Fifth meeting of the CIOMS Working Group XV:

Harnessing the Potential of Pharmacoepidemiology for Public Health

Geneva, 4 & 5 December 2024

Participants (in person)

CIOMS: Hervé le Louet (HL) (President); Lembit Rägo (LR) (Secretary-General).

Academia: Bernard Bégaud (BB) (University of Bordeaux, France); Jennifer Lund (JL) (University of North Carolina, USA); Yola Moride (YM) (Rutgers University, USA).

Industry: Ana Sofia Afonso (Eli Lilly, The Netherlands); Alex Asiimwe (Gilead); Selin Cooper (AbbVie, UK); Alicia Gayle (Chiesi, UK); Karin De Haart (IQVIA, The Netherlands); Marie-Laure Kurzinger (MLK) (Sanofi, France); Innocent Ngwa (Roche, Switzerland); Patricia Saddier (MSD, USA); Montse Soriano-Gabarro (MSG) (Bayer, Germany).

Intergovernmental organization: Noha Iessa (WHO, Switzerland).

Regulatory: Craig Allen (MHRA, UK) (4 December only); Miguel Ángel Maciá (Spanish Agency for Medicines and Medical Devices, Spain).

Participants (virtual)

Academia: Kate Gillespie (Institute for Health Metrics and Evaluation at the University of Washington) (4 December only); Masao Iwagami (University of Tsukuba, Japan) (4 December only).

Industry: Véronique Kugener (VK) (Takeda, USA) (4 December only).

Regulatory: Takashi Ando (Pharmaceuticals and Medical Devices Agency, Japan) (5 December only); Doris Oberle (Paul Ehrlich Institute, Germany); Hui-Lee Wong (Food and Drug Administration, USA) (4 December only).

DAY 1: Plenary

Welcome and opening remarks

Hervé Le Louët (HL) opened the meeting and welcomed participants. The agenda was adopted.

Lembit Rägo (LR) updated participants on recently-published CIOMS working group reports, the recent CIOMS webinar on real-world data (RWD) and real-world evidence (held on 3 December and to be repeated on 23 January 2025), upcoming CIOMS working groups (WGs) and the agreement just reached between ICH[1] and CIOMS regarding the *Glossary of ICH Terms and Definitions*. He also referred to the latest revision of the Declaration of Helsinki of the World

[1]International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

Medical Association,[2] which is now aligned more closely with CIOMS' *International Ethical Guidelines for Health Research Involving Humans*.[3] Given this closer alignment, it is not anticipated that the *Guidelines* will require substantial modification to take into account the revised Declaration.

Patricia Saddier (PS) continues to work on securing a site, hosted by Merck, that can be used safely by all WG members.

Bernard Bégaud (BB) was invited to oversee updates on the original two sub-groups**4** and on the four groups5 created during the meeting in Paris in May 2024.

Sub-groups 1 & 2 updates

Since Sub-groups 1 and 2 have been superseded by the four sub-groups created in Paris, the text developed by Sub-groups 1 and 2, and the glossary developed by Sub-group 1, must now be merged into that of the four sub-groups.

The "why" and "what" of pharmacoepidemiology (PE) that was developed by Sub-group 1 has already been integrated into Section 6 of the draft document.

Content relating to the pharmacoepidemiological framework (in Section 2) has been incorporated into the draft document, although no further work to develop it has been undertaken.

Paris sub-group updates

How to perform (or use of) PE in different settings (original title)
Types of public health (PH) issues that can be addressed with PE (revised title in draft document)
Section 3 of the draft document

Karin de Haart provided the update on behalf of Véronique Kugener, the group lead.

The group has been reviewing the different types of scenarios where PE can contribute to PH health, including to:

- **evaluate implementation and effectiveness of different interventions**
- **contribute to development of new interventions, especially medicines and vaccines**
- **assess access to medicines and health care**
- **reflect on and provide insights into delivery of health care in different health settings.**

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[2]Declaration of Helsinki, amended by the 75th World Medical Association General Assembly, Helsinki, Finland, October 2024. https://www.wma.net/policies-post/wma-declaration-of-helsinki/

[3]CIOMS. International Ethical Guidelines for Health Research Involving Humans. Prepared in collaboration with the World Health Organization. Geneva, Switzerland, 2016. https://doi.org/10.56759/rgxl7405

- [4]**Sub-group 1**: to draft a new definition of the use of PE, i.e. focusing on "the what" of PE (led by Yola Moride). **Sub-group 2**: to focus on communication to, and use of PE for public health by, politicians, regulators, public health professionals, regulators and others in decision-making with respect to drugs or health technologies, at local, national or global levels, i.e. focusing on "the who and how" and on what evidence (led by Véronique Kugener).
- [5]How to perform (or use of) PE in different settings (led by Véronique Kugener); When not to conduct a PE study (led by Bernard Bégaud); The use of PE in crises (led by Ana Sofia Afonso); Interpreting the results of existing PE study data (led by Patricia Saddier).

Work is still needed on use of PE to compare interventions, on access to medicines, and on infodemics, although this last topic may overlap with Section 6 of the draft document.

Discussion:

- LR had shared the draft report of Working Group (WG) XII on benefit-risk balance for medicinal products. No potential overlap with the work of this WG has been identified.

Interpreting the results of existing PE study data (original title)
Evaluating existing PE evidence to support public health decision-making (revised title in draft document)
Section 4 of the draft document

PS provided the update for this group. A brief overview and goal was developed. It would be useful for each report section to have the same. A workflow to follow when evaluating PE study data was further expanded and references to tools that can be used to support critical appraisal of pharmacoepidemiological evidence were provided. The sub-group's key recommendation when existing PE evidence is being sought to help inform PH decision-making, is to establish a small team with the relevant specialties, to identify the evidence and critically appraise and synthesize it. The team would also identify any gaps and determine whether additional PE studies might be helpful to fill these. Finally, the team would come to its conclusions and recommendations, including with reference to communication. The team would reassess when new evidence becomes available. Use cases considered included acute communicable diseases, chronic diseases, preventative interventions such as screening programmes, and inappropriate or insufficient use of medicines. But a decision needs to be taken as to which use cases should be worked on further. COVID could be a good use case, but the report is unlikely to be published before 2026, rendering it less interesting as an example. Use of glucagon-like peptide-1 (GLP1) agonists might become a more acute issue and thus be a better use case. (It would be good to have a common use case across the report, but this would not preclude inclusion of additional use case examples in the individual sections.)

Discussion:

- **Communication was also considered by this sub-group but it was uncertain whether it should be included in this section. It may even merit its own section** since several communication issues have been referred to during this meeting: infodemics; communication during crises; the peer-review process; guidelines for publishing or reviewing studies. It was noted that communication of PE information in a crisis situation is very different from communication in a non-crisis situation.
- **Communication of scientific results needs to be distinguished from communication of a PH decision.**
- **The CIOMS report *Real-world data and real-world evidence in regulatory decision making* includes some references that are relevant to this section (Section 4.)**
- **GLP1 would be a good use case since use of it and associated health risks are increasing.**
- **COVID and GLP1 agonists could both serve as use cases:** COVID is now a crisis of the past, with lessons learned, and a lot of information available about preventive measures taken, decisions made on who should have access to vaccination, supply shortages, etc.

Conversely, issues associated with GLP1 agonists, and what PH actions to take, are only just starting to be considered.

- **Many of those involved in PE studies have no medical background which means that they may make poor decisions when designing and implementing a PE study, and/or interpreting its results.** They may also not know with whom they should collaborate or what questions to ask during a study. The recommendation (see below) that a PE study should not be conducted if the relevant expertise is not available is relevant here.
- **The team to be established for a PE study may need to include non-PE expertise.** Different studies require different expertise. In high-income countries, the necessary expertise is likely to be available, but this may not be the case in low-income countries.
- **Another problem area relates to data science expertise.** Data is now more available and accessible. But a lot of people use it without having the necessary expertise. This can lead to poorly-designed PE studies.
- **What about AI?** It's just a tool; it won't do the work for you.

When not to conduct a PE study (original title)
When a PE study may not be the best option (revised title in draft document)
Section 5 of the draft document

BB provided the update for this sub-group. From an academic perspective, there are no or few reasons not to conduct a PE study. Yet perhaps 80% of PE studies are not useful for advancing science or promoting PH.

The group discussed seven situations in which a PE study would not be recommended:

1. **The proposed study does not a priori provide adequate guarantees of competence or independence since the technical capacity required to ensure this is unavailable.** Many PE studies are conducted by people with a poor knowledge of PE or of statistics, who cannot control for bias. PE studies should be conducted by people with broad experience of PE and of using it for PH purposes.
2. **The proposed evaluation criteria are irrelevant from a PH perspective because they do not enable a global overview to be developed or do not provide information about impact.** The group identified over 50 PE studies on use of hormonal therapy (HRT) in menopausal women and the benefits–risks. But the studies focused on e.g. myocardial infarction or prevention of fractures. Not a single study allowed benefit–risk to be evaluated from a global perspective, which would have enabled advice to be generated for women and prescribers regarding treatment with HRT.
3. **The proposed study would duplicate existing research, without providing significant added value.** Such a study would waste time and resources.
4. **The proposed study is unlikely to be conclusive,** i.e. it will not advance knowledge on the topic. Sometimes a study may be initiated but should be stopped when it becomes apparent that its results will not be statistically significant.
5. **The proposed study focuses on a narrow aspect or sub-population and will fail to provide a comprehensive view or balanced analysis of the problem.** During COVID 19, studies of many narrow aspects of safety or efficacy in sub-populations were performed

rendering development of a global view of the benefit–risk of COVID 19 vaccines difficult.

6. **Sufficient information is already available, and the proposed study could delay or complicate a PH decision.** For example, if the number of deaths prevented by a vaccine is significant, it would not be useful to continue to run a clinical trial for those vaccines for an additional year. Similarly, in southern Europe, use of benzodiazepine is extremely high. More than two-thirds of 47 PE studies have concluded that there is a possible association between long-term use of benzodiazepine and increased risk of Alzheimer-type dementia. An additional PE study is not needed since it is already known that long-term use of benzodiazepine carries a risk.
7. **The proposed study could trigger or exacerbate a crisis situation, or obstruct PH action, or complicate the management of a health or media crisis, or further complicate decision-making.** Instances can also be cited where a study caused a PH crisis.

Discussion:

- **Regarding point 6 above, and the example of benzodiazepine and dementia, it was questioned whether the issue is about patients or practitioners.** A lot of practitioners do not prescribe benzodiazepine to people over 45 years of age, whereas others do. Should patients be advised not to take benzodiazepine even if their practitioner prescribes it, or should practitioners be advised not to prescribe it to patients over 45 years of age? Or should a recommendation be made for a change in product labelling? In the draft document it is assumed that no effective treatment is available for Alzheimer-type dementia. Given this assumption, the recommendation proposed is to estimate the proportion of benzodiazepine users in a given country who would fall into the at-risk category if they exceeded the maximum recommended duration of use, to help determine targeted interventions (in line with the precautionary principle). Additional, inconclusive PE studies would not be needed. However, treatments for Alzheimer-type dementia have in fact been available since 2023 and so this example should be revised.
- **The context, rather than PE itself may be problematic.** If a drug is used widely and brings significant health risk, then its removal from the market may be justified. But if the drug is not used widely, its removal from the market may be unjustified. In other words, how the results of a PE study results are interpreted may be problematic, rather than the methodologies applied in the study.
- **Another problem relates to the decline in the quality of reviews undertaken by journals,** even though the journals have a responsibility regarding the studies they publish. **Is guidance available to reviewers of PE studies? If not, some such advice could be included in the WG report. The framework section of the draft report cites some relevant guidelines.** (See section 2.3.)
- **It may not be sufficient to simply recommend when a PE study should not be undertaken. Suggestions as to what should be undertaken instead of a PE study could be useful for the reader;** for example, a pharmacogenetic analysis to explain differences

between populations, or a biological study to investigate why benzodiazepine can trigger amyloid formation in dementia.

- **The draft report is biased towards medicines and safety. Yet PE studies, particularly on effectiveness, have contributed to critical decision-making by national and international organizations in the area of vaccines.** Perhaps the report needs to tone down its criticisms of PE studies. However, although much is known about the efficiency of COVID vaccines, there is little understanding of the impact of COVID vaccines on the global population.
- **The report of this WG should complement the upcoming WG benefit–risk report.** For example, if the benefit–risk report indicates that PE can be used to investigate safety, then the report of this WG should discuss how PE can be used to investigate safety.
- **Although the foregoing discussion suggested that PE studies in sub-groups are not likely to be worthwhile, they can in fact produce useful results.** A signal in Botswana related to use of dolutegravir (a well-known medicine for HIV) by pregnant women was detected. A PE study to confirm the risk was needed. Similarly, when the relevant WHO advisory group discussed the Mpox vaccine it concluded that the vaccine was generally safe, but that for some sub-groups, such as immunocompromised children and pregnant women, additional information was needed before this could be confirmed.
- **When planning a PE study it is necessary to have a clear picture of the PH decision-maker targeted.** A PE study that excludes a certain sub-group for which the decision-maker must take decisions should be avoided since it will not generate all the information needed by the PH decision-maker. A study design should match the population for whom or about whom the PH decision-maker will be making a decision.
- **The discussion highlighted the need to work on the science communication content for the report.**
- **The aim of a PE study may be to raise a question, rather than to provide an answer.**
- **The WG risks limiting PE to being a mere tool.** It is more than a tool. PE may be more important in terms of generating hypotheses than in finding answers to specific questions.
- **What can PH do for PE?** The discussion has focused only on what PE can do for PH. This remains to be covered in an introduction to the report; some content in the concept paper could contribute to this.

The use of PE in crises (original title)
When to use PE in times of PH crises and emergencies (revised title in draft document)
Section 6 of the draft document

- **Ana Sofia Afonso provided the update for this sub-group,** which split the work among its members as follows: definition; introduction; overview of how to respond to a crisis or emergency; use cases. The WG is now invited to review and comment on the text prepared. Thereafter, it can be reorganized, and the conclusions and recommendations drafted.
- **Jennifer Lund explained that the group described and organized different phases of a PE crisis, and provided use cases to serve as examples of how PE has been used in PH**

crises. The table in Section 6.1 maps study objectives and designs to the different stages of PH crises.

Discussion:

- **Current PH crises are more unexpected than previous PH crises. So does PE remain a useful tool for crisis management?** And if it does, what would be the criteria to immediately initiate a PE study? What criteria should be applied?
- **The term "PH crisis or emergency" was defined very broadly and considered to include, for example, climate change, natural disasters and man-made disasters.** Heatwaves, or other situations related to climate change, may trigger increased health risks due to increased transmission of dengue or malaria, and PE certainly has a role to play in analysing such risks.
- **The clinical studies conducted during COVID were very disappointing.** The USFDA concluded that 95% of randomized control trials conducted during COVID did not produce useful results. Ethical committees should have blocked many of them, while journals should have reviewed the resultant papers properly and decided not to publish them. No analysis appears yet to have been made of PE studies carried out during COVID. Many COVID studies probably did not produce useful results or were methodologically unsound. It would have been better not to have published them since results published in a peer-reviewed journal tend to be considered sound.
- **Previously, the principal medical journals carried out a thorough review process. Now, however, studies may be published simply because a fee has been paid. PUBMED now also cites studies that are worthless.** Additionally, many examples of newspapers referring to papers with poor results can be found.
- **During COVID, there was a surge in publications because there was a need for treatment and for vaccination.** It was not possible for journals to check all the studies that were submitted for publication. Yet as a result of lessons learned during COVID, it is likely that needed vaccines will be developed more quickly.
- **The role of regulators during crises should not be forgotten.** During crises regulators use accelerated pathways, conditional licensing and reliance on other regulators' decisions to expedite access.
- **Can PE be used to prevent crises?** There are, in fact, some good examples of PE being used to do this. This aspect of PE has not been captured in the table in Section 6 but should perhaps be added (although the focus of this section is on use of PE during a crisis).

DAY 2: Plenary

Discussion about report contents and structure

- **The report has to be aligned with the flow of the concept paper.**
- **PE studies can be used to generate hypotheses and robust questions that are worth pursuing.** Much can be learned from studies of population exposure to different medicines. For example, during long-term follow up of the use of aspirin to prevent cardiovascular disease (CVD), it was observed that carcinoma incidence was lower in the group using aspirin.
- **Key considerations for conducting a PE study could be put into an appendix.** The aim is not to tell readers how to conduct a PE study, but they could be referred to guidelines on how to conduct a PE study.
- **Does the report need to cover data?** Many data issues have already been covered sufficiently in the WG XIII report *Real-world Data and Real-world Evidence in Regulatory Decision-making,* but not all the data used in a PE study will be RWD. During a PH crisis, data and data sources may be problematic.
- **Possible use cases were discussed.** These should cover all geographies and populations. The following were considered: acute diseases and chronic diseases; antibiotic shortages or antibiotic resistance; Mpox; dengue; GLP1 agonists; COVID; statins for CVD prevention; HRT; obesity; mental health; dementia; antimicrobial resistance; climate events; adverse drug reactions. COVID could be used to illustrate what PE studies should have been done. GLP1 agonists could be used as an example of a growing PH issue for which PE studies could prove helpful. Mental health is too broad an issue to be covered in this report. Use cases should include PH conditions for which treatment is available. Finally, the following use cases were selected: COVID (as a PH crisis); antibiotic use (as a PH issue); obesity; CVD; GLP1 agonists; statins.

Next steps

- **A single text for review by all group members should be produced.** (Seven sources are available: the original concept paper; the two sets of content produced by Sub-groups 1 and 2; the content produced by each of the four "Paris" sub-groups.) **Each of the four groups shall designate a group member to revise and consolidate its text.**
- **The WG will select an editorial group to produce a full draft text that will then be made available for public comment. CIOMS will create a single, consolidated file of comments. It will discard any irrelevant comments and, where needed, tidy up the language of comments. The editorial group will be responsible for reviewing and deciding which comments should be incorporated in the report.** Ideally, the consolidated file of comments will include "creative" comments and not only negative or critical comments. CIOMS will incorporate accepted comments into the report.
- **Comments have to be submitted in a prescribed format, otherwise they are discarded.** Organizations should be requested to submit a single set of comments. It will not be necessary to respond to each individual or organization regarding the comments they have submitted. If any query is received regarding a comment(s) that were rejected, CIOMS' will respond that all comments were reviewed by the editorial board and

accepted or rejected as it considered appropriate, and that the report is a consensus report of the WG experts. If the editorial board is unable to reach agreement on a comment, it will consult the relevant section lead.

- **Ongoing work:**
  - **BB to revise the report introduction.**
  - **The PE framework drafted by the original Sub-group 1 requires some additional work, as does the section *How to perform (or use of) PE in different settings / Types of public health (PH) issues that can be addressed with PE (revised title in draft document).***
  - **Relevant WG members to review and refine Sections 2.1 to Section 2.4, and Sections 3, 4 and 5.**
  - **Section 6.3: Communication of the evidence will be refined by Selin Cooper.**
  - **The report conclusions and recommendations will form Section 7.** Everybody should contribute to these.
  - **Marie-Laure Kurzinger will revise the glossary (Section 8).**
- **WG members should provide references in full at the end of the sections.** A shared folder for references will be made available on the shared Merck site. Where possible, the actual reference document, in PDF, should be submitted. If not, a link should at least be shared. PS's assistant can assist in formatting references. Each reference should have been read!
- Case studies were selected as follows:
  - PH crisis example: COVID – Noha Iessa
  - antibiotics as a PH issue (in terms of a drug shortage or pneumonia-resistance) – to be decided
  - obesity & CVD, GLP1 agonists – Jennifer Lund to outline.
- **Deadlines:**
  - 20 December 2024
    - editorial board agreed: at this meeting the following were proposed: Anasofia Afonso; Alex Asiimwe; Bernard Bégaud[6]; Alicia Gayle; Yola Moride; Patricia Saddier. One additional member to be added from the group working on *The use of PE in crises / When to use pharmacoepidemiology in times of public health crises and emergencies.*
  - 31 January 2025
    - case studies completed
    - first refined and complete draft available (following finalization of the seven report sections by their respective leads).

[6]The co-chair is a mandatory member.

- 30 June 2025
  - following review by editorial board, circulation of the draft among WG members
- 31 July 2025
  - draft available for public comment.
- 15 August
  - closure of time period for public comment.

A final in-person meeting of the WG, to accept the draft, finalize any editing and agree on release of the draft for public comment may be held in June. ***Dates when such a meeting could be held should be selected as soon as possible.***

- **The report layout** will be checked by the editorial board or CIOMS.