



Eighteenth meeting of the CIOMS Working Group XIII: Real-World Data and Real-World Evidence in Regulatory Decision Making

4-5 October 2023, Geneva, Switzerland

Meeting Minutes

In-person participants

Enrica Alteri (formerly European Medicines Agency), Yoshiko Atsuta (Japan Data Center for Hematopoietic Cell Transplantation), Elodie Aubrun (Novartis), Elodie Baumfeld Andre (Roche), Stella Blackburn (formerly IQVIA), Andres Gomez-Camirero (Merck, Merck Sharp & Dohme Corp), Sanna Hill (CIOMS), Alar Irs (State Agency of Medicines, Estonia), Michele Jonsson Funk (University of North Carolina, US), Juhaeri Juhaeri (Sanofi), Monica da Luz Carvalho Soares (Agência Nacional de Vigilância Sanitária, Brazil), Andrea Machlitt (Bayer), Heather Rubino (Pfizer), Lembit Rägo (CIOMS), Julia Wicherski (Bundesinstitut für Arzneimittel und Medizinprodukte, Germany), and Kristina Zint (Boehringer Ingelheim).

Virtual participants

Mariette Boerstoel (Bristol-Myers Squibb), John Concato (US Food and Drug Administration), Gracy Crane (Roche), Britta Haenisch (Bundesinstitut für Arzneimittel und Medizinprodukte, Germany), Sean Hennessy (University of Pennsylvania, US), Jie Li (US Food and Drug Administration), Laurie Lambert (Canadian Agency for Drugs and Technologies in Health), Miguel-Angel Mayer (Universitat Pompeu Fabra Barcelona, Spain), and David Shaw (University of Bern, Switzerland).

Regrets

Laurent Azoulay (McGill University, Canada), Thomas Brookland (Roche), Wim Goettsch (Utrecht Centre for Pharmaceutical Policy, Netherlands), Steffen Heß (Bundesinstitut für Arzneimittel und Medizinprodukte, Germany), Solomon Iyasu (formerly Merck, Merck Sharp & Dohme Corp), Moriya Junji (Pharmaceuticals and Medical Devices Agency, Japan), Lu Hong (National Medical Products Administration, China), Cynthia de Luise (Pfizer), Takahiro Nonaka (Osaka Metropolitan University, Japan), Manami Nomura (Pharmaceuticals and Medical Devices Agency, Japan), Monika Nothacker (Association of the Scientific Medical Societies, Germany), Andreas Rudkjoebing (World Medical Association), Anja Schiel (Norwegian Medicines Agency), and Julia Stingl (University of Aachen, Germany), David Townsend (University of London, UK), Shirley Wang (Harvard Medical School, US), and David Wormser (Novartis).

Introduction

- Lembit welcomed the Working Group (WG) members and provided updates regarding other CIOMS WGs:
 - The [Good Governance Practice for Research Institutions](#) WG is preparing to publish its report in the coming months;



- The [Working Group XII – Benefit-Risk Balance for Medicinal Products](#) carried out its Public Consultation in June-July 2023 and is working through its comments;
- The [MedDRA Labelling Groupings](#) WG is finalising its draft;
- The [Severe Cutaneous Adverse Reactions to Drugs – SCAR](#) WG is finalising its draft;
- The [Recommended Standards of Education and Training for Health Professionals Participating in Medicines Development](#) WG is still in the stage of drafting the first draft, slower than expected progress;
- The [Working Group XIV – Artificial Intelligence in Pharmacovigilance](#) started in May 2022 and is working on its report content;
- The Working Group XV – Harnessing the potential of pharmacoepidemiology for public health will be launched during 2-3 November 2023.
- Potential topic area for WGs starting in Q1 2024 include *Long-term safety monitoring* and *Microbial resistance*. CIOMS always welcomes suggestions for new topics from all stakeholders.

Update from Editorial Committee on the Public Consultation

- The Editorial Committee includes WG members representing regulators, academia and pharmaceutical industry; and has had 21 meetings (plus associated homework).
- The Editorial Committee's work process is to work in track changes, all responses to comments are logged and will be made accessible to the WG members, and the WG will get to approve the report before the final publication.
- The nature of the editorial work has included addressing: 1. Repetitions, 2. Depth (Is the text too narrow or deep in places?), and 3. Scope/Direction (Where are we going?). Sean has focused on the Preface-Executive summary-Introduction, Jenni has focused on Chapter 1, Juhaeri has focused on Chapter 2, and Yoshiko has focused on Chapter 3. Chapter 5 will require separate attention.
- David T and David S continue to work on Chapter 4.
- The WG XIII received 900+ comments including 519 public comments and 382 peer comments i.e. from colleagues of WG members. This is very positive and shows there is great interest for the report.
- All the comments and proposed edits from Solomon's and other WG members received in May are being considered at this time.
- As some commentators have requested to not be named, the company/organisation names will not be listed here as these minutes will be for public use. WG members are welcome to contact the CIOMS Secretariat for a full list.
- The commentators' locations included: Australia, Belgium, Canada, France, Germany, India, Japan, Netherlands, Norway, Singapore, Sweden, Switzerland, UK, and US.
- Questions received during the Public Consultation included the following:
 - Q: Does CIOMS publish the Public Consultation comments or how they were dealt with?
A: No, but CIOMS will be prepared to respond to queries regarding how the Public Consultation comments were handled and for this reason we keep records.
 - Q: What does it mean to be listed as a commentator?
A: In an appendix of the report we list the commentators unless the commentator has specifically requested to not be listed.



- Public Consultation comments are provided for the WG's consideration and yet occasionally commentators express dissatisfaction that their comments have not been implemented. The Editorial Committee has conducted a thorough, conscientious and fair process; consulting the full WG where necessary, and therefore it is confident with its decision making.
- CIOMS has carried out Public Consultations with the following previous reports:
 - [International ethical guidelines for health-related research involving humans \(2016\)](#);
 - [Clinical research in resource-limited settings \(2021\)](#);
 - [Patient involvement in the development, regulation and safe use of medicines \(2022\)](#).

Discussion on the report

The version of the draft report in use at the meeting was entitled "CIOMS WG XIII_01Oct2023", as circulated on Monday 2 October 2023 (available on the WG website members only section).

Preface

- There were no comments to discuss relating to the Preface.

Executive summary

- Once the report has been revised, we will revise the Executive summary accordingly; some comments may become redundant.

Introduction

- How do we motivate the need for RWE?

Several commentators said the report is too pro-RWE and anti-RCT. We give the motivation for RWE as based on 1) the limitations of RCTs and 2) due to ethical and practical reasons RCTs are not always feasible. We would like to reverse the order of emphasis and discussion: 1) there are circumstances where we cannot use trials, and 2) limitations of trials e.g. the non-representativeness and size (which are not inherent elements of trials as trials can be more or less representative and bigger or smaller).

 - Increase emphasis on places where trials are not feasible and reduce the emphasis on the limitations of trials throughout the report. This seems consistent with regulatory expectation: a trial will be done unless it is infeasible. All Editorial Committee chapter leads, and Chapter 4 leads, need to switch this emphasis.
 - Mention the utility of using RWE to expedite development and have relevant drugs sooner to patients. For someone with medical needs, this is also a motivator to use surrogate arms etc. It is part of the limitation of trials. Mariette will re-read and draft something if she feels text can be added. In the same way, we don't want to only position RWD to when we cannot do clinical trials. The Roche case study relates from the pandemic time when Covid-19 tests generated a lot of data and the idea was launched as to how to make use of the data in conjunction with the small clinical trials done at the time in the context of the totality of evidence approach.
 - Bring out the advantage of using RWE throughout the report also in areas such as rare diseases and long-term follow up (long-term safety and effectiveness). This will bring a positive tone away from competing with trials.



- Be impartial, highlight the importance of RWD without blaming RCTs. List the trials where it cannot be done. We will always have to do trials except when it is not feasible.
- Whether a trial is feasible or ethical is a deeper topic, the advantage of RWE is almost self-evident. We don't have to go too deep into this.
- Get away from the impression that RCTs are always the gold standard. We know that is not always the case. In the same way we know that RWE is not inferior. The balance is shifting but we shouldn't go too far.
- Certain limitations do exist, such as we can only conduct a safety study on a drug in the real world once it has been approved, before approval, the gold standard is clinical trials. There was slight disagreement as to whether approval is needed in order to address safety issues.
- If the clinical trials yielded the information that we wanted, we wouldn't need the post-authorisation safety study, but gaps exist and additional risks need to be quantified. That's not a criticism on the clinical trial. Investment in RWE studies do not preclude investment in stronger clinical trials.
- Even in development, RWD can be used to study the natural history of disease, what to expect in terms of the rate of events and class effects.
- The way medicine is going, we no longer have broad categories and everything is going to become a rare disease. It will become increasingly difficult to carry out the number of clinical studies needed and we will find it more difficult to recruit patients towards clinical trials. We need to think to the future. We may have one way of doing things for efficacy (clinical trial) and another way for safety (hybrid, tokenization).

There was a discussion on the concept of adaptive pathways, as worked on by Massachusetts Institute of Technology (MIT) and EMA whereby clinical trials work on efficacy such that a drug is introduced slowly to the marketplace to those with the greatest need and willingness to accept the greater degree of uncertainty, and RWD is collected and the licence is expanded gradually. This pilot was carried out but there were few submissions from industry. In terms of the regulatory framework, it was considered to be something of a contradiction in terms. This concept eventually gave rise to the [PRIME scheme](#) and to the [Parallel joint consultation with HTAs](#) to expand the label in a way that was useful also for HTAs to get on board.

- Definitions of RWD
 - The definition should not be limited to clinical practice. An example was given of the signal related to the Covid-19 vaccine and heavy menstrual bleeding. The seminal work used and evaluated app data, not from clinical practice, but from women reporting their own menstrual cycles.
 - The ISPE/ISPOR definition needs to be added to the table but it seems from an epidemiology perspective.
 - As we are on the topic of regulatory decision making, should we support the definition of the FDA or the EMA? They were felt to be incomplete. The FDA definition is very high-level.
 - If we adopt a third-party definition, we should explain why this was done.
 - It is best to use a definition that was chosen at the start and we had in mind as we wrote.



- We did not write the report with a definition in mind; we do not have to provide one.
- As there is no consensus on a definition in the field at the moment, but rather several definitions under consideration, we could proceed without consensus.
- The comment about our definition excluding data from physicians has been taken on board.
- Juhaeri revised the Introduction definition for completion to go beyond healthcare data sources to spontaneous reporting systems and surveys.
- What we mean by RWE is expanding as new data sources are arriving e.g. data from wearables and apps, so we need to keep our definition open to what the future might bring.
- We are taking the common ground; we need to refine the terms. As long as we define what we use for our purposes and keep with that, it will be clear.
- Some commentators said the CIOMS WG XIII definition was more narrow than the IMI GetReal definition. Consequently, we are in favour of adapting the IMI GetReal definition with additions of physician-reported data, data from registries, and emerging data sources e.g. social media.
- We will add our working definition in the beginning of the report as a footnote: In the context of this report RWD is defined as We may wish to add a comment that the definitions are evolving with time and refer to further harmonization efforts of RWE terminology by ICH (new ICH Reflection Paper available at https://admin.ich.org/sites/default/files/2023-06/ICH_ReflectionPaper_Harmonisation_RWE_Terminology_Endorsed-ForConsultation_2023_0613.pdf)
- We would need to re-read the report to check that we are aligned with our definition.
- The ISPE/ISPOR definition is to be added to the box of definitions.

"The RWD is defined here briefly as data obtained outside the context of randomized controlled trials (RCTs) generated during routine clinical practice [1,2]. This includes data from retrospective or prospective observational studies and observational registries; some consider data from single arm clinical trials as RWD."

Source: [Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making](#)
- Definition of “evidence”

A commentator said we define RWE but not “evidence” itself and therefore the following definition was drafted: “information constituting grounds for belief”.

 - It was felt that the meaning of the word “evidence” derives its meaning from its context.
 - In our context, RWE is the value we gather from RWD after a thorough analysis, something that could be actionable.
 - There was a suggestion to paraphrase “evidence” with “information” but it was felt it was too narrow.
 - “Evidence” can be looked up by readers in a common dictionary.
 - The FDA and EMA do not define “evidence”. If they do not feel the need, do we need to?
- “Evidence” will be left undefined.



Chapter 1

- Balance between detailed vs general
 - Decision making by who? Physicians and patients (should we consider caregivers and public opinion?). Manufacturing and drug developing companies. Regulators and HTAs (do we want to give more detail regarding HTAs?)
 - Previously there were two pages on HTA content. This was removed in favour of focusing more on regulatory decision making. We can bring this content back in.
 - The HTA content was considered complete from a US perspective at one of the recent Editorial Committee meetings and Wim has offered to review the draft report from a European perspective. [Post-meeting comment: Anja has offered to take on this task instead.]
 - Laurie offered to coordinate getting in touch with different HTA stakeholders. We may return to this at a later stage.
 - Including the public opinion may be very interesting but it may be difficult to define and decide on its objective/influence.

- At section 1.1.1 on *Regulators, HTA and payers: variety of stakeholders*, line 671, re Patients and physicians, we received a comment from Karin de Haart, IQVIA:
[Please consider noting caregivers as a stakeholder.](#)
[Secondly, could the general public be recognised as a stakeholder to RWE use by regulators for decision making? In my opinion the COVID pandemic, and vaccination campaigns demonstrated the value of public trust in evidence generation; I would think the larger public is a stakeholder in transparency of RWE generation.](#)
[Finally, is there a reason to switch from noting physicians here specifically and not Health Care Providers \(HCP\) as we see for the majority of this report?](#)
 1. Regarding the issue about physicians and HCPs, it seems currently our use of “physicians” is too narrow. This touches on the capacity to make treatment decisions. We can be more inclusive and include caregivers as stakeholders in an appropriate place. The CIOMS WG XI report included the patient community and that encompassed patients and caregivers in a wider sense. Do caregivers directly use RWE? Are they impacted downstream by physicians and patients. Yes, parents will decide on treatment options for their children. We should use



healthcare professionals¹ and patient community². Do we prefer healthcare provider as it is wider? Is it too broad? Laurie: The term "professional" is vague; the term provider is clear. Healthcare provider is the broadest term and that is what we want. John: Healthcare provider and healthcare professional can be used interchangeably: see [here](#). We need to be clear which we mean throughout the report.

- Jenni to decide. Suggest using patients, caregivers, and healthcare professionals, and give definitions.
- 2. Public. In the pandemic, all members of the public were patients. This is maybe too philosophical and for Chapter 4. Stakeholders only become relevant in relation to RWD/RWE in regulatory decision making. CADTH has a patient and citizen committee and citizens have opinions on value. Many deliberative committees in HTA include a citizen representative to bring societal perspective on value of different health technologies. John: Stakeholder has been defined as an "individual or group that has an interest in any decision or activity of an organization" ...but if we expand to include anyone impacted (e.g., the public) we might be going too far.
 - Do not include the public.
- Role of synthetic control arm
 - At section 1.4 on *RWE use in lifecycle of the development of medical products*, line 887, re Figure 3, we received a comment from BfArM:
In figure 3, it is suggested to replace control arms based on cost considerations which would not be acceptable. Not complying with the standard requirements for initial MAs, requires specific justifications why it is considered possible to conclude on a favourable benefit/risk balance in the absence of a concurrent control group. Only if these justifications are acceptable, alternative fit-for-purpose approaches can be pursued.
 - Jenni agrees we are not entirely there yet and proposes addressing this in the text.
 - John had two considerations: 1) is an Adaptive Clinical Trial (ACT) replacing an RCT, and 2) the participants in the would-be RCT are replaced by hybrid / historic / synthetic controls; they are not replacing the design in its entirety. It seems the commentator has misinterpreted the source.
 - Keep the draft as it is.

¹ For information, please note the definition used in the CIOMS report: [Practical Approaches to Risk Minimisation for Medicinal Products: Report of CIOMS Working Group IX](#), published in 2014:

Healthcare professional (HCP): A person who is qualified and trained to provide healthcare to humans. This includes doctors, physician assistants in some jurisdictions, nurses, dentists, pharmacists and midwives. For the purposes of reporting suspected adverse reactions the definition of healthcare professional additionally includes coroners and medically qualified persons otherwise specified by local regulations.

Combined and modified from: Lindquist, M. *The need for definitions in pharmacovigilance*. *Drug Safety*. 2007, 30: 825–830 and ICH *Harmonised Tripartite Guideline post-approval safety data management: Definitions and standards for expedited reporting E2D* (Nov 2003).

² For information, please note the definition used in the CIOMS report: [Patient involvement in the development, regulation and safe use of medicines](#), published in 2022:

Patient community: broadly encompasses individual patients, family caregivers, and the organizations that represent them. The patient community is heterogeneous and brings to the discussion different perspectives informed by their experiences, trajectory or stage of disease, level of expertise, and many other personal, community, and societal factors.

Source: *The National Health Council Rubric to Capture the Patient Voice: A Guide to Incorporating the Patient Voice into the Health Ecosystem*. June 2019. Washington, DC.



- National data protection laws & Federated research approaches; and inspections of data owners
At section 1.5 on *Adapt good clinical practices concepts of data integrity to RWD*, line 1076, we received a comment from the Global Self-Care Federation:
This requirement by the FDA and recommendation by CIOMS ignores national data protection laws in many countries and ignores the suitability of federated research approaches to create robust evidence.
Comment / suggestion for re-wording:
At least mention the national restrictions and proposed federated approaches. Further, please consider the inspect-ability of the “data owners”, their data and code and their researcher practices by Health Authorities rather than a requirement to ship subject-level data to the HAs. Consider that what is enforced by the FDA is being picked up as standard requirements in other countries as well.
 - Some Scandinavian countries will not allow registry data to leave their countries.
- Regarding the first part about data protection laws, we need to frame the content as a global approach and provide the US information as an example.
- Suggested removing the sentence: “The authors believe that sharing analytical programming code used for creating all analytic results, as well as code for cohort creation in the context of health care database studies, should be required of sponsors for regulatory submissions, and highly encouraged of all investigators in published literature.” This is at lines 1080-1084. We could also consider removing the preceding sentence commencing “Franklin et al. suggest that the submission of raw study data” or say “For example, Franklin et al. suggest that ...”. This is at lines 1078-1080.
- The Editorial Committee to consider making cross-references between sections 1.5, 3.4 and 3.6.
- Regarding the second part about inspections of data owners, keep with the principles of quality, integrity and transparency but avoid too much detail of how it is done.
- There seems to be slight repetition between sections 1.5.6 and 3.5.4.
 - Editorial Committee to review.
- References need to be updated in several places in Chapter 1.

Chapter 2

- Spontaneous reporting systems and surveys
At section 2.1 on *Traditional sources*, line 1324, we received a comment from AstraZeneca:
The text in line 1319 suggest that the “traditional data sources” include spontaneous reporting systems and surveys. It is not clear from that statement that it would include health care databases, and some of the other data sources presented in Section 2.1. Consider revising the definition of traditional data sources in line 1319 to improve clarity.
 - Juhaeri revised the definitions to align Chapters 1 and 2.
- Common Data Models (CDMs)



At section 2.1.3 on *Federated systems*, line 1460, we received comments from Jeffrey Brown, TriNetX and Harvard Medical School; Judith Maro, Harvard Pilgrim Health Care Institute and Harvard Medical School; Darren Toh, Harvard Medical School; and Karin de Haart, IQVIA ... all to say more or less that “this is factually incorrect and ignores several historical CDMs that pre-date OMOP”.

→ Juhaeri revised the text accordingly.

- Harmonisation across CDMs

At section 2.1.3 on *Federated systems*, line 1505, we received comments from the ISPE members:

Details about CDMs have been provided to both OHDSI and FDA Sentinel but not PCORnet.

Comment / suggestion for re-wording:

Provide details about PCORnet CDMs in the section, which will complete the idea of harmonization across CDMs.

→ There were suggestions to remove examples of CDMs from the report in order to not endorse any. There will be more CDMs over time. Or we could provide a link to a public website of CDMs. Alternatively, we could put basic information in an annex/appendix. Juhaeri to consider. He could also add a CDM for Taiwan.

- We discussed the distinctions between “traditional” and “new”. When do these terms change?

Chapter 3

- Data quality and integrity: how much detail to provide?

At section 3.1.2 on *Feasibility considerations for evaluation/selection of the database*, line 1803, we received a comment from Karin de Haart from IQVIA:

“Should this section also include the data format (it is transferable to a CDM, can it be analysed by validated tools; can data be linked to other sources?)”

Yoshiko felt this was a good suggestion. The topic is a scientific issue as well as a quality issue. Previously we had a section on multiple databases but it was deleted due to redundancy.

→ No change needed. Prefer to keep high-level and general. We do not want to get too much into implementation; do not want to endorse a model. This will future-proof the report.

- Data integrity

At section 3.1.3 on *Quality considerations for evaluation/selection of the database*, starting at line 1819, Yoshiko requested the WG’s assistance with selecting guidance to cite with regard to data integrity. Do we want to cover 'ALCOA' (Attributable, Legible, Contemporaneous, Original, and Accurate)? How is completeness assessed?

→ Lembit provided a reference.

→ Juhaeri will provide FDA guidance citation. There are several options.

→ GxP guidelines can be helpful too perhaps?

- ICH E9 Estimand query



At section 3.3.4 on *Adjusted analyses*, line 2555, we received a comment from Susan Gruber, TL Revolution, Putnam Data Sciences, and Mark van der Laan, TL Revolution, UC Berkeley; whom represent the American Statistical Association:

The interpretation of coefficients in an outcome regression model makes an unwarranted assumption that the outcome regression must be restricted to a parametric model, and that coefficients in such a model represent interpretable causal effects.

Comment / suggestion for re-wording:

We suggest this paragraph be revised to better reflect recommendations of the International Council on Harmonisation (ICH) to begin with a model-free definition of the target parameter.⁴

The interpretation of a coefficient in a parametric regression model depends on what other covariates are included in the model and on the validity of the model. Often such models are main terms only, encouraging simplistic, incorrect interpretation of coefficients as causal effect estimates.

4. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (2020). "ICH E9(R1) Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials," Available at <https://www.ich.org/page/efficacy-guidelines>. [accessed March 6, 2023].

- Prefer to leave out estimands as otherwise the report becomes more of a textbook.
- Causal inference would be more appropriate than estimands.
- Stella suggested adding "usually".

- Machine Learning techniques

At the start of Chapter 3, line 1734, we received a comment from Susan Gruber, TL Revolution, Putnam Data Sciences, and Mark van der Laan, TL Revolution, UC Berkeley; whom represent the American Statistical Association:

The report would be strengthened by acknowledging the growing importance of electronic health records (EHR) and genomic data in RWD studies.

Comment / suggestion for re-wording:

Machine learning techniques will be required for estimation in high dimensional settings, for both PS-based methods and DR estimators. Natural language processing will play an important role in assembling RWD from EHR. We recommend adding a subsection on methods for causal inference in high dimensional settings that mention these important tools and the Targeted Learning approach that incorporates them in evaluating causal effects.⁵

5. Williamson BD, Wyss R, Stuart EA, Dang LE, Mertens AE, Wilson A, Gruber S. An Application of the Causal Roadmap in Two Safety Monitoring Case Studies: Covariate-Adjustment and Outcome Prediction using Electronic Health Record Data. 2023; arXiv:2305.07564.

- Michele will assist off-line. This topic is not regulatory-ready. We can specify it is for the future.
- ML is already captured elsewhere in the report and in references.
- It could be made more explicit in a different place. Perhaps under Transparency? Chapter 5?
- In the context of electronic health records (EHRs) database, awareness of manipulation is important – how data becomes a proxy of the original. Interfaces will change what the data was at the point of collection.
- We can give a warning that there can be negative effects.



→ The Pharmaceutical Inspection Co-operation Scheme (PIC/S) has suggested that ML tools can pose challenges.

- Links to case studies

At the start of Chapter 3, line 1734, we received a comment from BfArM:

This chapter provides a textbook-like overview of considerations when performing research with health care data. It would benefit from delineating typical challenges and acceptable ways of overcoming them when RWD might be considering within specifically defined regulatory contexts. More in depth review of the use cases (successful and unsuccessful!) would also be helpful to optimise lessons learned.

- For marketing authorisation procedures, there are high requirements based on well-justified reasons (safety - selection of non-vulnerable patients; expected confounding randomisation; non-objective outcome measures - blinding, acceleration of development process - selection of patients most likely to benefit).
- Depending on the time point of the drug lifecycle, requirements may differ. Especially for initial MA of a new product, a favourable benefit/risk balance has to be based on verifiable source data available in strict timelines. In depth description of study population (baseline + follow-up) and pre-specified study performance ultimately allow causal inference according to outcome measures not necessarily performed in clinical practice in a sufficiently standardised manner. Both missing data/low return rate of e.g. questionnaires as well as reasons for discontinuation can be very informative and contribute to the benefit-risk considerations.

All type of analyses exploring the validity of the data typically require rich data set in order to be able to perform them. Experience is that current information is still too limited / fragmented / siloed (e.g. molecular characteristics for newly developed biomarkers). RWD are likely therefore especially limited with respect to new drug developments and initial marketing authorisations, but prospective planning of RWD data collection may accelerate knowledge gaps on prognostic impact of molecular markers post approval.

Absence of protocol-determined definition or target populations with detailed baseline description and standardisation of outcomes measures may critically impact reliable interpretation of findings.

- We will keep with the case studies we already have, including the new ones arriving from Japan Data Center for Hematopetic Cell Transplantation, Novartis and Roche.
- We could also consider linking from the case studies to the chapters.
- We will look to link Chapters 1 and 2 to case studies too.

- The word “Disease”

At section 3.2.1 on *Case-control studies*, line 1865, we received a comment from Stella:

In the sentence: “Case-control studies compare the exposure history of individuals with a disease (cases) to that of individuals without the disease (controls).” Is “disease” too narrow as this could be for adverse event too?

- We could change this to: “outcome of interest such as”.



- Selection bias
At section 3.2.3 on *Study design considerations in context of RCTs*, line 2376, we received a comment from European Association of Hospital Pharmacists (EAHP):
There should be the inclusion of geriatric/paediatric or female patients, since these patient groups are often not included in the selection bias, as suggested on the column in the right side.

Comment / suggestion for re-wording:
Selection bias may be addressed to a certain extent by employing various study design elements to increase comparability of the trial and RWD control arms in important prognostic factors for the study outcome. These include techniques such as restriction, stratification, matching, modelling, and weighting. Sometimes matching on all the important variables may not be possible or efficient and the use of propensity score methods may be preferably used. Also, there should be the inclusion of geriatric/paediatric or female patients, since these patient groups are often not included in the selection bias.

→ The use of the term “selection bias” is slightly different here from the typical term used. We would need to use the term confounding to be consistent on this occasion.
- Subpopulations
At section 3.3.7 on *Principles of sensitivity analysis*, line 2668, we received a comment from Susan Gruber, TL Revolution, Putnam Data Sciences, and Mark van der Laan, TL Revolution, UC Berkeley; whom represent the American Statistical Association:
According to ICH E9(R1), subpopulation analysis is considered supplemental but not sensitivity analysis.

→ Michele agrees. This is “subgroups analysis”.
→ Suggest starting a new section on heterogeneity.
→ Michele proposes removing the part about sensitivity analysis.
- Bayer’s example
At section 3.4 on *Evidence-generation process, study registration, transparent reporting, audit trails and responsible communication*, line 2798, we decided to remove the example on the basis that it was illustrative but not generalisable.
→ The text at lines 2798-2807 is to be removed.
- Missing data classifications
At section 3.3.8 on *Missing data*, line 2688, there is an opportunity to improve the way the types of missingness are described.
→ Michele to help with re-drafting better descriptions.
- In general, Michele offered to check the PubMed references proposed in the comments. It was agreed that in principle we will avoid unpublished articles as pre-prints can be less valuable.



Chapter 4

- David S reported that Chapter 4 received many minor comments that were quick to address but also many major comments saying it was too high-level and theoretical.
- David S addressed a first round of edits and the chapter is consequently shorter. It was easier to remove the normative introduction, i.e. section 4.1, which was akin to a beginner's guide to moral philosophy. The chapter now begins with 4.2, i.e. the ethical arguments for incorporating more RWE. Another main difference is towards the end, after having made a number of concrete recommendations, where some philosophical reflections have been removed.
- David T is in the process of addressing comments relating to Data protection and data management.
- There may be a few more minor editorial comments to address.
- One comment that David S disagreed with from AstraZeneca was with regard to “beneficence” and “nonmaleficence” which asked for us to use simpler language however these are technical ethical concepts and necessary to keep with explanations.
 - All agree that this chapter is needed in the report.
 - The chapter does not address sufficiently some of the specific ethical issues relating to RWD use for evidence generation and regulatory decision making, i.e. the technical parts of the rest of the report do not reflect in Chapter 4.
 - We may need to add new ethical considerations e.g. those presented by artificial intelligence.
 - The public will often provide wider informed consent provided they trust the governance of the data.
 - Many principles are included already in the CIOMS report [2016 International ethical guidelines for health-related research involving humans](#).
 - In some countries, the data owner is the patient himself/herself.
 - Do not overly emphasise the challenges of RCTs and the promise of RWE; we would like to offer all data sources as options.
 - The chapter feels separate from the rest of the report and needs to be integrated better. We need to make clear connections to the other chapters.
 - It is written in a different style/voice and would need to be harmonised with the rest of the report. An editor can be brought in to do this to a certain extent but it can be difficult for an outsider to do this without changing the meaning of the content.
 - There is wastefulness in endless data capture without an idea of how to make use of the data.
 - It is unethical to not make the most of the data that has been captured.
- David S invited the other chapter leads to let him know if there are other ethical issues in their chapters that have not been covered in Chapter 4.
- David S reiterated his earlier request to the other chapter leads for specific real-world examples to be mentioned in Chapter 4. (From Juhaeri: The reason we use RCT data is to respect rules. For existing databases, e.g. claims databases, maybe patients in the US sign a document to allow their data to be shared, but which data and for what purpose? Maybe this could be included in Chapter 4? This is already touched on in Chapter 4 but it can be expanded on.)



- Laurie offered to re-read the chapter again after its revision.
- The revised Chapter 4 will be sent on 6th of October to the CIOMS Secretariat.

Chapter 5

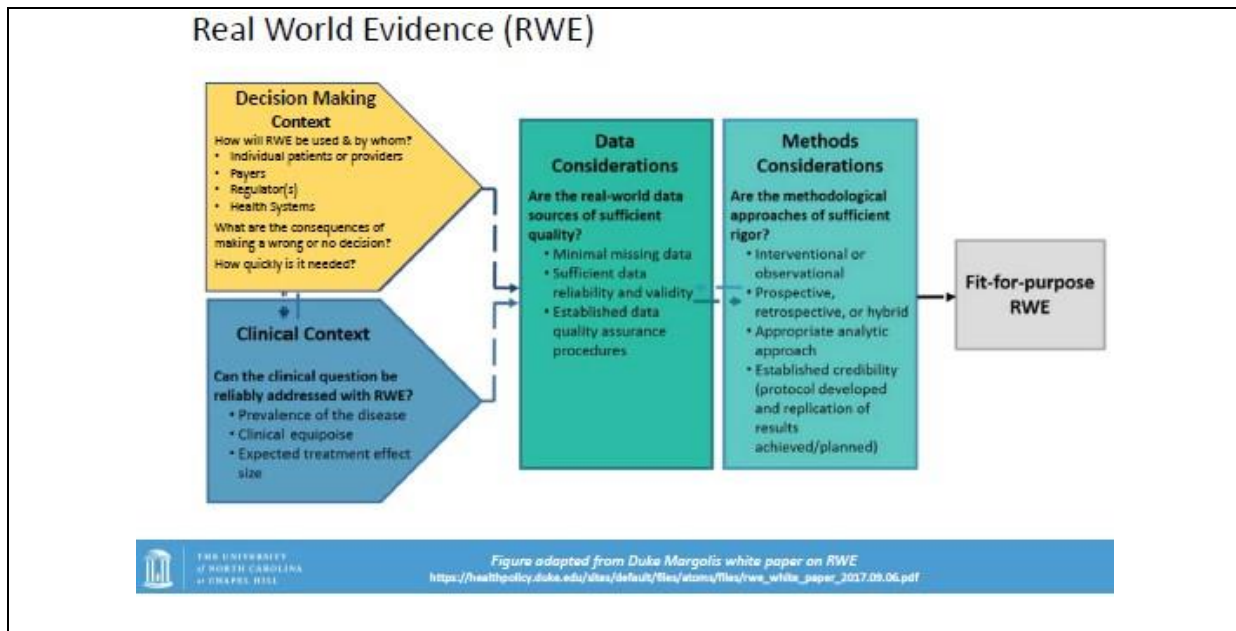
Putting aside the content we have already, what would be the conclusions and recommendations we would like to put forward?

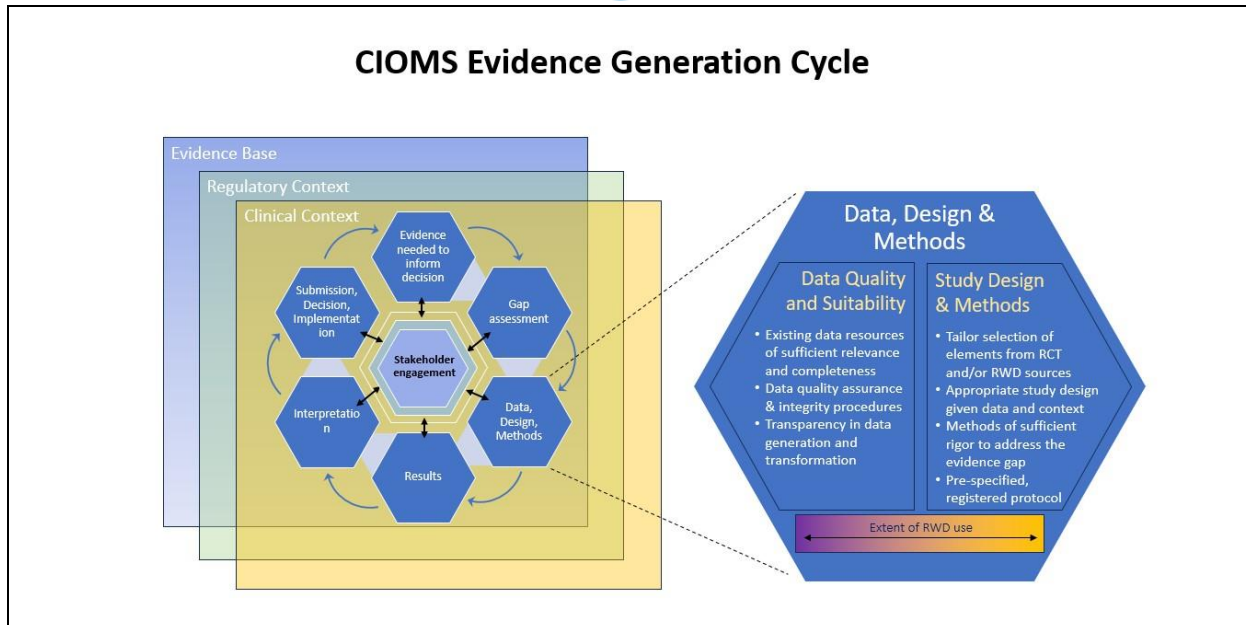
- There is much variability in RWD/RWE and what is considered fit for purpose.
- Overall, we would like RWD to be accepted more.
- Goals will change and RWD/RWE will become more robust - we need to keep pushing forward.
- Return to the question “Why are we doing this?” and “What would be successful?” We need this feedback loop. What are the principles?
- We collect more and more data but how can we benefit more from it in the interests of public health in the hands of the decision makers?
- Data is often not collected with the response/use in mind.
- Need to place emphasis on the technical elements of data capture as this will affect how we can make data available.
- Regarding data collection, we need to address quality, and this involves thinking about why we collect data, both the primary and secondary uses.
- Need to tell those doing the collecting, e.g. physicians, what we’ll be using the data for so they know what our concerns are. They may be unaware of how the data will be used.
- Need to highlight a mind-set shift. Over the past 30 years there has been a change in what we want to collect and what we want to see. We need to align with safety and efficacy. We have so much data but only a fraction of it is useful. This shift could be captured. The burden of proof is on those who want to make a statement. It is about understanding methodologies and sources. We are pushing boundaries; we need to ensure we provide evidence that is fit for purpose.
- Need to have a scientific discussion about what is needed for this shift to happen.
- The boundaries between trials and RWE are unclear.
- Link datasets without losing privacy.
- Emphasise early dialogue.
- Recommendations/principles to include:
 - Start early and maintain frequent conversations with regulators;
 - Understand your data;
 - Know your methods;
 - Ensure clinical expertise;
 - Build a multidisciplinary team (or interdisciplinary team).
- There was a discussion about whether “Early and frequent conversations with regulators” should also include the term “binding”. It was felt that any legal element would make this too rigid e.g. with regard to assessing class effects before approval. Working with RWD needs to be able to allow flexibility. Binding is not helpful at planning stage. If “binding” is unsuitable, maybe we can speak about “regulatory pathways”?
- Consider the full product development lifecycle.
- Leave the either/or thinking and start using both.



- Regarding the changing mind-set, we need to identify where the box is more malleable, e.g. in relation to safety and rare diseases – innovation will happen in these places.
- It would be helpful to have diagram with the questions of different stakeholders, showing the evidence needed at the different stages, the evidence gaps, and discuss how to address the evidence gaps.
- What is the question? What is the evidence? A lot of questions can be answered with RWD.
- Some past diagrams considered as a starting point included:
 - Eastbourne Pharmaceuticals value flower diagram;
 - TRUST4RD Tool as in Figure 2 in the draft report;
 - IQVIA “Who are the decision makers for Pharma?”
 - Duke Margolis White Paper on RWE

Who are the decision makers for Pharma?





- Is there any indication we are focusing on in particular? Are we ready to recommend the use of RWD/RWE for all products? The full ecosystem is evolving and so RWE will be used for everything. Our report will not take a position.
- Regulators taking decisions are looking to fill in knowledge gaps.
- Not all regulators are the same.
- There is a responsibility to use data that is available.
- We could mention the pandemic and explain why the report publication date was delayed. Covid-19 brought much in terms of RWD.

Implementation activities

A number of implementation activities can be prepared in advance of the report publication to ensure a coordinated, successful launch.

Webinars

- We could organise two webinars in different time zones, similar in style to those offered by CoRE/Duke-NUS.
- These should be no longer than 20-minute information packages.

Scientific article for an open access journal

→ Juhaeri will make a start on this once our work is a little more advanced.

e-Learning modules

- Two former CIOMS report publications, [2016 International ethical guidelines for health-related research involving humans](#) and [Drug-Induced Liver Injury](#), were accompanied by e-learning modules: please see [here](#). The WG XIII report could have a similar set of modules.



Standard PowerPoint slide set

- We will have a shared slide set for everyone to use for promoting the report to ensure consistent messaging.
- Everyone will be at liberty to use them but we ask all to keep other WG members informed.

Launch event

- The [ICPE ISPE Annual Conference](#), August 24-28, 2024, Berlin, Germany, was considered as a venue for the report launch because all the major stakeholders are expected to be present.

Speaker engagements

- We need to consider what languages other than English the WG members can cover among them and who might be willing to present.
- At first sight: Dutch: Wim, French: Elo, Estonian: Alar / Lembit, German: Andrea / Britta / Julia / Kristina / Monika / Steffen, Italian: Enrica, Portuguese: Monica, Japanese: Moriya / Takahiro / Yoshiko, and Spanish: Andrès / Miguel-Angel.
- Some event suggestions included [International Society of Pharmacovigilance \(ISoP\) Annual Meetings](#) and [DIA events and conferences](#).
 - Andrès offered to take responsibility for the implementation strategy and draft a formal plan. He will begin by compiling a set of target speaker engagements for promoting the report.
 - Heather volunteered to participate in the implementation team.
 - Implementation activities will be shared among the WG members.

Case studies

We have an internationally balanced set of case studies.

Letter	Title	Country/Jurisdiction
A	Fosdenopterin approved for treatment of a rare, genetic disease with external control data from a natural history disease study	US
B	Comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different COVID-19 vaccines in an international network cohort study	The study used datasets from France, Germany, the Netherlands, Spain and the UK
C	Contextualising adverse events of special interest to characterise the baseline incidence rates in 24 million patients with COVID-19 across 26 databases: a multinational retrospective cohort study	The study included 23,840,986 patients with COVID-19 from 26 databases representing a diverse set of care settings from North America, Europe, and Asia including the following 11 countries: Belgium,



		Estonia, France, Germany, Japan, the Netherlands, Serbia, Spain, Turkey, the UK, and the US.
D	N-Nitrosodimethylamine (NDMA)-contaminated valsartan and the risk of cancer	Germany
E	Cardiovascular risk of urate-lowering drugs: a study using the National Database of Health Insurance Claims and Specific Health Check-ups of Japan	Japan
F	Nested case-control study utilising MID-NET® on thrombocytopenia associated with pegfilgrastim in patients treated with antineoplastic agents	Japan
G	Evaluating real-world performance of Elecsys® Anti-SARS-CoV-2	US
H	Post-authorization safety studies for CAR-T (Chimeric Antigen Receptor T-cell) products	PMDA, FDA, EMA

- One more case study is expected from Novartis, Switzerland and potentially another from Roche, US.
- The Sanofi case study will be removed.

Any other business

- Final publication is anticipated for Q1 2024.
- Kind thanks to everyone