CNODES too. Andrea has an example of a multi-site database study for safety perspectives. She understands this was also run as a methodology experiment, and that to some extent, it may also count towards an effectiveness assessment.
- It was agreed that distributed networks would go under chapter 3 or 4 and that aspects of the subject would be covered under other chapters too if needed. In a distributed data system, the analysis would be distributed too.

### **Data source and quality, and fitness for purpose**

- There seems to be some duplication across Chapter 3 and Section 4.4.
- Most content is to be covered in chapter 3.

### **Next steps**

- It was agreed that WG members would volunteer for chapters 1-4 according to their individual strengths, giving their 1<sup>st</sup> and 2<sup>nd</sup> choices, for use in the event that some chapters attract too many volunteers and others too few.
- During draft revisions, everyone will have an opportunity to contribute to all subjects.
- Chapter 5 will be left for a later time once we have more information.
- As everyone writes towards their chapter, they are encouraged to note ideas for the next steps chapters and ethical issues.
- Lembit encouraged all to share background materials and their drafts, which can be placed on the shared CIOMS web pages.
- Solomon mentioned a number of papers in the US setting he is involved with:
  - International Society for Pharmacoepidemiology (ISPE) Task Force on RWE  
Whitepapers on:
    - External controls;
    - Comparative studies;
    - Validation procedures for RWE studies;
  - Framework whitepapers by the Duke-Margolis RWD Initiative.
- Alar suggested that some WG members may get started with drafting case studies even if they would fit under other chapters than their own.

### **Any other business**

- The Covid-19 situation permitting, the now mature WG overview will help towards inviting North American regulators to join the WG, even if at a later date.
- Lembit is open to receiving recommendations especially regarding recruiting US regulators. He has one ex-EMA person in mind based in the UK.