

## First meeting of the CIOMS Working Group on Harnessing the Potential of Pharmacoepidemiology for Public Health (PEPH)

Geneva, Switzerland, 2 & 3 November 2023

### Attending 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); Alicia Gayle (Chiesi, Italy); Véronique Kugener (VK) (Takeda, USA); Marie-Laure Kurzinger (MLK) (Sanofi, France); Innocent Ngwa (Roche, Switzerland); Muhamad Younus (Pfizer, USA).

**Regulatory:** Takashi Ando (Pharmaceuticals and Medical Devices Agency, Japan); Miguel Ángel Maciá (Spanish Agency for Medicines and Medical Devices, Spain).

### Attending virtually

**Academia:** Masao Iwagami (University of Tsukuba, Japan)

**Industry:** Justyna Amelio (AbbVie, USA); Karin De Haart (IQVIA, The Netherlands); Patricia Saddier (MSD, USA).

**Regulatory:** Katherine Donegan (KD) (Medicines and Healthcare products Regulatory Agency (MHRA), (UK); Doris Oberle (Paul Ehrlich Institute, Germany); Sabine Straus (Medicines Evaluation Board, The Netherlands); Hui-Lee Wong (Food and Drug Administration, USA).

## DAY 1

### Plenary: welcome and opening remarks for participants attending in person

CIOMS president Hervé le Louet (HL) welcomed meeting participants and described the use of pharmacoepidemiology (PE) today, which today may suffer from misinterpretation or even misuse.

One of the reasons for creating this working group (WG) is to respond to the need for advice for decision-makers in regulatory agencies, governments or industry, on the best use of PE and on the best use of resources for PE. It will be important that WG members — in contrast to academia and industry — talk the same language and share the same objectives. HL indicated that the work of this WG differed from that of other WGs. Its debate will tend to the speculative and its conclusions comparable to an editorial rather than to an original paper.

HL stressed to participants that they could talk freely and that they represented themselves. He requested that they be loyal to the group and not delegate their role to anyone else. He indicated that the work of the WG would continue between the plenary meetings.

## Overview of CIOMS

Lembit Rägo (LR) gave an overview of CIOMS.

A science-based umbrella organization, CIOMS was founded by WHO and UNESCO in 1949. Currently, it has 44 members, including national organizations, international organizations and associate organizations. Its work differs from that of regulatory guidelines in that it is more “how to do” guidance rather than establishing norms, it provides real-world examples and is geared towards implementation. Since its recommendations are not mandatory, its discussions are open. It provides a platform for testing new ideas which have not yet become or been incorporated in regulatory standards.

CIOMS has three areas of work:

- research ethics
- pharmacovigilance (PV) and safety
- product development.

Seven working groups are under way at the moment, on the following topics:

- artificial intelligence in PV
- real-world data and real-world evidence in regulatory decision making
- benefit–risk balance for medicinal products
- severe cutaneous adverse reactions to drugs
- MedDRA labelling groupings
- educational standards for health care professionals participating in medicines development
- good governance practice for research institutions.

## Discussion

**This WG is not a typical working group:** It will not be issuing guidance or proposing good PE practices. Plenty of both already exist. Rather, the WG will move away from the current over-emphasis on PE tools and techniques and regulation, to consider PE from the point of view of global public health assessment, to place it within the context of public health, and to identify when it is useful or not useful to conduct a PE study. PE is a powerful tool, but one that is at times misused and the results of which can be misinterpreted, with a detrimental impact on public health. For example, during COVID, PE studies focused on the very specific risks of COVID vaccines and did not adopt a global public health view of what was needed to combat the pandemic. Indeed, the vast quantity of published information relating to COVID studies often hindered sound decision making. PE study results were even at times contradictory and contributed to the COVID infodemic.

**Similarly, in France, benefit–risk analysis of COVID vaccines may have missed the most important factor.** Studies were conducted on, for example, the relative risk of a given cardiovascular effect in individuals of 20–40 years of age. But since COVID vaccines are not available as a single dose, old people living at home and difficult to reach were likely not to be vaccinated. This group was at high risk of dying from COVID. That is, the greatest risk of COVID vaccines related not to cardiovascular health but to the non-vaccinated population. The needed analysis was inverted and the result was that COVID vaccines were not used to maximum public health impact. Yet regulators appeared to be very satisfied with the studies conducted, even though these did not inform them who had or had not received the vaccine. Pharmacoepidemiologists were also very satisfied with the studies because sophisticated techniques had been used to generate the study results.

**USFDA collected information from all available databases regarding randomized controlled clinical trials that targeted repurposing of existing medicines for treatment of COVID-19.** Its analysis showed that even though these studies were published, over 95% of them were not meaningful scientifically, and could also be harmful from a public health perspective.

**In the pharmaceutical industry most PE studies are conducted to assess the safety outcomes and confirm the benefit risk of a drug and to meet regulatory requirements.** A comprehensive feasibility assessment may be made ahead of a study, looking at what data sources could be used, what would be the estimated sample size, and how exposure and outcomes could be assessed. The assessment may indicate that the planned PE study will not generate valuable data since, for example, the population size will be very small, or, in the case of a new drug, considerable time will be required before a sufficient number of patients has accrued, or, in the case of long-term outcomes, sufficient data will not be available for several years. Yet the study will go ahead so that regulatory requirements are met. In brief, balancing the need to release new drugs onto the market while ensuring long-term safety can be difficult.

**From an industry perspective, PE studies are driven too much by regulators, meaning that a study may focus on a single risk rather than relative benefit or risk:** The limited time available for conducting a study will not permit the entire situation and context, or the patient's perspective, to be taken into account. Sometimes it appears that a high risk is associated with a certain product and so the product is withdrawn from the market, but if the benefit and patient perspective were to be considered, withdrawal of the product might not occur, or it might at least continue to be made available to a certain part of the population or within a specific context. A good analysis of the context in which drugs have been withdrawn is yet to be made. In many cases, the response has been emotional or political, rather than scientific and even though, for certain patients, if used carefully, the drug could be beneficial. (Withdrawal of certain analgesics may have contributed to creation of the opioid crisis.)

**For industry, PE studies are also commercially driven:** for example, a company's strategy may be to be first or best in class, which leads to focusing only to a limited population. The restriction of a study to certain populations may also limit the usefulness of study results. For example, if a study is conducted only in Europe, where populations are older, its results may not be relevant to populations in low-income countries where populations are much younger and communicable diseases much more prevalent.

**In academia, when students are conducting their own research studies, the focus is on getting the best estimate relating to whatever is being studied, which is usually an effectiveness outcome or a safety outcome.** But training programmes could place more emphasis on global assessment of benefit and risk (including where it can shift and change), the burden of disease and unmet need. Introductory epidemiology courses teach students about the etiologic fraction (or population attributable risk), but this is not taught in PE courses. Yet it enables prevalence of use to be calculated and the public health impact of a drug to be estimated.

**Publication requirements or trends influence the type of PE studies that are carried out.** If a study applies modern techniques, it is more likely to get published. But such studies may not be of great use to decision-makers. Indeed they may serve to create a public health information gap. And sometimes published results are misinterpreted because those using them do not have the necessary background knowledge and expertise. Many journals request that the researcher writes about the clinical impact of the study findings when it is

the public health impact of the findings which is of greater relevance. Of great concern is that peer-reviewed journals either no longer conduct proper peer review of papers or, if they do, conduct it poorly. The situation is not helped by the fact that journals are competing with each other and that researchers often have to pay a journal in order to get their paper published.

**PE neglects some areas, such as the interactions or non-interactions between drugs and populations, the public health impact of not treating some of the population when it should have been treated, and/or misuse of the drug in question.**

Pharmacoepidemiologists need to map all the possible interactions between a drug and a population, and to consider the whole “ecosystem”.

**A drug use study provides a first approach to describing the target population,** to discussing benefit–risk and to dealing with the super-imposition of population. (The first definition of PE that was proposed was not about studying benefit and risk in real live settings, but rather the study of interactions between drugs and populations.) The problem is not one of precisely quantifying the risk, using whatever technique (“technological determinism”), but of ensuring that the starting point is data relating to what percentage of the population is using the drug in question. Niches of drugs may also need to be considered.

**PE should be viewed as a public health activity.** Pharmacoepidemiologists need to provide decision-makers with information that they can assimilate: for example, what age groups can safely use a particular drug vs. those age groups for which use would be unsafe. Any decisions that pharmacoepidemiologists make or support should not be based only on the regulatory perspective or only on a communication perspective. They should also apply a global perspective, although the way in which pharmacoepidemiological data is assessed and any decision taken may depend on the specific country. (I.e. think globally but act locally.) Moreover, decisions regarding a specific drug may not be forever but may need to be modified in the light of changing circumstances.

**It is time to step back (perhaps even to go back to fundamentals), to think about the current state of PE and its outcomes.** Too great a focus on PE design and methodological tools, and not enough on public health, is observable, along with too little consideration of the perspective of prescribers and patients.

**Working with policies and how they apply to and can be evaluated by different stakeholders, rather than benefit–risk might be a pragmatic approach.**

(Pharmacoepidemiologists are interested primarily in effectiveness and the balance — not ratio, which is not a good term to use — between benefit and risk.) If a policy or goal is to “Reduce child mortality by 5% by 20XX”, the relevant decision makers and the kind of pharmacoepidemiological information they need can be identified, together with the studies and the timeframe for generating it. In so doing, pharmacoepidemiologists would be focusing on the population, rather than only on a drug or other single intervention.

**Communication has become problematic.** In the past, regulators and pharmaceutical companies were the principal decision makers. But today decision makers include social networks and the media, and politicians pay attention to them. *In the UK little thought was given to the evidence surrounding use of COVID vaccines and how it could be communicated clearly, without any bias, to patients and healthcare practitioners. Similarly, in the US, there was a communication gap between the Centers for Disease Control and Prevention (CDC) and public health frontline workers. A conversation is needed between*

*those we may term “the influencers”, i.e. those who make the decisions, and with the students of today. The latter will be the health professionals of the future.*

## **Breakout into two sub-groups**

The WG was split into two subgroups, each of which included representatives of academia, industry and regulatory agencies:

- **Sub-group 1<sup>1</sup>**: to draft a new definition of the use of PE, i.e. focusing on “the what” of PE
- **Sub-group 2<sup>2</sup>**: to focus on the 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.

The work of Sub-group 1 involves contextualizing PE or the application of PE. The work of Sub-group 2 will be more extensive since it will work on how to improve the application of PE, how to trigger change, how to convince others pay more attention to the public health aspect of PE and to take the necessary action, and give them the tools to do so. Subgroup 1 will probably conclude its work ahead of Subgroup 2, in which case its members can join Subgroup 2.

## **Sub-group 1 breakout**

### **Sub-group 1: key discussion points**

**Tentative titles proposed and discussed** for the work of this sub-group included:

- The rationale (“why”) and scope (“what”) of PE for public health. (Sub-group 2 will cover the “how”.)
- The evolving rationale and scope of PE for public health
- Defining/scoping/contextualizing PE for public health
- The added value of PE for public health
- Public health for epidemiology
- PE in public health
- Scope and rationale of interaction between PE and public health
- Optimizing the use of PE to meet public health goals and objectives
- Can PE meet global public health goals?
- The best use of PE for selecting public health interventions
- The best use of PE for addressing public health issues.
- The best use of PE for greatest public health impact.

Perhaps PE has to be defined, its current state and how it is being used described, why this is or has been problematic. (E.g. a PE study could be wrongly focused or of low quality, but its results could have high media impact, serving to delay or complicate decision making or deviate research). Better use of PE could be proposed, i.e. by bringing back the concept of population into the practice of PE.

Sometimes real-world data can replace clinical trials. But sometimes real-world data cannot answer questions for which we need an answer. We may have real-world data relating to an

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<sup>1</sup> Chaired by Yola Moride. Other members: Takashi Ando; Alicia Gayle; Marie-Laure Kurzinger; Jennifer Lund; Miguel Ángel Maciá.

<sup>2</sup> Chaired by Véronique Kugener. Members: Ana Sofia Afonso; Bernard Bégaud; Innocent Ngwa; Muhammad Younus.

association, but a clinical trial is ruled out. It is important to put each piece of experimental or non-experimental evidence in its proper place.

**Needed definitions:**

- **Epidemiology vs. PE** (but perhaps in the overall report introduction).
- **The three pillars of PE: use, effectiveness and population. Each of these should be defined.** Currently, the focus of PE and much of the PE evidence generated is on effectiveness, relative risk and measures of association, and rather less on drug use or population impact. Moreover, insufficient attention is given to drug use studies. More emphasis needs to be placed on the interaction between use, effectiveness and population.
- **Public health**
- **Public health goal**
- **Global public health goal**
- **Population**, including the different levels or types:
  - General population including health and non-healthy
  - Primary prevention population
  - Secondary prevention population
  - Healthy population
  - Non-healthy (e.g. diabetes, dementia)
- **Determinant of disease**
- **Risk factor**
- **Predictor.**

**Scope of topics to be covered:**

- **Situation analysis:** How is PE currently used in public health? What are the goals in using PE data? Where is alignment and misalignment occurring? In seeking to understand where PE is aligned with public health goals, all the evidence, both interventional and non-interventional, should be pieced together.
- **The need to bring use and effectiveness of drugs in the population back into focus**, to underscore how PE could be better harnessed for the purposes of public health. The public health role for PE when new drugs are being considered or launched should also be noted.
- **PE for new medicines differs from PE for existing medicines, i.e. the sub-group should define scenarios where PE may usefully be applied:**
  - as a contribution to the development of new medicines and how they can be best introduced to a population to achieve a public health goal (while noting that the trend in development of new medicines appears to be for very specific or restricted populations, which is almost counter to the concept of public health)
  - to help optimize the use of existing medicines or repurposing of existing medicines (especially since some countries cannot afford new medicines) and noting that for new medicines, clinical trials may not be feasible or ethical, but that in such cases, PE could generate observational evidence, that could be fed into meeting public health goals.

In both cases, PE studies should be on medicines targeted at the highest burden of disease.

- **Multidisciplinary nature of PE studies:** PE studies may be led by pharmacoepidemiologists but implementing them is likely to require input from clinical experts, statisticians, data scientists, pharmacists, etc. Moreover, those non-PE disciplines should be involved in interpreting the study results for global public health. One of the WG recommendations should be greater involvement of public health professionals in the conduct of PE. (Such involvement is more easily organized in the academic world but a lot less so in industry.)
- **Defining a research question:** Pharmacoepidemiologists typically write research questions around use and effect, and sometimes involving a comparison between two drugs, but may fail to address a public health issue. How can pharmacoepidemiologists become better at formulating a research question to address a public health issue, before a PE study is initiated? Two or three PE research questions that address public health issues, and bringing in the concept of absolute numbers, could be included in the report as real or theoretical illustrative examples. But it was noted that the questions addressed by a typical PE study and the approach applied (from research question to methods to analysis to response to research question) tend to be at a different level from those targeted at addressing a public health issue. Examples of current PE studies that adopt a more public health approach include those analysing the decline in cancer mortality in the US and whether this decline is attributable to, for example, improved treatment or screening, or lifestyle change. Examples of research questions that failed to address public health issues could also be presented. Similarly, WG scope could include consideration of how to determine a public health goal, how to plan a study with a public health goal and how a PE study could contribute to “One Health” (for example).
- **Sampling, including surveys** should take into consideration the structure of the population. Public health experts have gained considerable experience in sampling while conducting long-term surveys.

**PE could better address public health issues by:**

- refining or broadening research questions
- improving sampling
- using the best measurements, such as attributable fraction of the risk in the population
- refining the outcomes of impact measures.

- **Metrics and measures:** PE needs to focus also on absolute number, not just relative risk measure of association and magnitude of effect. PE needs better impact measures, that take into account both use and effectiveness. Other measures routinely used in public health, such as the etiological fraction of the risk, which is a function of the relative risk, and the use of the drug or other intervention in the population, and which are designed to measure public health impact, have not been included in PE studies of recent years. In order to apply them, good data on use in the population is required. But very often such data is unavailable, or if available, has been collected in a reactive mode (e.g. during a health crisis). Pharmacoepidemiologists should build a research agenda incorporating public health metrics. They should generate data on the use of a drug or application of an



intervention at the same time as they generate data on relative risk, irrespective if of whether it is safety or an effectiveness outcome that is being studied. In so doing, the value and contribution of PE for public health would increase.

- **“Transportability”(extrapolation) of data:** If the aim is to optimize treatment outcomes, consideration needs to be given as to how to generalize or “transport” the results of a single study or trial to a broader population. (See references below.) Trial data and traditional real-world data relating to a small population can be “transported” to a broader, more heterogeneous population of interest. Some methods (reweighting, generalizing) that are used to extend inferences from one population to another, to help determine where treatment resources can best be directed, could be presented.<sup>3</sup>
- **Communication and training:** Do public health practitioners know how to critically appraise PE studies, how to read PE evidence and how to synthesize it? Do they understand its limitations? A well-designed, implemented and published study that demonstrates the benefits or risks of a medicine may not be useful to a public health practitioner if s/he does not know how to interpret the study results in order to reach the best decision for public health. Does the responsibility for correct interpretation of a study lie with those who generated the PE evidence (and assuming that the data generated is the data that public health practitioners need) or with those who use the data? PE education and training are clearly needed. This topic belongs to Sub-group 2 but should be referred to in e.g. the report introduction.
- **Lack of access to data on population-wide drug usage (both at a point in time and across time) hinders the contribution of PE to public health.** The WG should encourage those generating use data, including a description of how they change over time (for risk minimization), to publish it. Sufficient tools for investigating drug use exist but not enough use data is generated, probably because it is difficult to publish descriptive studies and if they are published it is not in high-impact journals. There is little incentive to publish descriptive data.
- **The scope of public health issues that PE could contribute to could include:** over-prescribing; under-prescribing; deprescribing (e.g. in elderly patients); misuse; non-use; over-use; sub-optimal use (adherence); drug-resistance; drug-resistant diseases; and drug repurposing for use in low-resource settings.
- **Health and socioeconomic databases:** Some of these are already used quite extensively in PE. Health data can be linked with health determinants such as socioeconomic level or geographic location (rural vs. urban). The information collected in health surveys, via questions about lifestyle, ethnicity and ethnic background, can serve as modifiers for the topic of a PE study for which no data is available. Health surveys can be made more useful for PE by including questions on drug use. It was noted that public health relies heavily on cross-sectional and population-based surveys, and that pharmacoepidemiologists have vast experience, expertise and knowledge in the analysis of population longitudinal healthcare data. France’s national health database contains data collected across its entire 65 million

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<sup>3</sup> See for example: <https://pubmed.ncbi.nlm.nih.gov/28535275/>; <https://pubmed.ncbi.nlm.nih.gov/30675984/>; <https://pubmed.ncbi.nlm.nih.gov/36843494/>; <https://pubmed.ncbi.nlm.nih.gov/33015888/>; <https://pubmed.ncbi.nlm.nih.gov/30312378/>.

population. Data from such a database can help to bring back the concept of population into PE, not simply the exposed population but the “global” population.

- **True collaboration:** Tackling issues such as misuse, over-prescribing, deprescribing and drug-resistant diseases, requires true collaboration between PE and public health. If PE and public health are to be integrated, multidisciplinary effort and input from clinicians, data scientists, pharmacists and others are required.
- **Advances in information technologies:** These can encourage the belief that anyone can conduct a PE study (e.g. apply propensity scores). But the resultant analyses may be lacking in terms of clinical input and mislead public health practitioners. Vetting and evaluation of PE study results by pharmacoepidemiologists are needed. Nevertheless, AI and other new tools can contribute to PE and the report could provide some examples of this. That said, the report will not be available for around three years and by then these new technologies — which are already being used quite widely — will be ubiquitous.
- **What’s in it for the pharmacoepidemiologists?** It is beneficial to have data on usage because these can be of great use to safety departments and public health. But for those in industry who carry out studies within a regulatory context, a study on usage may not be needed for their purposes. Others in industry may carry out use studies for a medical affairs purpose or to understand market access (e.g. to understand where is it being used, whether it is being used in the right populations, in order to target messaging or to discuss access in a country where the company currently has no access). However, such studies will not provide definite use numbers as to how many patients are using the drug since the data used for the analysis is only of market sales, which may not equate to the actual quantity of medicine prescribed, and which do not indicate whether the medicine was used appropriately or taken as prescribed. Ideally, use data should not be based only on sales, but also on e.g. the characteristics of the patients.

**Topics out of scope or to be referred to only briefly:**

- PE methodology.
- Clinical trials.
- Precision medicine is out of scope since it attempts to predict a treatment outcome for an individual whereas PE collects data for a population and attempts to pinpoint effects and to understand whether a cause is indicated or simply an association. It was noted that although precision medicine is embedded in the process of developing new drugs it risks creating greater inequality (i.e. is almost counter to public health). The impact of innovations in precision medicine on screening has been beneficial for public health though: the more successfully the different types of markers of disease can be identified and understood, the greater our capacity to screen for them, to diagnose disease earlier and determine the most effective treatment. Thus in future, PE studies will be a mix of clinical epidemiology and molecular / biological investigation. Integration of OMIX data with large healthcare databases, with genetic data, with biomarker data that are being developed now and that will inevitably become more commonplace, offer potential for increasing the contribution of PE to achieving public health goals. In brief, some limited discussion of this area could be included in the report given that it represents the future and will become more mainstream.

**Potential stakeholders** include those in public health practice with some awareness of PE, who use real world data and who could bring a public health perspective to the WG:

- WHO (those working in data science)
- European Centre for Disease Prevention and Control (to be contacted via an EMA contact)
- World Federation of Public Health Associations
- Public Health Agency of Canada
- UK Health Security Agency and Office for Health Improvement and Disparities
- US Centers for Disease Control
- London School of Hygiene and Tropical Medicine
- Institute for Health Metrics and Evaluation (IHME) (responsible for the Global Burden of Disease study (GBD) which provides a comprehensive picture of mortality and disability across countries, time, age, and sex)
- Surveillance, Epidemiology, and End Results Program (of the National Cancer Institute)
- European Public Health Association
- Asia-Pacific Academic Consortium for Public Health
- World Federation of Public Health Associations
- Ministries of health that also serve as a national public health agency
- Politicians who make decisions on health initiatives is another stakeholder group for consideration, but are difficult to define precisely; it was acknowledged that many of them have little knowledge of public health or PE but that the impact of social media on this group can be significant. A social media specialist could contribute to future discussion.

#### **Sub-group 1: additional comments**

- The concept paper is about what PE can bring to public health whereas during the plenary discussion the emphasis was more on how to give a public health perspective to what pharmacoepidemiologists do. Ideally, a title is needed that covers both of these angles.
- The term PE does not need to be redefined since the recently revised definition of the International Society for Pharmacoepidemiology (ISPE) is considered to be adequate.<sup>4</sup> But it was agreed that within the scope of this group the interaction between medicines and people must be highlighted (population).
- The premise is that drugs are introduced in order to achieve public health goals. But how do we define what is a public health goal? What is the rationale of PE with respect to public health?
- *How is uncertainty dealt with in PE evidence or studies and how can we address such uncertainty within a public health context? How do we achieve population-level reasoning?*

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<sup>4</sup> A scientific discipline that uses epidemiological methods to evaluate the use, benefits and risks of medical products and interventions in human populations.

- If a drug decreases mortality, what is the impact on the prevalence of a disease and how then should prevalence be measured (point prevalence, period prevalence, etc.)?
- The regulatory world is strict. It mandates that PE studies are of high quality and apply the appropriate methodological tools. PE studies could therefore be used to assess interventions other than drug interventions.
- Clearly, the world of public health and the world of PE are separate worlds. For public health practitioners, drugs and PE represent just two elements of their work, and not its totality. Thus the scope of public health is wider than that of PE which focuses primarily on drugs. But PE can make an important contribution to the development of public health policies. This sub-group should include a public health practitioner.

## Sub-group 2

### Sub-group 2: key discussion points

- **The proposed title for this group is:** How to harness the potential of PE for public health. (I.e. the "how".)
- **Sub-group 2 needs the definitions of PE and public health from Sub-group 1** in order to structure its own work.
- **Sub-group will focus on how to conduct PE for public health.** Its proposed outline incorporates 7 questions:
  1. What is the current definition of pharmacoepidemiology? What are pharmacoepidemiology studies and what are public health studies?
  2. How is E being assessed and measured (e.g. populations, drugs, emergencies, issues)? Has PE become self-centered?
  3. What are the gaps in PE communication?
  4. What constitutes effective communication of PE for public health?
  5. What is the impact of effective PE communication?
  6. How can we "reconcile" and integrate PE and public health into a single ecosystem?
  7. How can we convey this reconciliation to the different stakeholders?  
(See also page 15, which presents the list as later refined.)
- Sub-group 2 should include a **representative of a regulatory stakeholder and a representative of a patient organization** (but see also page 13).
- **Care should be taken to ensure that the work of Sub-group 2 does not overlap with any of that of Sub-group 1.**
- **Sub-group 2 deliverables** should include recommendations and education methods.
- **The WG should create an action plan**, including drafting of, for example, a white paper, recommendations, or educational material.

### Sub-group 2: additional comments

- Interactions between medicines and population were considered, focusing not only on benefit–risk ratio or balance, but taking a global perspective, meaning that two populations not covered by a PE study, i.e. those who were not treated with a drug but should have been, and those using the drug in the absence of any justification, are also taken into account. Poor outcomes for these two populations may be greater than the totality of the adverse effects of those who were/are treated.
- The concepts of benefit–risk and treatment exposure needs to be reviewed. Is benefit–risk really the key issue?
- The voice of the patient is important. PE studies are communicated to and read by patients. If they are not communicated well, misconceptions may result.
- If PE studies are conducted only to meet regulatory requirements or only for academic purposes they may not meet public health needs.
- PE studies are generating an overwhelming amount of information, which may be intellectually satisfying, but what is its intent and how can it be simplified?

- More examples of the application of PE in the non-pharma world are needed to help inform and expand the discussion.

### **Day 1 plenary discussion with participants attending virtually**

*The sub-group chairs gave an overview of the morning discussion of their sub-group and the topics proposed by their sub-group for inclusion in the WG report.*

**The role of Sub-group 1 is important strategically** since it will be responsible for clearly explaining what the WG wants to achieve, including by presenting theoretical and/or real examples, and explaining how PE can be applied for best public health results. The aim is not to create a set of guidelines which provide steps on conducting a PE study.

**Much of Sub-group 2's earlier discussion centred on the need to bring the focus of PE back to population** (both exposed or non-exposed), be it local, national, regional or global, which is what public health is interested in, whereas often the focus is on an individual patient who is benefiting from a medicine. Sometimes not all of a population must take a medicine in order for that population to benefit.

**The WG must define how best to describe the interaction between medicines and population** and question whether, in any given country, or globally, we are doing the best we can with the medicines we have, and ask what proportion of the population is treated, what proportion of the population is untreated, what is the impact of treatment or non-treatment. Doing so would enable PE to move beyond the individual benefit–risk and towards the whole population.

**The scope of the WG is broader than preparing for future health crises.** Up until now public health professionals have been interested in PE in only a limited way: for example, during pandemics or vaccines campaigns. Thought should be given as to how the WG can engage them.

**Some consideration was given to “innovation”,** as illustrated by the current digital and data revolution, including novel methods for data analysis and digitized data collection used for PE purposes, and what these mean with respect to building patient trust. HL reminded the WG that its role is to look at PE strategy rather than tools used for PE. That said, as a result of the application of novel PE methods, more data will emerge around public health issues and patients will form their own opinions. This needs to be taken into account when planning communication. The interface with other initiatives such as the European Health Data Space which contains a lot of sensitive information gathered from patients may be relevant. It too tries to build trust, although more so from the point of view of ensuring that patients are willing to provide data.

**Attaining a balance between the quality of the PE data and results, and the speed at which they are published or communicated,** was stressed.

**Perhaps nine out of ten PE studies are not published.** Moreover, a lot of PE studies are carried out for regulatory reporting requirements and not translated into publications that can inform or help patients, or increase their trust in PE. As mentioned earlier, many journals request discussion of the clinical impact of PE results but not the public health impact of the results. Yet the latter could contribute to “population thinking”.

*Lessons learned from public health practice could be included in recommendations focusing on the “how”. Very powerful PE tools have been developed but sometimes technique and sophisticated statistical approaches take precedence, and the population is ignored.*

*Instead of producing an original paper, the WG could produce an editorial which presents ideas and thinks beyond PE’s current status. But an editorial could be too similar to an opinion piece. A framework covering the dimensions of public health where PE could be brought in, might be a good alternative.*

## DAY 2

### Plenary discussion

**LR recommended that, to avoid overlap, a mapping exercise of other groups working on the same or similar topic be carried out.** Other groups could be invited to present an overview of their work to the WG. Going forward the WG should also seek to be aware of any new initiatives involving PE that may overlap with the work of this WG.

The chair of each sub-group provided a brief overview of its Day 1 discussions and conclusions.

VK stressed again that **Sub-group’s 1 definition of PE will be critical to the work of Sub-group 2** since the current intent of PE is not always very clear, as evidenced by the current focus on methodology which can lead to a “restrictive” conclusion which is not applicable to public health. The focus on methodology could be said to have derailed PE.

LR mentioned that selecting a patient organization for participation would be difficult since patient organizations have very different profiles and even within them there can be very diverse views. HL’s view is that patient organizations can be invited to comment on the draft report but should not be invited to participate in either of the sub-groups. **It was agreed that patient organizations would not be invited to participate in the WG or WG sub-groups.**

Communication channels are very competitive and focused on sales. **Therefore a lot of communication material is produced very quickly, often by writers/journalists/social media contributors who are not particularly knowledgeable about public health.**

Counteracting their influence and impact, or trying to improve how and what they write on public health issues, is very difficult. But this area should at least be acknowledged in the report. One-page policy briefs could be a tool for communicating with policy-makers.

**Many interactions between drugs and population could be explored.** PE is only a tool. It describes effect but not cause. It should not drive public health decision-making but be used together with other tools and disciplines.

**Confounding by methodology can lead to very misleading results.** It was noted that many PE papers are reviewed by junior professionals who do not have a broad view of PE.

**Pharmacoepidemiologists are trained in association and regression analysis and think more in terms of conditional distribution as opposed to counterfactuals which may provide a means of handling a bigger population and inform decision-making.** AI can be applied for counterfactual modelling. The aforementioned “transportability” methods can be likened to counterfactuals since they are based on a study performed in one

population but then ask questions such as, “What if X had been done in this bigger population?” (i.e. you are standardizing to that bigger population).

**The concept of population appears to have been lost from PE but is still very much present in epidemiology**, geography of health and spatial epidemiology when you compare regions or countries and apply standardization. PE should incorporate analysis of trends and changes in the use of drugs.

### Sub-group 1 breakout: comments additional to Day 1

- Sub-group 1 aims is to propose how PE can be applied to epidemiology and made useful for public health. The WG is seeking to extend traditional PE outputs, to make them useful for public health decision-makers, but not by changing its methods or research questions.
- How can what is done in PE be measured against public health goals?
- The definitions of terms needs to communicated to Sub-group 2, together with a description of the three pillars of PE (use, effectiveness, population) since these will guide the direction of their work. Following the meeting, JL forwarded the ISPE’s revised (but not yet publicly available) definition of epidemiology: “A scientific discipline that uses epidemiological methods to evaluate the use, benefits and risks of medical products and interventions in human populations.” The aim of the revision was to make it more inclusive by focusing not only on drugs but interventions in general, including devices and genomics. However, it was noted that only “populations” are now referred to in the definition, and not “large populations” as formerly.
- Probably the public health collaborator (TBD) will be best placed to define public health and public health goal. In PE, when population is referred to, it is in terms of effects on the population (of a drug). But in public health, population is more broadly viewed as consisting of people with different characteristics living in different countries, with different needs and different levels of access to health care. Old definitions of “population” referred to large populations, whereas for current definitions this is not always the case.
- Determinant, risk factor and predictor - each need to be defined because they are not interchangeable.
- In defining “use”, non-use, misuse, contraindicated use, etc., could be incorporated.
- The impact of treatment and of non-treatment were discussed in the plenary sessions. A population measure for those could be defined.
- Sanofi worked with the Institute for Health Metrics and Evaluation (IHME) on development of a co-morbidity tool and how exposure to drugs/treatment could be incorporated in GBD. Someone from GBD would certainly be able to contribute to the WG.
- In showing that use of a drug decreases the duration of a disease, an impact on prevalence could also be demonstrated, and therefore the impact of a drug. Similarly, improved screening might contribute to reduced incidence of a disease which would also affect prevalence. These are examples of how PE can contribute to public health when it studies the interaction of drugs with the population. PE can quantify



parameters such as the number of people who did not die, the resultant increase in the size of the population, etc.

- A PE study may have been carried out to e.g. analyse the impact of a drug which reduces respiratory conditions in pre-term babies and to reducing infant mortality, but from a public health point of view the interest will be not in one particular indication for one particular situation, but in what could be the impact of such a drug globally.
- In PE, the journey is from populations to patients: the results relating to a population are applied, in clinical practice, to individual patients. i.e. PE focuses on the effects of a medication in the population with the indication for treatment. But it is also important to study the effects of a medication on the broader health of the population and to do that the research question has to be appropriate. The section on research questions should be not necessarily on how to write a research question but on understanding the context around it.
- By definition, populations used for a PE study will represent only a sample of a population. The section on sampling should discuss not sampling methodology, but extrapolation from a sample to a population. (Whole population PE research is not possible in most countries since many countries (unlike France) do not maintain a national health database.)
- The Westreich et al. paper could be used as a case study.<sup>5</sup>

### Sub-group 2 breakout: comments additional to Day 1

Its goal is to analyse any current gaps in PE with respect to public health.

The sub-group reduced its list of topics from seven to five (see page 11):

1. **What is the intent of PE?** PE provides an overwhelming source of information with respect to published studies but their impact on public health is questionable. PE studies are very diverse but their appropriateness can be questioned. What are their intended outcomes? Has “super” PE derailed the impact of PE in public health?
2. **What aspects of the population are included in public health?** What is global population? What does it mean? Are exposed and non-exposed individuals being referred to? (This topic was considered as potentially overlapping with the work of Group 1.)
3. **PE frameworks:**
  - for academia this is likely to be publication and ensuring a robust methodology
  - for regulators, the focus will be on effectiveness and safety
  - for industry the focus is calculation of benefit–risk, but sometimes PE studies are mandated by regulators and sometimes industry conducts PE studies for its own needs
  - healthcare provides an additional framework.
  - Are the different frameworks aligned?
4. **What are the gaps in PE with respect to public health?** Are simpler and faster approaches available for study design? Can common sense be applied to study

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<sup>5</sup> <https://pubmed.ncbi.nlm.nih.gov/28535275/>

design? Can we measure or score the appropriateness of a study? Does a measure of appropriateness need to be developed? What is a good use of PE studies? Is the high expense of PE studies justifiable to society? How are the results of PE studies used in/for public health?

5. **The channel of communication to public health and the quality of the communication.** PE studies are made available, but only those with PE expertise can interpret them. What information should a PE study generate or not? How are PE study results translated and communicated (for public health)? What should be communicated or not. Examples will be provided of what has worked well and what has worked less well. Who decides on the interpretation of a PE study and what is to be done thereafter? Who are the stakeholders and audience?

### **Day 2 plenary discussion with participants attending virtually**

*The sub-group chairs gave an overview of the morning discussion of their sub-group. There appear to be three areas of possible overlap between the two sub-groups:*

- *How is PE operationalized in current practice?*
- *Why has this been problematic?*
- *The concept of populations.*

*A PE study may be overly restrictive. If propensity scores are used and as a result a large number of people are excluded, then statistically the result is a less biased estimate but at the cost of excluding that large number of people. So how can we use standardization or extrapolation so that a piece of evidence can be applied to another population setting?*

*Examples or use cases should be included in the report to illustrate the report recommendations or suggestions, as well as examples of what could be done, more often, of use of PE at the public health level. These examples could include missed opportunities. Ideally, examples and use cases should be selected from all over the world.*

*Are drugs or vaccination being referred to? Vaccination generally covers everyone within the population whereas drugs may cover only part of it. So it may be advisable to focus on vaccination, as opposed to drugs for rare diseases. This consideration brings us back to public health and what are the populations targeted by public health goals. But public health is very interested in chronic diseases, such as diabetes and cancer. So the focus is not only on two extremes (vaccination and the general population vs. rare diseases), but everything in between.*

*Pharmaceutical companies carry out PE studies in line with their own commercial strategies but public health priorities are likely to be different. If public health priorities are known, existing PE studies can be reviewed to identify any gaps in PE data.*

*A large number of PE studies were conducted on COVID vaccines. Before starting the vaccination campaigns the number of coincidental associations that were likely to be observed within two weeks of administration could have been estimated and decision-makers, public opinion and the media informed as to likely medical events. This lack of preparation served to strengthen the position of anti-vaxxers, to exacerbate the infodemic and to increase the level of vaccine hesitancy. In Europe a lot of data on vaccination adverse events of interest was available but perhaps not as publicly available as needed.*

*Also, expected vs. observed events were investigated only after a signal or potential signal had been observed.*

*During COVID 19, the level of coordination at global public health level was unprecedented: USFDA engaged with WHO, other regulators and other governments. But there was a mismatch between communication directed at the public sphere (posted on government websites or published in peer-reviewed papers) and how that communication was used by others. This issue may be out of scope for Sub-group 2 but the question as to what should be communicated is valid.*

*It needs to be borne in mind how difficult it is to act wisely during a public health crisis and especially for politicians who have many issues demanding their attention. The question is why pharmacoepidemiologists did not advise them. Information was available but not communicated to them. How can PE studies and results be explained to politicians?*

*Crisis scenarios (e.g. during a pandemic or acute short-term situation, when there is rapid circulation of information) should be distinguished from “normal” scenarios. We may have different WG recommendations for the former when deadlines are tight and decisions have to be made quickly and the latter when a longer-term condition or health issue (such as maternal outcomes) is under consideration. The “safety profile” of a crisis changes every day and people are needed who can question the situation every day; epidemiologists could probably play that role. In effect, we are talking about different use cases.*

*To what extent should something be presented in lay terms to facilitate understanding of outcomes? Pharmacoepidemiologists are able to determine whether a study design was appropriate or not, but others such as journalists, public health practitioners or members of the general public are unlikely to have this capability. The quality of communication, and strategies for communication, are important. A framework around what is appropriate evidence to generate for the public, and how to make it insightful, could be created.*

*The benefits or risks of conducting or not conducting a PE study also need to be considered. Sub-group 2 discussed examples of misuse of PE studies. Conducting a PE study and announcing that the results will be published could worsen a problem if the results are misunderstood or the research question was not answered by the study. Sometimes many PE studies are conducted with the same objective. In such a situation what is the outcome or impact?*

*How does one decide between a study that takes two or three years and a much shorter study? If a shorter study is carried out, information on long-term outcomes and rare outcomes might not be gathered.*

*Some WG members may not have considered their work from a global public health perspective before and the wider impacts of their work. So this WG may offer them a new way of thinking.*

## **Agreed WG structure**

It was decided that HL and BB will serve chair the WG.

Following selection of a sub-group by the virtual participants, the full composition of the sub-groups is as follows:

**Sub-group 1:** Chaired by Yola Moride. Other members: Takashi Ando; Katherine Donegan; Alicia Gayle; Masao Iwagami; Marie-Laure Kurzinger; Jennifer Lund; Miguel Ángel Maciá; Patricia Sadler, Masao Wagami.

**Sub-group 2:** Chaired by Véronique Kugener. Other members: Ana Sofia Afonso; Justyna Amelio; Bernard Bégaud; Karin de Haart; Innocent Ngwa; Doris Oberle; Sabine Straus; Hui-Lee Wong; Muhammad Younus.

CIOMS will contact WG members who were not present in person or virtually during this meeting to ask them which sub-group they wish to join. However, the balances have to be considered so that each sub-group has best possible composition in terms of representatives of academia, industry and regulators.

### Process and next steps

**Agreement on the content of the concept paper can be assumed.** But the WG may provide additional points to be considered as work progresses. A WG concept paper is always a starting point, to initiate discussion and then the WG decides on what and how best to take it forward.

**The bulk of the work of the WG must be carried out between the in-person WG meetings.** The role of the WG meetings is to provide a forum for discussion. The meetings of the sub-groups should be organized by the sub-group chairs, but the CIOMS Secretariat can assist. Ideally, each group should prepare a set of slides to be presented at the next in-person WG meeting. By the next in-person WG meeting, each sub-group should have a mature proposal as to the topics it will cover and that it wishes to see included in the report. During the next in-person meeting the list of topics to be included in the report should be agreed. Comprehensive minutes of the WG meetings (but not of sub-group meetings) are usually produced and made publicly available on the CIOMS website.

**Once the two sub-groups consider that they have completed their work, a virtual meeting can be organized to discuss how to create a single product,** and whether an in-person meeting is also required for further development and finalization.

**In-person meetings can take place in locations other than Switzerland,** provided that the cost would be no greater than if held in Switzerland, and provided logistical support is available in that location. MLK indicated that the next virtual meeting could possibly be held at Sanofi in Paris. The location of the next virtual meeting should be decided within the next two to three weeks.

**The format and length of the WG report (or whatever is selected to be the deliverable) should be decided by the WG itself.** Previous WG reports have ranged from 60 pages to almost 300 pages. But it is up to the group to decide on the key messages to be communicated, how to communicate these and how to reorient PE.

**Given that the report will be a consensus report, all WG members must feel comfortable with the report draft before it goes out for public consultation** (for about six weeks) including by regulators, academia, industry and patient organizations. WG members themselves should encourage review by those whom they consider can provide useful input. Working through the comments received can be a significant task since some reports receive extensive comments. Once these have been dealt with, the WG has to review and endorse the revised report before it undergoes final editing and layout.

**Although the mandatory deliverable is a report, this does not preclude other deliverables.** Webinars can be organized when the report is launched, papers submitted to

scientific journals and training modules developed. The concept paper could also form the basis of a short submission to a journal.

**WG members are free to talk about the WG at any other meetings they attend** but should inform the rest of the WG when they plan to do so and share any information or slides they have presented.

A WG is usually operational for three years (but can exceptionally extended). Each WG generally hold up to two in-person meetings per year and sometimes one- or two-hour virtual meetings in between so that WG members can update each other and some decisions can be taken quickly.

**A dedicated and password-protected space will be created on the CIOMS website** so that WG can share drafts and materials of interest.

***Action items Subgroup 1***

- The list of proposed topics to be forwarded to Sub-group 1 virtual participants for comment and input.
- A skeleton/table of contents (TOC) to be created, and then each piece of the skeleton/item in the TOC to be developed.
- MLK to contact IHME to seek participation in the WG.
- JL to draft a definition of the three elements ((i) use, (ii) benefits and risks of medical products and (iii) interventions in human populations) of the ISPE definition of PE.
- Monthly virtual meetings to be organized by the sub-group, on Mondays, using the Teams platform, at: 07:00 EST; 13:00 CET; GMT +9. The first meeting will be held on Monday, 11 December 2023.
- Everyone to give some thought to possible visuals that could be incorporated in the report.

***Action items Subgroup 2***

- A coordinator (from on-site attendees) was assigned for each of the 5 topics of the outline.
- The outline was distributed to all Sub-group members
- Sub-group 2 plans to hold a virtual meeting the week of November 13.