Third meeting of the CIOMS Working Group:

Harnessing the Potential of Pharmacoepidemiology for Public Health (PEPH)

Paris, 23 & 24 May 2024

Participants (in person), both days

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

Academia: Bernard Bégaud (BB) (University of Bordeaux, France); Kate Gillespie (Institute for Health Metrics and Evaluation (IHME) at the University of Washington); Yola Moride (YM) (Rutgers University, USA).

Industry: Ana Sofia Afonso (AA) (Eli Lilly, The Netherlands); Alex Asiimwe (Gilead); Selin Cooper (AbbVie, UK); Alicia Gayle (Chiesi, UK); Karin de Haart (IQVIA, The Netherlands); Véronique Kugener (VK) (Takeda, USA); Marie-Laure Kurzinger (MLK) (Sanofi, France); Innocent Ngwa (Roche, Switzerland); Patricia Saddier (MSD, USA); Muhamad Younus (Pfizer, USA).

Intergovernmental organization: Noha Iessa (WHO, Switzerland)

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

Participants (virtual)

Academia: Masao Iwagami (University of Tsukuba, Japan) (23 May); Jennifer Lund (University of North Carolina, USA) (23 May).

Industry: Montse Soriano-Gabarro (Bayer, Germany) (23 & 24 May).

Regulatory: Hui-Lee Wong (HW) (Food and Drug Administration, USA) (23 May).

DAY 1

Welcome and opening remarks

Hervé le Louet (HL) opened the meeting and thanked participants for their sustained contribution and commitment to this working group (WG). He indicated that now is the time to pull together the work of the two sub-groups. He stressed that participants must be comfortable with any recommendations.

Lembit Rägo (LR) expressed CIOMS' appreciation of Sanofi's hosting of the meeting. He gave a brief status update of the work of the other WGs:

- in March 2024, CIOMS published *MedDRA Labeling Grouping (MLG): a Standardized Approach to Grouping Adverse Reactions in Product Safety Labels*
- *Real-world Data and Real-world Evidence in Regulatory Decision-Making* will be available as of 30 May 2024

- The public consultation on the draft report on the *Benefit-risk Balance for Medicinal Products* is now closed and comments are being reviewed and incorporated as appropriate.
- The draft report on Severe Cutaneous Adverse Reactions (SCARs) is available for public consultation until 6 June 2024.

The work of other WGs is progressing, including that of the WG on *Artificial Intelligence in Pharmacovigilance* . This is a controversial topic and the need to avoid harm has to be balanced with enabling its application to development and innovation.

Bernard Bégaud (BB) commented that pharmacoepidemiology (PE) is underpinned by its long practice. Many international societies have issued documents on PE, making it difficult for this WG to focus on its principal objective. **PE is a bridge science** incorporating medicine, public health, epidemiology, computing science, social sciences, etc. **It also represents a key approach to optimizing the contribution of medicines to public health (PH).** But despite the PE developments of recent decades in statistical computing, artificial intelligence, use of propensity scores, etc., it is not certain that the contribution of medicines to PH is being optimized. Rather, there is an obsession with the tool and its methods.

The outcomes of this WG will be for the benefit of decision-makers, including regulatory agencies and manufacturers. The WG will not be producing a methodological guideline since many such guidelines already exist. The questions this WG must try and answer include when should a PE study be conducted, the information such as study should generate, the time frame for the study, what might be its limitations or its untoward consequences, and whether a simpler or faster approach to generating the desired evidence could be applied instead.

BB mentioned that 124 PE studies were conducted on COVID-19 vaccines, including on their effectiveness, their side effects and the number of deaths that they prevented. But not one study developed a global view of the benefit : risk balance of the vaccines. In brief, the PE studies undertaken were a poor use of PE. They were too narrow, focusing on a particular adverse event such as pericarditis. Conversely, PE studies that were sorely needed were not conducted. Didier Raoult claimed that hydroxychloroquine was effective in treating COVID-19 in the early phase of infection. He based his recommendation on the results of a few studies conducted at a research hospital in Marseille. The mistake of the French Ministry of Health was that it did not conduct a study to determine whether or not Raoult's claim could be substantiated. In the absence of such a study, the surrounding debate continued for two years, amidst ongoing media frenzy. PE studies should examine medicines : public health interaction, and public health impact.

HL commented that the situation concerning Raoult demonstrated the confusion between strategy and truth. Creating and implementing a study to determine whether or not hydroxychloroquine was effective in treating COVID-19 would have taken a lot of time. Yet decisions regarding COVID had to be made quickly. **The question therefore is how can we be better prepared to respond to such issues in the future.**

LR referred to a *Nature* article ("Trends in COVD-19 therapeutic trials") written by US Food and Drug Administration (FDA) staff, which analysed the results of clinical trials that led to the repurposing of medicines for treating COVID-19. It concluded that 95% of the studies concerned

were poorly designed. Yet if model trial designs had been available early on during the pandemic, pooling of data would have been facilitated.

BB indicated that, during COVID-19, studies in France could have been conducted promptly using reimbursement data. He provided examples of negative public health impact that could have been avoided if PE tools (e.g. to monitor and measure exposure thresholds) had been used (or used correctly).

Overview of discussions to date of sub-group 1

Yola Moride (YM) referred to some work currently under way which underscores the importance of this WG. In the USA a society of clinical pharmacists, is very interested in PE and PH, is conducting a survey as to which universities have departments or faculties that combine PE and PH.

YM described **the work of Sub-group 1, which focused on addressing the why and what for harnessing PE for PH. Its proposed title for Sub-group 1 is: *The role of pharmacoepidemiology for public health: scope and enquiry*.**

The sub-group considered what PE studies need to generate in terms of metrics and what PH concepts are important for PE purposes, and vice versa.

The sub-group was split into two further sub-groups tasked with going back to the foundations of PH and PE, to identify already-established definitions and concepts. Currently, the focus is often on complex analytics, meaning that fundamentals are overlooked. Additionally, topics such as PH priorities vs. priorities for PE studies, which may not always be aligned, were discussed.

Some PE and PH definitions were not so straightforward and not easily extracted from dictionaries or textbooks. For these the mission statements and websites of relevant PH organizations were consulted.

The terms and concepts reviewed should be mapped against those that Sub-group 2 worked on.

Ana Sofia Afonso (AA) presented a paper on **a proposed framework for PE** that she and Doris Oberle had drafted. (See below.)

Miguel Maciá (MM) researched **a framework for PH,** including WHO's global framework for PH.[1] He concluded that PH decision-makers have some tools for making decisions regarding vaccines, but rather fewer for helping them to make decisions regarding medicines. Similarly, **when conducting a PE study, pharmacoepidemiologists do not usually consider social, economic, educational and cultural factors as relevant co-variates, even though these may have an impact on the medicines use or health outcomes being studied.** Conversely, PH programmes (e.g. for tobacco cessation, to tackle obesity or HIV/AIDS), at local, regional or global levels that use medicines as a tool, do not make full use of PE data or tools to evaluate their programmes' effectiveness or safety. HL commented that **PE could be the tool that not only facilitates consideration of the efficacy and safety of a medicine from a clinical pharmacology point of view, but also to generate a more holistic view of a medicine's safety and efficacy.**

[1] MHRA also has a PH framework that integrates good pharmacovigilance practice. The Duke-Margolis Center for Public Health Policy has also proposed a PH framework that incorporates PE principles.

Overview of discussions of sub-group 2

Véronique Kugener (VK) reported on the Sub-group 2 discussions that she had led. These focused on three aspects of PE:

- **The intent of PE.**
- **A draft framework for PE** (recognizing that different groups participate in PE decision-making, including academics, pharmaceutical companies, regulatory agencies and civil society) was prepared by Ana-Sofia Afonso and Doris Oberle, and circulated across both sub-groups for comment).
- **Establishing a framework to communicate the value of PE as applied to PH,** covering what is to be communicated, the target audiences, how to strategize communication.

Additional discussion points

- **The WG needs to provide guidance (for decision-makers) as to when PE can be used.**
- The big "bullet points" could be:
  - what PE needs to generated, which may vary according to different situations
  - when "the what" applies.
- **An inventory of situations could be developed as to when PE should be applied.** A specific example could be presented and worked through.
- **A major gap exists with respect to interpretation of PE results.** Interpretations tend to be based on what regulators want and not in terms of PH.
- **The target audience will influence how we frame the report.** Is it:
  - those conducting PE studies (for whom the questions would be, do you need a study, is the study appropriate, etc.)
  - those reading and interpreting PE studies (for whom the question would be, do you understand the results correctly, are you able to synthesize the study, etc.)
  - those who will implement according to the results of the studies, be this at local, national or regional level (for whom the questions would be, have you selected the relevant findings, do they apply to your population, etc.).

  An even more fundamental question would be: Do we even need a PE study? (For comparison, not, how should we perform X surgery, but do we need to perform it at all.)
- **But in low-income countries, the data needed to perform a study are often not available. So how can PE methods even be applied in these countries?** The WG could make recommendations as to how low- and middle-income countries (LMIC) can best use and customize PE data from another country, in accordance with their legal requirements and resources. We need to cover such issues since we do not want the report to neglect any aspect of global PH.
- **However, during COVID-19 it took a long time for LMIC to generate the relevant PE data.** By the time it became available, the pandemic had declined and the data was not needed. So **perhaps the focus should be more on preparedness.**

- **It should be borne in mind that very sophisticated PE techniques are not always relevant.** It is not necessary to calculate a high-dimensional property score. Rather, with common sense, a computer, some drug utilization data, and what has been learned from PE studies on related issues in other countries, many PH questions can be answered.
- **In many countries the problem was not lack of data, but infodemics.** The WG needs to listen to the voice of those representing those countries and not make assumptions about what it thinks they need in terms of PE.
- **PE is of especial importance in relation to the safety and effectiveness of new therapies, but it just one tool that PH experts can use to address their needs.**
- **There is a tendency to think that causal effects are global, as reflected in the efforts of decision-makers such as FDA and EMA to reach the same decision on efficacy and safety, even though such a decision may not be relevant or appropriate in all countries.** The pharmacological effects of a medicine will not be the same everywhere**,** given differences in terms of e.g. genetics or drug utilization. Drug utilization studies can answer many PH questions. **Currently, frameworks applied to make PH decisions about medicines tend to be limited to those used by regulators or industry.**
- **Access is an issue.** Some countries have little or may never have access to some medicines. It is important to understand at what level access is blocked. Is it, for example, due to reimbursement issues, a problem with the healthcare system or with the patients themselves? Such questions can be answered through a proper study or framework.
- **Access is not always insurmountable.** Sometimes it can be increased rapidly, as in the case of HIV medicines and some vaccines. PE can be a powerful tool for encouraging decision-makers to increase availability. It can also be a key driver for accelerating drug development or treatment development and approval, with high public health impact. There are many good examples of this. But access is not an issue that can be solved by this group.
- **We need to distinguish between total absence of data vs. data access.** Always, something can be done with what exists. It is up to this WG to show how PE methods can, for example, be adapted and supplemented with surveys or by promoting use of standardization.
- **Interpretation of the results of an existing PE study (taking into account its limitations and biases), and implementing and communicating its findings is an important topic, given the explosion of social media** and, for example, the growth of the anti-vaxxer movement.

Break-out groups

Four break-out groups were created to consider the following topics:

- **How to perform (or use of) PE in different settings (led by VK).**
- **The use of PE in crises (led by AA).**
- **When not to conduct a PE study (led by BB).**
- **Interpreting the results of existing PE study data (led by Patricia Saddier).**

The question was raised regarding as to where in the report the issue of PH questions that PE can answer should be covered. (Such questions can include: Are the right people using the intervention? Could it be used more efficiently by targeting different people? Is it safe as used? Is it effective as used?) It was proposed that the report include an introductory chapter on such questions, and possibly also a chapter on principles to follow during PH decision-making processes.

Overview of discussion of break-out group: How to perform (or use of) PE in different settings

- **Potential examples could include:**
    - *Metamizole (dipyrone) analgesic for moderate pain which is associated with a low risk for agranulocytocis.* A lot of PE data has been generated but with contradictory outcomes, which were not useful for PH. The studies involved focused on the risk and not the advantages of the drug, and did not compare the drug, with other drugs with the same indication. I.e. the report needs to underscore the (negative) impact on PH of contradictory evidence generated by PE studies and data.
    - *Cyproterone acetate is indicated for serious acne.* Data was accumulating relating to the use of this product for contraception (but not for treatment of acne). A health care professional prescribed it to a woman who did not have access to contraception because it was not reimbursed. Two years later the product was associated with a risk of meningioma and received a lot of attention from a PH perspective. But the availability of data, and evidence of no access to contraception given non-reimbursement, meant that it had not been necessary to wait until the crisis associated with meningioma erupted before taking action.
    - *HIV prevention in high-risk populations* offers an example of a PH health expert reaching out to a PE expert to demonstrate the effectiveness of treatment.
    - *PE studies on malaria or Ebola vaccination programmes* could demonstrate a very positive application of PE studies.
- **In brief, a range of examples could be presented to show the negative or mixed impact of PE, the failure to use PE data when it would have been helpful, and most positively, how PE studies can advance PH.**
- The above examples present four different scenarios for which evidence generation was at a different stage, and which could be evaluated in terms of PE's contribution to PH and what might have been done differently in order to enhance that contribution.

Comments from the broader group:

- **With respect to LMIC, is it assumed that secondary data sources are used in the same way as in Europe?** Maybe not, but LMIC do have some very good surveillance systems for new interventions. For example, a very large programme has been put in place to assess both the safety and effectiveness of the GSK malaria vaccine. Such a programme requires effort to build up the necessary infrastructure, but once established it can be used for other vaccines. In other words, the set up may be different in LMIC but nevertheless a very good source of date for PE research. See related article: "Assessing the safety, impact and effectiveness of RTS,S/AS01E malaria vaccine following its

introduction in three sub-Saharan African countries: methodological approaches and study set-up".

Overview of discussion of break-out group: When not to perform a PE study

- **The focus is on decision-making from a PH health rather than a research perspective, and on determining when it is better, safer and easier not to undertake a PE study.**
- **For PH purposes, PE study results need to be relevant, obtainable in good time and feasible.** In cases, such as that of a rare disease, recruitment of the needed number of participants would be lengthy; a case-series could be performed instead.
- **Other strategies, such as pharmacovigilance (PV), routine surveillance, or qualitative research, to follow how and where a product is used, may be more useful than a PE study.** If doubt exists around a product, decision-makers should identify a means other than a PE study (if it would require too much time to complete) of finding the information they need. Also, if good data is already available and a meta-analysis has been conducted, a PE study may not be needed. Other examples of situations when a PE study would not be appropriate include those for which there are specific sub-groups at high risk and which vary across countries, and for which a cross-sectional study would be more useful.
- **Instead of a new PE study, it may be possible to "transport" the results of a single study or trial to a broader population,** to extend inferences from one population to another, to help determine where treatment resources can best be directed.
- **Could include examples of studies the results of which were not useful for decision-makers, or which arrived too late, or the results of which created problems, or which are needed but have not been conducted.** E.g.
    - *The possible link of an anti-hepatitis vaccine with multiple sclerosis.* A PE study conducted to investigate the link showed an increased risk of 20%, but the risk was not statistically significant. Yet communication of the results led to increased vaccine hesitancy.
    - *The association of paternal exposure to the antiseizure medication valproate and an increased risk of congenital malformation.* But the results of PE studies were confusing. In combining the results of PE studies in three countries, the risk appeared significant. But data quality was questionable and it was unclear what was being measured. Further complication was due to the length of time that had passed between conception and diagnosis.
    - *During COVID-19, health authorities required PE studies, but the results were sometimes misinterpreted and served to exacerbate vaccine hesitancy.*
    - *In France, 900,000 women are affected by the debate around hormone replacement therapy (HRT), i.e. there is an evidence gap.* A PE study to determine what the actual risks of taking HRT are, and its benefit : risk is badly needed. I.e. PE studies should not focus only on safety but take a more holistic approach. **Focus should not be only on risk or safety, but also on the benefits of a drug.** Otherwise, a PH decision may be skewed. Likewise, If communication of PE study results is likely to be challenging

(as for the cardiotoxicity of the Pfizer COVID-19 vaccine), a PE study of the the global benefit : risk of the intervention might be very useful.

- **If clarity regarding what to measure is lacking, it may be advisable to delay performance of a PE study** – even if there is pressure to carry out a study to investigate a safety signal – and to first conduct a drug use study.
- **Data quality and management are important.** The results of a PE study of auto-immune disease flares that compared 1st generation with 3rd generation contraceptives and HRT were skewed due to a lack of clear coding. Lobbying for PE studies of vaccines has led to PE studies that use existing but poor-quality data. (Database custodians sometimes push for PE studies, as do regulators.)
- **Is relative risk a good parameter for regulators?** Should the etiologic fraction be used instead?

Comments from the broader group:

- When a PE study is planned, **a desired sample size** should be set; if recruitment of a sufficient number of participants is not possible, the study should not be performed. But there is a difference between knowing even before a study is initiated that the desired sample size cannot be reached, and starting a study and realizing at a later stage the desired sample size cannot be reached.
- **A patient's family may have a strong reaction when it hears that it has been decided not carry out a particular study, but it may be possible to find the needed answer by an alternative means.**
- **See related article**: "Causal, analyses of existing databases no power calculations required". It seeks to make the argument for not worrying about sample size and precision, and that doing a study is better than not doing it, that having some evidence is better than having no evidence. I.e. it presents arguments from a research rather than PH perspective, but may be useful to the group for framing its own arguments.
- **It can be difficult to predict uptake and also the incidence of an adverse event.** Some of the outcomes for COVID-19 vaccines seen during spontaneous or active surveillance were very rare. As a result, multiple international groups did not have sufficient data to make a PH decision by themselves. But their studies nevertheless proved useful. So it may be that in PH emergencies different rules should be applied as to whether or not to conduct a PE study.

Overview of discussion of break-out group: When to use PE in PH crises

- **Four different levels of public health crisis were identified:**
  1. outbreaks (e.g. cholera, measles)
  2. epidemics (e.g. meningitis in Africa, Ebola, obesity)
  3. pandemics (e.g. COVID-19)
  4. emergencies (e.g. opioid epidemic, antibiotics resistance).
- The response to a crisis varies according to the type of crisis.

- **PE offers unique opportunities to support PH in times of crisis.** It is important to identify the use cases (e.g. monitoring through surveillance).
- **Management of PH crises has 8 elements;** PE contributes under points 2 to 8.
    1. detect the PH crisis
    2. understand the population affected and the natural history of disease
    3. define the unmet medical needs
    4. monitor the crisis and estimate its magnitude
    5. perform prediction and modelling
    6. take action (e.g. develop, test and monitor an intervention, and assess its safety and effectiveness, and compare different interventions)
    7. interpret and communicate the science; two examples were identified:
        - ➢ *Lancet* article, MMR vaccination and autism, see: https://www.thelancet.com/journals/lancet/article/piis0140673605756968/fulltext
        - ➢ retraction by *Lancet* and *NEJM* of surgisphere studies on COVID- 19 patients.
    8. contribute to the assessment and harmonization of patient-level healthcare data sources for PH priorities.
- **The following user cases were identified:**
    - *Disease outbreak or pandemic:* During disease outbreaks or pandemics, such as COVID-19, PE can be vital in the rapid development and evaluation of various treatments (including vaccines) with respect to: assessing their impact on the population; characterizing the natural history of disease; monitoring use, safety and effectiveness; identifying adverse drug reactions and drug−drug interactions in real world settings; repurposing of drugs (e.g. adjuvant drugs in hospital patients with COVID-19).
    - *Drug recall:* If a particular drug has been observed to have unforeseen adverse effects and raised safety concerns (e.g. thalidomide), PE can help to assess the potential impact on the population.
    - *PH emergencies:* In crises, such as the opioid epidemic, PE can help to investigate the cause and effect relationships, monitor trends, and study the safety and effectiveness of specific medications in the population.
    - *Drug resistance:* In drug resistance crises (as with antibiotics and anticancer drugs), PE can help measure drug use in the population and its association with patterns of resistance.
    - *Vaccine crises:* When vaccine shortages occur, or when a new vaccine has been introduced, PE can contribute to study of the efficiency of the vaccine, and to monitoring of its safety in larger populations.

- Platform protocols exist for clinical trials. **Similarly, a PE study protocol could be prepared, that could be modified according to the PH crisis in question.** Additionally, the readiness of regulators and scientists to respond to a PH crisis could be improved. For example, scientists could prepare for harmonization of data (including by preparing templates), to facilitate analysis across hospitals or countries. A library of phenotypes could also be created.

Comments from the broader group:

- **By definition, a PH crisis cannot be predicted. But perhaps in some instances a PH crisis can be predicted.** For example, incidence of some adverse reactions can be anticipated during a vaccine campaign and, as a result, some "noise" from social networks or particular groups. PH decision-makers can prepare for such situations and start an investigation promptly when they arise.
- **One example of the usefulness of PE studies concerns COVID-19 and the effectiveness of vaccines that were deployed to tackle the emerging variants.** It would have taken a long time for clinical trials to provide the responses needed. (Indeed the results of huge clinical trials that were conducted explained little about effectiveness and could not be used to determine what vaccine worked best in what age category or when a booster would be required.) Instead, the results of a number of PE studies were used to inform regulatory decision-making in some countries.
- **The PH crises we see today in the 21st century differ from those of the 20th century.** The latter were often foreseeable and could be solved with a ready-made solution. Today, crises are multifaceted and evolve over time. (E.g. climate change. Extreme weather such as heat waves impact vulnerable populations who have certain health conditions or who are using medications that are negatively affected by extreme heat.) Since PE can be a very long process, is it valid in times of crisis? Some initiatives seek to shorten this process. For example, by ensuring that data sources are available from networks working with the same model, in particular data on side effects or the effectiveness coverage of a vaccine or drug. Similarly, "study-a-thons" whereby people meet during a week, organize a study protocol and apply it to existing data, can be a means of generating useful results in a short time. E.g. during COVID-19, in only four days, a study-a-thon attended (virtually) by around 250 people prepared a protocol and ran an analysis using data on one million patients.2
- **Data sources in Europe and the US have been harmonized.** (In Europe a considerable sum has been spent on harmonizing data on prostate cancer and lung cancer. Germany is creating a common data model for its data.) **They are being harmonized in China, Japan and Latin America. and harmonization is being initiated in Africa.** But there is no coordination. **Data needs to be harmonized at the global level.** WHO needs to play a

[2]On "study-a-thons" see, "Evaluating a novel approach to stimulate open science collaborations: a case series of "study-a-thon" events within the OHDSI and European IMI communities, *JAMIA Open* ("https://academic.oup.com/jamiaopen/article/5/4/ooac100/6832031) and see appendix to these minutes for examples of Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) – an open community data standard, designed to standardize the structure and content of observational data and to enable efficient analyses that can produce reliable evidence – as applied during COVID-19.

bigger role with respect to this issue. Real world data would be much more useful if data sets were accessible and could be combined and used to generate real-world evidence. A mapping exercise is under way in the EU and has already shown that some very interesting databases are already available.

- **Preparedness can include making different data sets more readily available.** Various initiatives are reviewing what kind of data sets are available and what kind of data can be pulled from them. Some progress has been made in this area but its potential for speeding up PE studies remains to be exploited.
- **Access to the data that is being generated during a crisis can be problematic.** During COVID-19, some good epidemiological studies were published but these were behind a pay wall. If a study is published in in a journal of restricted access, some people will be prevented from accessing information that could be very useful to them when evaluating possible PH responses or contributing to PH decision-making.
- **How can a common decision be reached if some countries report a signal but others do not?** This occurred during COVID-19, with some countries, but not others, reporting a particular signal linked to a vaccine. Those who had not seen this signal did not want it publicized because of the risk that it would increase vaccine hesitancy. (See also comment page 4 about the **tendency to think that causal effects are global**.)
- **Communication during a PH crisis should pay particular attention to the terms and concepts to be used.** When it was suspected that there was an association between the Astra Zeneca vaccine and cerebral thrombosis, EMA warned that if information was made available about this, that vaccine hesitancy would increase. Later EMA published an official statement indicating that the risk of cerebral thrombosis in vaccinated people was the same as in the general population. With this statement EMA aimed to avoid creating vaccine hesitancy. However, the end result was the opposite since it was discovered that the computation was erroneous. What has to be communicated clearly in such cases is that a risk exists, that for example, one death may ensue, but that 1,000 deaths may have been be avoided.
- **The WG report could include a recommendation for:**
    - coordinated international effort, including by ensuring common elements in PE studies to facilitate comparison across studies and consider replication, and for totality of the data
    - a coordinated response during PH crises.
- **WHO did promote coordination during COVID-19. Similarly, in the US,** ahead of vaccine deployment, agreement is reached on how to verify an incident, the common elements in a master protocol, etc.

Overview of discussion of break-out group: Interpreting the results of existing PE study data

- **Examples of PH questions that PE studies could answer** could include: Is the intervention safe? Is the intervention effective?
- **The first step in assessing whether existing PE data can answer a PH question should be assessment of that data. Assessment should also be made of whether the question**

can be answered by existing PH data, which might include, not surveillance data, but published pharmacology papers, conference abstracts and studies of PE data.

- For a PH decision-maker who is not a pharmacoepidemiologist, who has to assess whether a PH question can be answered by existing PE data, the recommendation would be to:
    - **Create a small team, covering the relevant specialities (including PE, clinical statistics) and request it to identify the relevant PE data by conducing a literature review**. (Guidance on how to do this already exists.)
    - Then **if the literature review produces relevant PE data, it should be subject to a critical appraisal by the PE experts.** (Likewise, major journals should use pharmacoepidemiologist(s) to review PE studies submitted for publication.)
    - **Critical appraisal** should include: evaluation of the studies; interpretation of the results; assessment of the relevance and applicability of the study data to the PH question under consideration. The report could include some key references.
    - The team should **identify any PE data gaps** with respect to the PH question to be answered.
    - The PE data should be summarized with an overall conclusion as to whether they are sufficient for answering the PH question, whether additional PE data are needed, what might be missed if only existing PE data are taken into account.
- Additionally, the pharmacoepidemiologist(s) should provide the information needed to ensure that any communication is accurate.
- **If new PE data become available, the above steps may need to be repeated.**
- **A range of examples for which the above steps could be applied** were discussed.
    - *Roll out of a varicella vaccine at national level, even though that it may have an impact on zoster epidemiology.* Controversy around this issue meant that, in the UK, the decision to roll out varicella vaccine was taken almost 20 years after other countries had rolled out the vaccine. In such a case, the aforementioned small team should include vaccinologists, vaccine pharmacoepidemiologists, paediatricians and modellers, who would review the literature on varicella vaccine safety, effectiveness and use, the impact of vaccination programmes on children, and the epidemiology of zoster at all ages. (One of the big questions might be: Do you need boosters if you are in contact with individuals who have varicella, to maintain your level of immunity so that you do not develop zoster as an adult? If all children are vaccinated, would adults in their 20s, who had varicella when they were children, have varicella given that they are not boosted? Could this question be considered a PE gap?) Thereafter the team would draw a conclusion and communicate to the PH decision-maker what it thinks is appropriate with respect to recommending this vaccine.
    - *Non-infectious disease examples, such as the use of statins:* Are they are used appropriately or for long enough in the right population? Does the right age group receives statins as a means of primary cardiovascular (CVD) prevention? Should

statins be prescribed for people who have CVD risk factors but who do not have high cholesterol?

- *Breast cancer screening.* It is unclear what is the best screening to recommend. In fact, recommendations on screening procedures (the age at which it should start, the frequency, specificity and sensitivity of the testing, etc.) change often. There is considerable debate and screening is done differently in different countries. So even though breast cancer is very common, screening recommendations are far from universal. In order to reduce the likelihood of incorrect diagnosis, PE could be applied to defining the best, most efficient and most appropriate form of screening.
- *The new screening measure applied to babies – taking a blood sample at birth to screen for serious health conditions*.
- *Ensuring appropriate use of opioids.* Could PE assist with e.g. determining the right indication, right duration?

Comments from the broader group:

- **What about biologic drugs?** Generating the safety profile of such drugs is very difficult given the many possible delayed interactions that can ensue. How is collection of PE data for these drugs best managed? It may require modernizing PE studies and the expectation of what these can generate. When PE data is yet to accumulate, when use is insufficient, or duration of use is not long enough, or the number of people exposed is low, monitoring and planning are possible, but PH decisions cannot be taken. I.e. uncertainty has to be dealt with and care taken to communicate what is not yet known and that PE studies will be carried out to try and fill the evidence gaps. The reaction of patients to such communication will be very dependent on the degree of need they have for a new drug and the level of risk they are ready to accept.

DAY 2

Plenary discussion

- Questions were raised about the **structure of the report and possible overlap** in content among the breakout groups of Day 1.
- There was considerable discussion (and mystification) as to **what should be the focus of the report.**
- **HL reminded the group that the target audience for the report is decision-makers.** E.g. a decision maker who must make a decision related to health, a PH concern or to the use of drug devices or vaccines. Decision-makers may be advised by PE experts (although these experts do not necessarily know what is the truth, or may be biased in their opinion). Rather than the capacity to validate a PE study, these decision-makers need to integrate all aspects of a PH problem. They need to understand when PE can be usefully applied to answer a problem and when not – i.e. the when and when not to do, but not the how – and when to use another means to solve the problem. The guidance could serve to start a dialogue on these issues.

- **The term "public health concern" can mean many different things.** E.g. FDA considers a rare disease for which there is lack of treatment to be a PH concern. At the other extreme, COVID-19, and climate change, are PH concerns. Plenty of research has been carried out on PH concerns as defined by regulators. Whereas for WHO, a PH emergency is a PH concern. So does the target audience consist of regulators or rather of WHO and governments when they are dealing with a PH crisis?
- **The WG should should not limit itself to a particular type of PH concern. Any PH concern is relevant,** be it related to allocation of resources, screening, reimbursement, of appropriate use of an available drug.
- **Pharmacoepidemiologists need to adapt the way in which they promote PE** so that decision-makers listen to them. This is an opportunity to explain the importance of PE, to promote PE, to explain to decision-makers how they can use PE more optimally.
- **BB underscored that the aim is to improve the contribution of medicines to PH** – to understand where there are gaps, where there is under-treatment or over treatment, what are the risks, etc. – and to recommend when a PE study would be necessary to improve this contribution. The target audience should therefore include both politicians and regulatory decision-makers, and the higher levels of the pharmaceutical industry.
- **Many PE studies are conducted that investigate only one aspect or part of a PH problem, and do not present a clear balance of the benefit vs. risk.** HRT, cited on Day 1 (see page 7), is case in point. It is a major PH concern but it is still not clear whether to recommend its use or not.
- **When a PE study is planned in response to a PH issue it should be strategic,** taking into account all the elements of the PH decision to be taken and clear as to how the study could contribute to this decision.
- **In terms of existing studies, the issue is how to select PE studies that are relevant to the PH concern.** If none of those conducted to date has been meaningful, it signifies a major gap in understanding and that a decision cannot yet be taken.
- **The WG report should frame the types of questions that PE studies could help solve.** (However, it can be difficult to keep the PH dimension in mind when designing a PE study since PE studies are usually designed for a specific purpose. But sometimes you have to do so: when data is requested from CPRD or SMDS, the PH relevance of the study has to be described.)
- **The report should define situations (but without going into methodology) where PE is not well established, and where trust and confidence in its methodology need to be increased**. Once PH practitioners have trust and confidence in PE, they will start to use it and these guidelines when talking to their leaders in decision-making bodies. Rob Califf, FDA Commissioner has given a good example of use of PE data. The FDA relied on Israel for COVID-19 vaccine-related data to inform its guidance on booster administration, including the decision to authorize a fourth dose. i.e. FDA did not need clinical trials or super-complex, randomized clinical trials on which to base its decision, but instead used high-quality research done on existing data sources.

- **The report should stress that any PE study to be used in responding to a PH issue must be implemented correctly, and be relevant and valid from a technical point of view. But it is not necessary for the report to describe how to ensure this.**
- A full **flow process of decisions and stakeholders** could be included:
  - identify the situation (medicines could be one element) from a PH perspective
  - identify whether PE would be useful or not to answer the PH question
  - if so, determine the relevant data sources and the relevant methodology
  - perform and interpret the study.

Drafting the report

It is very important to describe what PE cannot do. Keeping this in mind will help the WG to structure the report. The two drafts produced by Sub-groups 1 and 2 can be used to create introductory text for the report.

The topics and content that the four groups of Day 1 worked on will form the main body of the report. The chair of each of the four groups will use the notes that they presented on Day 1 as the basis for drafting text which can thereafter be circulated among the whole WG for review.

The next step would be integrate the Sub-group drafts and the content developed as a result of the four group discussions of Day 1.

It was also proposed that a section be included on communication.

Overview of 2nd discussion of break-out group: How to perform (or use of) PE in different settings

- **"Scenarios" may be a more useful and readily understood term than "settings".**
- **A decision tree as to whether or not to implement a PE study will be included.**
- **The text will define possible, different "scenarios":**
  - *Disease:* What are the existing and available treatment or prevention options? What comparative interventions already exist? What is the access situation? Access varies across countries.
  - *An infodemic* may be an important element of a scenario. (It may be a consideration when deciding not to do a PE study.)
  - *Different health care systems exist, range from those under development to that are highly sophisticated.* When a PH decision is taken, the context of the specific country must be taken into account. The results of a PE study conducted in a different country may not be translatable to another country.
  - *Assessment of benefit : risk*. Is the context one of monitoring and usage? Are we reacting to a safety signal? Are we investigating missing information; e.g. with respect to specific populations? Are we looking at long-term use?
- **Possible examples for inclusion** (see also page 6):

- *Benzodiazepenes:* for which many PE studies have been conducted but for which the results are contradictory, meaning that no clear position on use of this drug has yet been reached.
- *Cyproterone:* for which reimbursement was not available, resulting in off-label use.
- *Prevention of HIV/AIDS:* how can a non-interventional study contribute to demonstrating the effectiveness of the treatment?
- *Vaccine programmes:* since these are relevant to LMIC.

Comments from the broader group:

- **Infodemics have different sources.** E.g. an infodemic may be fuelled by social media, or by data coming from a single source.
- **Risk management planning, and customizing it according to the resources available** in different settings, could also be covered.
- **How should use of PE to support PH be covered?** By presenting examples to demonstrate when PE can be used to support PH decision-making. Maybe a general section on this topic should be included in the introduction.

Overview of 2nd discussion of break-out group: When not to perform a PE study

- A proposed study should be conducted only when it is thought to be useful and likely to deliver results in good time, etc. **The group further defined "usefulness".**
- **Some historical examples of PE studies that were not useful for PH will be included.** Sometimes a PE study is conducted that offers no possibility of interpretation or use of its results to assess benefit vs. risk.
- The question was raised, is it appropriate to conduct a new PE study when many studies have already been conducted, with conflicting results. (E.g. 34 studies were contracted recently on benzodiazepenes and dementia, and yet there is a demand for additional studies). Should the focus rather be on interpreting the results of the existing studies with a group of experts?
- **The issue of what to do when a planned study may create confusion,** or be taken to infer that a product is not safe or effective, could be covered.

Comments from the broader group:

- **The examples given were too limited.** PE studies are not limited to investigating safety. The examples should be more comprehensive.

Overview of 2nd discussion of break-out group: When to use PE in PH crises

- The points presented were the same as those presented in the 1st overview, but with two additions:
  - A ninth step was added to the eight steps involved in management of PH crises (see page 9) that were presented on Day 1: Contribute to evolving PH crises such as climate change by assessing its impact on vulnerable populations.
  - Investigation of the association of cerebral thrombosis with AstraZeneca's COVID-19 vaccine could be included as a use case for PE.

Overview of 2nd discussion of break-out group: Interpreting the results of existing PE study data

- **The group came up with some examples of intervention use.** Whatever the intervention, safety and effectiveness and use has many dimensions, including duration of use, the right target population, adherence and access. But use probably represents the most important PH dimension. Safety already benefits from a pretty well-defined framework. Examples could be given of the types of PE studies that can be carried out to investigate these issues.
- **A section on evaluation of existing PE studies (entitled "Evaluation existing PE studies") was proposed for inclusion.** Some context would be included, as well as a definition of PE evidence. It would be indicated that what was being referred to was published PE studies, abstracts and gray literature and underscored that reviewing existing PE evidence is the first step in using PE to support public health decision-making.
- **A work flow was proposed** (see also page 12):
  - Clarify the PH issue. Make sure the PH question to be answered is focused and not, for instance, an amalgam of several questions.
  - Identify the relevant information needed to make a decision.
  - Explicitly assess whether PE evidence can support the decision-making.
  - If it is determined that PE evidence can support the decision-making, establish a small team covering the relevant specialities such as PE, clinical biostatistics).
  - Identify the relevant PE evidence through literature review, critically appraise it and interpret the results. (Some references would be included.) Additionally, assess its relevance and applicability to the PH question at hand. Identify PE evidence gaps. Summarize the evidence provided, draw conclusions and make recommendations on what is available. A communication strategy may also be needed.
  - Reassessment may be needed if new evidence becomes available.
- Use cases could be included (see pages 12 and 13).

Comments from the broader group:

- Lots of different use cases involving COVID-19 could be presented but it will probably be more interesting for the reader if the report uses different PH issues as examples.

Next steps

- The next meeting will be held in November or December 2024. CIOMS will contact WG members with possible dates to choose from.
- The next in-person meeting could be held at CIOMS' new premises or another location, possibly in the US. Any offers to host the meeting should be sent to the CIOMS Secretariat.
- Ahead of the next in-person meeting, a virtual meeting will be scheduled for late September or early October 2024.

- WG members to formalize their outlines and draft texts, circulate these and remove any duplication. WG members can work on both the topic/section to which they were assigned during the meeting, and on the other topics. WG members who could not attend this meeting can work on each of the topics/sections, but VK and YM will reach out to the members of their sub-group that did not attend this meeting and ask them which of the four topics they wish to contribute to specifically.
- WG members to review other relevant guidance that is being drafted by other organizations, such as ICH, to identify not only overlap but also gaps that this report could fill.

Appendix: Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM)

By standardizing and facilitating the integration and analysis of data from diverse sources, the studies listed below demonstrated the importance of OMOP CDM in enabling multinational, large-scale observational studies. [1][2][3]

1. A large-scale study called "Characterizing and comparing individuals with COVID-19 or influenza" was conducted using the OMOP CDM. This study aimed to describe the baseline demographic and clinical characteristics, treatments, and outcomes of individuals tested for SARS-CoV-2 or diagnosed with COVID-19, as well as compare them to a population with seasonal influenza.[3]
2. The OHDSI community conducted a network study to characterize and compare COVID-19 patients living with and without obesity across the United States, Spain, and the United Kingdom. This study utilized data mapped to the OMOP CDM from multiple countries.[3]
3. Several observational studies of patients with COVID-19 were performed based on the OMOP CDM or similar common data models, as mentioned in the search results.[2]
4. The CHARYBDIS study, a large-scale characterization of 4.5 million COVID-19 cases, was conducted using data in the OMOP CDM format.[4]
5. The OHDSI community sought to understand the available observational data in the OMOP CDM to conduct analyses and generate real-world evidence to inform the COVID-19 pandemic response, including investigating the effectiveness of various treatments.[3]

These studies demonstrated the importance of OMOP CDM in enabling multinational, large-scale observational studies during the COVID-19 pandemic by standardizing and facilitating the integration and analysis of data from diverse sources. [1][2][3]

References:

[1] https://www.sciencedirect.com/science/article/pii/S1532046421001192
[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8416224/
[3] https://www.ohdsi.org/covid-19-updates/
[4] https://aacrjournals.org/cebp/article-pdf/30/10/1884/3082892/1884.pdf

Additional reference:

https://www.researchgate.net/publication/361508287_Preparing_for_the_next_pandemic_via_transfer_learning_from_existing_diseases_with_hierarchical_multi-modal_BERT_a_study_on_COVID-19_outcome_prediction

Further details on how the above were applied are given below.

1. Enabling large-scale multi-national observational studies:
   The OMOP CDM allowed for the integration and harmonization of diverse healthcare data sources from different countries into a common format. This enabled large-scale multi-national observational studies on COVID-19 to be conducted efficiently across distributed data networks.[1][2][3]
2. Characterizing COVID-19 patients and outcomes:
   By transforming data sources like the UK Biobank and SIDIAP database in Catalonia to

the OMOP CDM, researchers could comprehensively characterize COVID-19 patients, their demographics, co morbidities, treatments, and outcomes on a large scale.[2][4] This provided valuable real-world evidence to inform the pandemic response.

3. Investigating COVID-19 treatments and vaccine safety:
   The OMOP CDM facilitated studies evaluating the effectiveness and safety of COVID-19 treatments like remdesivir as well as monitoring adverse events following COVID-19 vaccination across diverse populations.[1][3][5] This evidence supported clinical decision-making and regulatory actions.

4. Leveraging open-source analytical tools:
   By converting data to the standardized OMOP CDM format, researchers could utilize the growing ecosystem of open-source tools and methodologies developed by the OHDSI community for large-scale analytics on the transformed datasets.[4]

5. Enabling distributed network research:
   The OMOP CDM allowed for the implementation of distributed research networks where analyses could be executed across multiple sites without requiring data transfer, protecting patient privacy while generating insights from large pooled datasets.[4][5]

In summary, the OMOP CDM played a pivotal role in facilitating multi-national, large-scale observational studies on COVID-19 by standardizing and integrating data from various sources, enabling characterization of patients and outcomes, evaluating treatments and vaccine safety, and supporting distributed analytics through open-source tools and networks. I wish we had more data from the LMICs.

References:

[1] https://pubmed.ncbi.nlm.nih.gov/37724311/
[2] https://academic.oup.com/jamia/article/30/1/103/6760234
[3] https://pubmed.ncbi.nlm.nih.gov/36227072/
[4] https://www.dovepress.com/transforming-the-information-system-for-research-in-primary-care-sidia-peer-reviewed-fulltext-article-CLEP
[5] https://www.ohdsi.org/covid-19-updates/