Section	Line no (start)	Line no (end)	Concern or text in question	Comment / suggestion for re-wording. Please provide suggestions on how to resolve the concern.
Introduction	134	138	Pharmacoepidemiology1 aims to appraise and understand the use and effects – both beneficial and adverse – of medicinal products in real-world settings. As such, it can be viewed as a bridging discipline that connects clinical pharmacology, epidemiology, public health, and social sciences. Although the systematic study of interactions between medicines and populations began to take shape in the late 1950s and early 1960s—galvanised by the thalidomide tragedy	The draft would benefit from a clearer operational definition of pharmacoepidemiology within a public health framework. While the conceptual definition is adequate, greater clarity is needed on how pharmacoepidemiology differs from pharmacovigilance and health services research. A visual framework illustrating overlaps and distinctions would enhance conceptual precision
Introduction	134	135	Pharmacoepidemiology1 aims to appraise and understand the use and effects – both beneficial and adverse – of medicinal products in real-world settings.	ISPE defines pharmacoepidemiology as "... a scientific discipline that uses epidemiological methods to evaluate the use, benefits and risks of medical products and interventions in human populations." The stated definition includes elements reflected in the ISPE definition, but could be written to explicitly call out 'benefits and risks'.
Introduction	143	143	heavily	drop text "heavily"?
Introduction	145	145	original	The term ‘original’ may be too strong here, as many methodological approaches are interconnected across fields. It is hard to claim it is original.
Introduction	151	151	entire population of a country or all users	not just the entire population, but in some places around the world (ie Nordics) they have a rich 'cradle to the grave' data capture which truly changes the scale for what research questions can be addressed in some instances.
Introduction	152	155	This change in scale, and the possibility of exhaustive recruitment, have led to a shift in our perspective on a variety of classical epidemiological and statistical concepts, including selection biases, statistical power, confidence intervals, and statistical significance3.	My additional comments: This sentence is a mix of challenges in traditional study (exhaustive recruitment) and what PE can overcome. Need to distinguish the two for easy reading. I would suggest to frame around "precision of estimates, greater power" rather than confidence interval and statistical significance. Selection bias is a separate issue, it's the quality of study design that can address selection bias, rather than availability of big data.
Introduction	152	155	This change in scale, and the possibility of exhaustive recruitment, have led to a shift in our perspective on a variety of classical epidemiological and statistical concepts, including selection biases, statistical power, confidence intervals, and statistical significance3.	While the text correctly notes that studies may now include entire populations or all users of a medicinal product, it implicitly assumes that exhaustive recruitment eliminates traditional epidemiological challenges. In practice, even population-wide datasets may suffer from incomplete capture, misclassification, missing data, or systematic exclusions (e.g., uninsured populations). Acknowledging these limitations would provide a more balanced perspective.

Introduction	154	155	including selection biases, statistical power, confidence intervals, and statistical significance3.	The discussion suggests a shift in perspective on selection bias, but it would be scientifically valuable to emphasize that selection bias is not removed by large-scale alone. Instead, it often manifests differently (e.g., database inclusion criteria, healthcare access patterns, or digital divides). Explicitly stating this distinction would prevent misinterpretation.
Introduction	156	157	The World Health Organization defines public health as "the art and science of preventing disease, prolonging life and promoting health through the organised efforts of society".	The document also frequently refers to global public health and global health. Consider including definitions for both of these terms and explaining the distinction between all three terms
Introduction	158	159	Medicinal products available today – whether older molecules with proven efficacy or innovative therapies	Can also add: older molecules with new indications
Introduction	166	166	all aspects	I would change to ... many aspects....
Introduction	166	166	an almost unlimited sources of information –	This is very kind of to say, but I think what is being conveyed the large availability RWD; too promising
Introduction	167	167	, it faces a series of new challenges.	this text does not fit. Drop?
Introduction	170	172	The popularisation of the One-Health4 and other global health concepts, which makes it inappropriate not to consider, for a given medicinal product or a public health intervention, both the benefits and risks as a whole. Indeed, accounting for all the direct.	the reference to one health and its relevance to the context of pharmacoepidemiology is not entirely clear
Introduction	179	179	in statistics and computing,	suggest to delete these words, IT does relate to computing. Statistics can be viewed as a separate discipline
Introduction	181	181	including the most recent ones.	these words are already covered by "approaches used to date".
Introduction	182	185	Another challenge arises from the fact that, over the same period, conventional chemically derived drugs have been complemented, in many therapeutic areas, by biotechnology-derived novel agents whose mechanisms of action bear little or no resemblance to those of conventional pharmacology. As a result, core pharmacoepidemiological concepts such as dose, exposure.	This sentence does not read well. Need a signpost otherwise "challenges" came out of blue. The text "over the same period.....complemented.... does not add.
Introduction	185	187	As a result, core pharmacoepidemiological concepts such as dose, exposure density, and duration of exposure may be called into question and may require new approaches or types of analysis.	The observation that traditional concepts such as dose, exposure density, and duration may be questioned is highly relevant. Nonetheless, the text could benefit from specifying why these constructs are insufficient for biologics—for example, non-linear dose–response relationships, target-mediated drug disposition, long half-lives, immune modulation, or intermittent dosing schedules. This would strengthen the causal link between the emergence of novel agents and the need for new analytical approaches.

Introduction	188	194	These profound changes call for a thorough re-examination of the concepts used to evaluate medicinal products. More than ever, the validity of therapeutic or preventive interventions must be assessed at the population level. Beyond – and in addition to – Evidence-Based Medicine (EBM), which has traditionally relied on the results of clinical trials, pharmacoepidemiology, in its open conception to the most recent advances, is increasingly becoming a cornerstone of public health decision-making. By reflecting, in real time, the overall impact of interventions on populations, it can also provide information on the consequences of this decision.	This is the key rationale however, the arguements dont come across very clear. Should articulate the links between traditional EBM to modern PE, and real-time impact more obvious
Chapter 1	201	205	The CIOMS XV document is intended to serve as a global reference for regulators, academic institutions, pharmaceutical and biotechnology companies involved in medicinal product development and marketing, as well as for health policy decision-makers at international, regional, and national levels. It is also relevant to researchers, academics, healthcare professionals, and patients.	Worthwhile to list audience of this report using hierachial approach. Academia audience is mentioned twice. Would regulators the same as health policy decision-maker? Patients represent a very narrow group - would it be more broad to say Health consumers?
Chapter 1	203	203	health policy decision-makers	It would be helpful to explicitly describe who the decision makers are (national immunisation technical advisory groups, health technology assessment agencies, departments/ministries of health, professional groups who publish clinical practice guidelines, such as the European Society for Clinical Oncology) and the types of decisions that pharmacoepidemiology informs - what to recommend, when and to whom, what to pay for etc. As the document focuses on optimising pharmacoepi for public health decision making, it might be helpful to presence the decision makers more prominently as the primary audience for the document - if they are the primary audience for the document. Also in many countries, national public health agencies have a formal mandate to conduct effectiveness, impact and safety studies, particularly for immunisation programmes and so it would be great to see them listed here
Chapter 1	206	207	critical public health questions related to medicinal products.	Perhaps list some examples of the types of questions?
Chapter 1	208	209	regulatory authorities, industry, and scientific communities	Consider adding public health agencies to this list.
Chapter 1	211	213	• Minimise unnecessary studies that do not contribute to informed decision-making and may even hinder or delay it—such as studies with questionable validity or those that fail to adequately address the intended public health issue.	need to articulate around public health decision making . keep at high-level, examples of validity or fail to address..... are very specific and can derail the over-arching aim
Chapter 1	215	215	(ISPE)	Is it citation of ISPE? Need to include year
Chapter 1	217	217	(Bégaud)	is it citation? Year?

Chapter 1	217	221	Medicinal products are inherently public health tools, representing major advances in the treatment and prevention of diseases. Over recent decades, requirements for demonstrating their effectiveness and safety have become increasingly rigorous. As a result, decisions related to the development and delivery of medicinal products must now account for profound paradigm shifts in public health and regulatory expectations. It is therefore essential	Consider distinguishing between medicinal products given for preventative purposes (such as vaccines and biologics given to large numbers of healthy people) from medicines given to sick people as the risk:benefit analyses differ for both, and also given that vaccines may be 1) deployed in emergencies, 2) recommended to one group (for example health care workers) to protect a different group (patients), are 3) subject to more misinformation
Chapter 1	224	225	As noted in the Introduction, the emergence of novel therapeutic agents –such as gene therapy, biologics, and mRNA vaccines –whose modes of action and interactions with living organisms	confirm it refers to the "biotechnology-derived novel agents" mentioned in the intro.
Chapter 1	231	231	An additional challenge for post-marketing assessment of therapeutic effect and the generation of real-world evidence arises	Could define the term "real-world evidence"
Chapter 1	239	239	geographic area or population,	or time period (for instance seasonal epidemics)
Section 1.1	253	253	(such as One Health)	The relevance of one health here is unclear, given that it specifically relates to the interface between human, animal and environment.
Section 1.1	249	255	Paradoxes in pharmacoepidemiology include: The field's investigative potential is virtually unlimited, yet it does not always meet public health knowledge needs. There is a tendency toward technological and methodological development as an end in itself, sometimes at the expense of integrated, holistic approaches (such as One Health). The demand for immediate answers often conflicts with the time required for rigorous research.	Consider supplementing the description of pharmacoepidemiologic paradoxes with concise, practical, solution-oriented guidance, as the underlying concepts currently appear separately across different parts of the document.
Section 1.1	259	261	exemplified this challenge: a flood of narrowly focused studies on vaccine effectiveness and adverse events (such as myocardial infarction, thrombosis, myocarditis, and neurological effects) were released rapidly.	The vaccine effectiveness studies were useful to inform the timing of booster doses in the schedule and therefore the results were needed rapidly. The studies investigating adverse events were conducted in response to specific signals and informed risk benefit discussions by decision makers such as the ACIP and MHRA. Rapidly publishing the studies was important to a) enable knowledge sharing and contribute to scientific understanding and public health decision making beyond the immediate setting of the study; b) for transparency purposes to contribute to public trust; c) to enable comparisons between studies and ensure studies were subjected to scientific scrutiny via peer review etc
Section 1.1	264	265	At the same time, health authorities sometimes made hasty decisions and 264 communications.	Are there specific examples that could be provided to support this statement?

Section 1.1	269	273	Many studies – sometimes reaching contrasting conclusions – have focused on limited aspects of the population impact of a medicinal product, such as specific types of adverse events, without providing an overall assessment that would enable definitive conclusions to be drawn regarding the benefits and risks associated with a given product, and/or an appropriate decision to be taken about its use.	The document would benefit from a description of the architecture for public health decision making relating to medicinal products. Individual studies are not really designed to provide overall assessments of risk benefit, rather they are designed to inform decisions on overall risk benefit. A number of frameworks for risk benefit assessments of vaccines have been published, there may be similar for other medicinal products - it might be useful to describe some of these frameworks and how they have been used. https://www.nature.com/articles/s44360-025-00027-4 https://www.thelancet.com/journals/landig/article/PIIS2589-7500(25)00025-1/fulltext
Section 1.1	280	284	Studies that do not appear to be a priority at first glance or that are unlikely to provide any responses to the questions concerning the interactions between medicinal products and public health, can even have effects that are contrary to public health objectives if they delay decision-making or lead to erroneous conclusions about risk or benefit and the real contribution of a medicinal product to public health.	This sentence is too long.
Section 1.2	286	286	1.2 Pharmacoepidemiology framework	The pharmacoepidemiology framework might be strengthened by expanding it to include public health agencies who in some settings have a mandate to conduct effectiveness and safety studies, especially for vaccines.
Section 1.2	287	287	The use of real-world clinical conditions	real-world setting??
Section 1.2	292	292	, analysing,	I think we analyze "real-world data" rather than "real-world evidence". Could say "evaluate" instead.
Section 1.2	304	304	Collaborative e	There is an unnecessary space at the beginning of this paragraph.
Section 1.2	306	306	patients	general public and health consumer?
Section 1.2.1	309	309	1.2.1. Academia	It seems to me that these headings 1.2.1, 1.2.2, 1.2.3, etc reflect audience of this report, --- they should be consistent with those listed at the beginning of Chapter 1
Section 1.2.1	311	311	methodological developments,	add "over the past decades"
Section 1.2.3	347	347	generate and integrate real-world evidence (RWE)	Real-world evidence has already been mentioned several times above, so it is unclear why the abbreviation (RWE) is introduced here.

Section 1.2.4	354	357	Pharmacoepidemiology lies at the intersection of epidemiology and pharmacology, the latter being the scientific discipline that characterizes pharmacotherapy as a population-level intervention. Similar population-level interventions—such as medical devices, environmental health actions, and diagnostic technologies—also rely on epidemiological principles.	already defined previously - no need to repeat
Section 1.2.4	358	358	Pharmacoepidemiology	why capital letter?
Section 1.2.4	361	361	requirements	refine requirments
Section 1.2.4	363	363	Adapting regulatory data systems	I dont think Adapting is the right world. does it mean, Promoting and Facilitaing the use of regulatory data systems to inform public health decision making
Section 1.2.5	374	379	Another example is the IMI-PROTECT ..	It is worth including the IMI-ADVANCE project which mapped key health data sources and developed interoperable methods to generate Europe-wide evidence on vaccine safety, coverage, and effectiveness. As well as it's follow-up (VAC4EU), non-profit collaboration platform which enabled rapid vaccine monitoring, timely detection of adverse events and informed decision-making during COVID-19 pandemic.
Section 1.2.5	383	383	Patient involvement	Health consumer?. If this term is adopted, need to change other part of the document
Section 1.2.5	383	383	Patient involvement	The term patient involvement is used broadly but not operationally defined. It would strengthen the manuscript to differentiate between consultation, engagement, co-design, and co-production. Clarify whether involvement refers to individual patients, caregivers, patient organizations, or Community representatives. Distinguish patient involvement from patient-reported outcomes (PROs), which are often mixed but conceptually distinct. Consider referencing implementation models aligned with guidance from CIOMS to anchor definitions
Section 1.2.5	387	388	research—such as defining study questions, selecting relevant outcomes, and interpreting findings—can enhance the relevance, acceptability, and impact of real-world evidence for public health decision making	Personally I dont think interpreting findings are "early stages of PE research", it would be mid-way. Unless, change to "involving patients across lifecycle of PE research"
Section 1.3	471	471	It has already been mentioned that confidence intervals and p-value may no longer be relevant when dealing with very large populations,	The previously provided reference from the ASA only referred to p-values. Do you have a reference for this? To the best of my knowledge confidence intervals are still useful, even for whole of population analyses.
Chapter 2	542	542	all levels	"all levels" seems too strong.
Section 2.1	581	581	Another type of misuse,	change to Underuse?? to keep consistency with other sub-headig

Section 2.3	680	680	external comparator	Could mention "external control", a more popular name.
Section 2.4	704	705	2.4 Understanding how access to medicinal products impacts public health	There seems to be some overlap between section 2.1 and this section. This section could be considered an extension of 2.1 and so could potentially be combined.
Section 2.5.1	771	773	Once a product is authorized, Health Technology Assessment (HTA) bodies use pharmacoepidemiological evidence to evaluate economic and clinical value to inform reimbursement decisions, pricing strategies, and clinical recommendations.	These are important points and could be presenced more prominently in the document.
Chapter 3	1081	1081	real-world evidence to accumulate.	What type of real world evidence is being referred to hear? Does this relate to data on burden of disease or data on safety and effectiveness of the vaccines in real-world populations.
Section 3.2.1	1164	1165	which age groups to vaccinate, are boosters needed and how often, could it have a negative impact on the epidemiology of the disease).	suggest giving an example of what you mean by this, for instance type replacement or shifting burden of illness or risk to different age-groups
Section 3.2.1	1176	1177	This is because healthy children often develop mild symptoms when infected 1176 with varicella; hence, the urgency lags behind that of other new vaccines (Lee).	Suggest spelling out that the shingles in adults can be a more severe disease than chickenpox in children, to set the context that shifting the burden of illness to older age-groups would be an undesirable consequence of selective vaccination by age-group
Section 3.2.1	1180	1180	small team	Wouldn't this team be the national immunisation technical advisory group? Or is the team providing evidence and recommendations to the national immunisation technical advisory group? It would be helpful somewhere in the document to outline the architecture for public health decision making as it relates to the introduction/use/funding of new vaccines and medicines. The infrastructure will differ for vaccines and medicines. Who are the main players? For this use-case example, presumably the main players were the JCVI, UKHSA, Physicians etc and there may have also been collaboration with academic institutions. Consider adding additional contextual information.
Section 3.2.1	1185	1186	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?	Suggest framing this question in terms of risk - does vaccinating children increase the risk of shingles in unvaccinated adults?
Section 3.2.1	1191	1193	Bernal et al (2019) used pharmacoepidemiological methods through a surveillance study of data from all NHS hospitals in England to identify varicella admissions between 2004 and 2017 (Bernal).	Consider noting that this was a study done by the national public health agency to inform the decision making process
Section 3.2.2	1199	1199	become established as	statins have established?

Section 3.2.2	1200	1202	They are among the most widely used drugs in the world, and the scientific literature on them (clinical trials, pharmacoepidemiological studies, modelling, etc.) numbers in the hundreds of publications and is undoubtedly one of the most extensive..	please check grammar
Section 3.2.2	1203	1204	Despite this abundance of information and the decades that have passed since their introduction, controversy and debate remain about the optimal prevention strategies..	it would be easier to read there have been ongoing controversy and debates ...."
Section 3.2.2	1206	1207	Are these drugs mostly used at the appropriate dose or for a sufficient 1206 period of time given the initial level of risk? What is the benefit-risk balance of treatment in 1207	the meaning of this question is not clear....
Section 3.2.2	1210	1211	or not? Finally, is the use of statins in primary prevention notoriously inadequate, as some experts claim (Xu)?	drop?
Section 3.2.2	1212	1218	Controversies exist around the cardiovascular disease risk calculators used by clinicians to determine the best course of treatment for their patients (Cook). Risk calculators can over- or underestimate risk in different patient populations leading to inappropriate treatment decisions. They can sometimes be based on outdated data and may not account for relevant CVD risk factors. Furthermore, many have not been externally validated with their predictions not tested against pharmacoepidemiological data. The overestimation of CVD risk can lead to millions of people..	What's the key limitation of the risk calculator? Was it developed based on generic population or a specific group, so that the calculator is not generalisable? Would be good to include some examples . I think controversy about statin use probably was partly due to incorrect CVD risk estimates,
Section 3.2.2	1234	1238	Such questions, which are of major importance for public health and remain unanswered more than thirty years after this class of drugs became available, demonstrate that the investigative potential of pharmacoepidemiology has not been optimally exploited. Given that this is about preventing one of the leading causes of death worldwide, the questions listed above should have been answered clearly years ago to guide health decisions and policies.	This is an important example of the under-realisation of pharmacoepidemiology for public health decision making. Does this example illustrate an opportunity to further realise the potential of PE for public health decision making? Does this call for a more systematic approach for identifying and addressing evidence gaps in relation to the safety, effectiveness and use of medicines? If so, who typically would be responsible for this? What is the typical architecture for this process? Most countries have well established systems for public health decision making relating to vaccine introduction, and the ongoing appraisal of evidence on use, safety etc. Are there equivalent systems and processes in place for medicines? If so, what are they? It would be great to contextualise this example to understand why these questions have yet to be systematically identified and addressed
Section 3.2.3	1247	1247	related conditions..	Repeated period here. This section is related to "drug repurposing"

Section 3.2.4	1265	1275	In 2019 the FDA approved extension of the label of palbociclib to include male patients with Metastatic Breast Cancer. Rarity of breast cancer in men limits the feasibility of large randomized controlled trials. During the four years after the approval for palbociclib male patients were treated off label. The real-world evidence derived from was three independent data sources: real-world data from insurance claims, a de-identified real-world data source derived from electronic health records (EHRs), and a global safety database. These were used to complement previous trial data (such as PK analysis) to confirm effectiveness and safety for male patients. The claims data was used to determine exposure (treatment patterns and duration). Using the electronic health records, researchers were able to establish real world effectiveness for male patients, and lastly the global safety database revealed no new safety signals associated with the off-label patient population (Wedam).	This is a very nice example. Consider outlining the main players in the process for label expansion for palbociclib - what the initiative driven by the MAH? Besides the FDA, who were the other main players? What was the role of clinicians in this process? How did it impact on the clinical practice guidelines? was it 2019 or 2015 - was the drug used off label for 4 years after approval for male patients, or 4 years before approval for male patients - check the syntax of the sentence
Section 3.3	1293	1293	• Provide absolute risks in addition to relative risks to contextualize potential harm or 1293 benefit. 1294	An infamous example of where this did not happen relates to the risk of cancer in women prescribed HRT, which has had long term impacts on womens access to HRT with knock on effects in terms of morbidity & quality of life
Section 3.3.2	1326	1326	sources of uncertainty	I would say acknowledge sources of systematic error. Uncertainty is more related to confidence intervals and precision.
Section 3.4	1377	1382	In summary, while urgent public health decisions may sometimes proceed without waiting for 1377 new pharmacoepidemiological data, these studies remain indispensable for evaluating real-world 1378 safety, effectiveness, and utilization of healthcare products. By systematically assessing existing 1379 evidence before commissioning new research, decision-makers can act swiftly, avoid 1380 unnecessary duplication, and ensure that policies are grounded in robust, timely insights— 1381 ultimately strengthening public health responses and optimizing patient outcomes. 1382	Conceptual balance is appropriate but could be sharper The conclusion appropriately acknowledges the tension between urgency in public health decision-making and the value of pharmacoepidemiological evidence. However, the phrase “without waiting for new pharmacoepidemiological data” could be misread as downplaying the importance of evidence generation. Clarifying that decisions may rely on existing or rapidly available data would better reflect current best practice.
Section 4.1	1445	1445	Pharmacoepidemiology can be pivotal particularly when the health of a population is..	For a stronger impact, the phrase can be replaced by "is pivotal"

Section 4.2	1469	1469	Epidemiology and pharmacoepidemiology	Its good to see the reference to both epidemiology and pharmacoepidemiology. Most countries have well developed systems for detecting, investigating and managing outbreaks and public health incidents through their epidemic intelligence service / national public health agencies. There are well established frameworks for this, including the 10/7 steps to an outbreak investigation and the WHOs national health emergency alert and response framework. Pharmaceoepidemiology activities will have a particular role within this wider framework - for instance withing the research and development pillar and the monitoring & evaluation pillar and may use epidemiology outputs from other parts of system, in particular the epidemiology investigation of the event itself. Consider describing these wider frameworks and systems and how pharmacoepidemiology fits within it and intersects with it. https://iris.who.int/server/api/core/bitstreams/a20f1fba-4dab-4cda-853d-52da98317234/content
Section 4.3.1	1504	1511	• Measles outbreaks: In 2023, an estimated 10.3 million people were infected with measles with measles outbreaks are happening in every region of the world (CDC measles) • Meningococcal disease outbreak remains a critical public health concern due to its rapid onset, high case fatality rate, and potential for large-scale outbreaks (the Virginia Department of Health (VDH) outlines a structured response for meningococcal outbreaks, emphasising rapid case identification, immediate chemoprophylaxis, targeted vaccination campaigns and enhance surveillance and public health communication (VDH).	The measles and meningococcal examples illustrate the burden of disease and the use of vaccines for epidemic response rather than how PE is applied during an outbreak. The COVID example provides a good example of the application of PE during a public health emergency. In addition to COVID, cholera and ebola provide good real life examples of the application of PE during outbreaks to asses the effectivenss of vaccines and therapies & to inform the optimal vaccination strategy. https://pmc.ncbi.nlm.nih.gov/articles/PMC9060364/ https://pmc.ncbi.nlm.nih.gov/articles/PMC9060364/ https://pmc.ncbi.nlm.nih.gov/articles/PMC7033511/

Section 4.3.1	1532	1532	epidemiological and pharmacoepidemiological research allows.	one of the best examples of PE in health emergencies comes from COVID where near real-time assessments of effectiveness were used to inform decision making on the timing of booster doses and where rapid identification, investigation and characterisation of adverse events were used to inform decisions on which vaccines to give to which population groups (for instance myocarditis risk in young men and decisions around deployment of mRNA vaccines). Similarly the nesting of ebola ring vaccination trials in several ebola outbreak responses in West Africa (Guinea, Sierra Leone & DRC) which not only enabled the control of the outbreaks, but enabled the evaluation of the effectiveness of the vaccines themselves. Consider more explicitly detailing these examples. Consider the example of the real-time rapid cycle analysis systems for COVID-19 adverse event signal detection and analysis developed by the US CDC and described in detail on their website, including the process for communicating the outputs of this system to the ACIP to inform policy recommendations for vaccine deployment Similar systems were operated by the MHRA with ongoing weekly publication of the results of their risk benefit assessments online
Section 4.3.2	1550	1552	The European Medicines Agency (EMA) referral process highlighted the importance of real-world utilisation data to estimate population exposure and inform risk-benefit decisions (EMA).	It is worth mentioning as an example the safety concern regarding TTS for Adenoviral COVID-19 vaccines https://www.ema.europa.eu/en/news/ema-raises-awareness-clinical-care-recommendations-manage-suspected-thrombosis-thrombocytopenia-syndromE
Section 4.3.3	1569	1569	prolonged or high-dose use	insert "codeine" for clarity
Section 4.3.3	1576	1577	Policies on opioid use might not have an effect on opioid-related deaths, likely because of the illegal market (Béliveau, Goyer).	This seems a big jump from licit opioid use to illicit opioids, and policies.

Sectin 4.3.4	1588	1596	Medicinal product resistance involves the reduction in effectiveness of a medication, such as an antimicrobials or an antineoplastic in treating a disease or condition. Examples of antimicrobial resistance include antibiotic resistances (e.g., antibiotics resistance due to excessive human use or utilization in animal production and not respecting doses or intervals of use) or antiviral resistance. Antineoplastic resistance is the resistance of neoplastic (cancerous) cells, or the ability of cancer cells to survive and grow despite anticancer medicinal products. Here again, the contribution of pharmacoepidemiology can be crucial, in terms of preventing, understanding and managing medicinal product resistance, for example by analysing levels and patterns of use at population level and their association with specific resistance patterns (Chiang).	This paragraph highlighted the pharmacoepidemiology contribution appropriately, particularly at the population level. This is a vigor. However, the contribution could be made more clearly by briefly documenting how these analyses inform prevention or stewardship strategies (e.g., surveillance, policy interventions, prescribing guidelines).
Section 4.3.6	1607	1614	The link between pharmacoepidemiology and earthquakes, floods, hurricanes, extreme temperatures, or chemical and radiological exposures may seem a long way off, but these events can disrupt communities, displace vulnerable populations, hamper the delivery of continuous and coordinated healthcare, especially among persons with serious or chronic health conditions. In addition, extreme heat and air pollution can interact with medicinal product exposures to adversely impact health outcomes at the population-level. The intentional or unintentional release of chemical and/or radioactive agents to the environment may also result in public health crises and/or emergencies when affecting communities and human health.	Consider elaborating on the role of PE in these circumstances
Section 4.3.6	1622	1622	the 10 stages of a public health crisis	Is there a reference for this framework for a public health crisis? How does this relate to other well established frameworks widely used in public health such as the 10 steps of an outbreak investigation or the various health emergency frameworks developed by the WHO
Section 4.5.3	1676	1679	In public health emergencies, interim results may need to be disseminated rapidly to inform urgent decisions. However, these must be clearly labelled as preliminary, framed with explicit explanations of what is known, what remains uncertain, and what the next steps are. This helps prevent premature conclusions or misinterpretation by the public and media.	Consider adding concrete examples from past public health emergencies to show how miscommunication of preliminary observational findings can erode public trust. For instance, during COVID-19, weak early signals about certain medications were promoted as proof of efficacy, causing confusion and undermining confidence in later, more rigorous trials. Such examples would underscore the importance of transparently communicating study limitations.
Section 4.6.1	1691	1691	1.6.1	The heading number should be 4.6.1 instead of 1.6.1. Same for "1.6.2".

Section 4.6.1	1693	1698	Between December 2019 and May 2023, during the viral pandemic caused by SARS-CoV-2, pharmacoepidemiology played an essential role in optimizing public health policies aimed at protecting the global population as quickly and effectively as possible. The challenge was to assess, in real time and under real-world conditions the efficacy, safety and the benefit-risk of the medicinal products and vaccines proposed or used as they were administered to hundreds of millions of people.	Consider detailing the infrastructure that was established to facilitate rapid and real time pharmaco-epidemiology during the pandemic - for example the rapid cycle analysis system for adverse events established by the US CDC - the protocol of which was published early on in the pandemic, or the work of the Brighton Collaboration in developing and disseminating definitions for adverse events of special interest associated with vaccination that could be used in PE research studies, or the work of multinational collaborations such as VAC4EU or ISARIC in developing and making publicly available protocols for vaccine safety and clinical research studies. https://vac4eu.org/projects-and-studies/ These enabling factors could be described in greater detail as examples of how to optimise PE for PH decision making in an emergency
Section 4.6.1	1708	1711	At the same time, several pharmacoepidemiological studies have helped to better characterize the 1708 SARS-CoV-2 pandemic, the conditions and the benefit-risk balance of treatments in this context, and the natural history of the disease, and to identify the sub-populations most at risk (Epi-Phare).	This citation relates to the determinants of vaccination. Surely the characterisation of the pandemic & natural history of disease were primarily done through routine public health surveillance activities and clinical research rather than pharmacoepidemiology?
Section 4.6.1	1764	1764	"ring vaccination" trial conducted in Guinea	This predates the previously mentioned DRC trial cited above and was the original use case for the ring vaccination study design during an outbreak,
Section 4.8.3	1915	1916	Several structural challenges illustrate how public health priorities can diverge from the industry-focused pharmacoepidemiology	Conceptual framing: The Phrase " industry -focused pharmacoepidemiology" is impressive but somewhat broad. Consider briefly clarifying that this refers primarily to regulatory market- access- oriented evidence generation rather than industry activity per se.
Section 4.8.3	1926	1926	public health equity	An important point emphasizes that pharmacoepidemiology is particularly crucial in low- and middle-income countries (LMICs), where original clinical trials often do not adequately represent populations with diverse genetic backgrounds and contextual healthcare factors. Many pivotal trials are conducted in high-income settings under controlled conditions, which may limit their generalizability to LMIC populations. In this context, pharmacoepidemiology—especially through the analysis of real-world data (RWD)—plays a vital role in assessing the real-world effectiveness, safety, and utilization patterns of medicines. Generating evidence from routine clinical practice allows for the evaluation of outcomes in heterogeneous populations and resource-limited settings. Such context-specific data are essential to inform public health policies, optimize therapeutic guidelines, and support regulatory and health authority decision-making in LMICs

Section 5.2.1	2272	2275	Alzheimer's-type dementia is a serious and prevalent condition with no recognized effective treatment currently available studies that have reported an association between benzodiazepines and dementia point to prolonged use (over 6 months), which contravenes with international guidelines recommending a maximum duration of 12 weeks.	this sentece is too long
Section 5.2.2	2282	2282	The study duplicates existing research without providing significant added value	I would say this is the general problem in academia, not specific to pharmacoepidemiology, given the "publish and perish" fact.
Section 5.2.2	2297	2298	when the information provided by the trials and studies carried out during the development phase seems, for the most part, to answer the question.	Need for clearer decision criteria The statement “seems, for the most part, to answer the question” is scientifically imprecise. From a regulatory and methodological perspective, it would be preferable to frame this in terms of whether residual uncertainty remains and whether identified limitations materially affect decision-making
Section 5.2.2	2300	2301	in order to design a protocol capable of answering all the missing points and to supplement information available rather than duplicating what has already been done.	Avoiding duplication is not only efficient but also ethically important, particularly in post-authorization research involving patients. Explicitly stating this would strengthen the argument.
Section 5.2.3	2307	2311	There are also instances where the study itself may generate a crisis or hinder, event prevent, beneficial public health actions. This may be the case, among many examples, of media coverage of a safety study conducted on a medicinal product without a reference group or time-window allowing comparison, or without the possibility of balancing the results with what would have happened in the absence of treatment.	In addition to no reference group, an inappropriate reference group can also seriously overestimate or underestimate study findings. Change “event prevent” to “even prevent”
Section 5.2.3	2325	2330	Similarly, as mentioned above, when a study aims to identify, and further characterize an adverse event, it is crucial to have information that put this risk into context, for example by balancing it with a reliable and credible measure of the benefit that the medicinal product brings, or will bring, to the population. For example, this could involve comparing the frequency of adverse event with the number of cases of the disease expected to be prevented by a vaccination campaign.	This paragraph is important for risk communications. Stating explicitly that the proper contextualization is essential for accurate interpretation by decision-makers and the public would strengthen its relevance, particularly in sensitive areas such as vaccine safety.
Section 5.2.6	2417	2417	generalizable results	Generalizability cannot be assessed without specifying the target population of interest.

Section 5.3	2497	2508	Regardless of situations where information and conclusions are lacking in order to optimize a decision, prevent or manage a crisis (the subject of the two previous chapters), there are cases where it seems preferable, even if it may seem paradoxical, to refrain from conducting a study: Either because the study it is deemed unnecessary from the outset, as it is unlikely to provide any new information that could inform the decision; or because waiting for the results would delay a decision that could be made on the basis of already available information or simple common sense; or, finally, because in certain situations, the implementation of the study or the publication of its results could be likely to generate doubt or even crisis. What should be called “the proper use of pharmacoepidemiology for public decision-making” is all the more important given that resources and high-level expertise in this field are limited and that it is therefore crucial to prioritize them, whenever possible, on major public health issues that remain incompletely explored.	should break these long sentences into shorter ones
Conclusions	2537	2537	all aspects	too promissing to say "All", would be OK to say Many aspects
Conclusions	2559	2559	decisions making	Could say "decision-making"
Introduction	Footnote1, page 6		1..finding out what the population does with the product (number of users, conditions of prescription and use, etc.) and what the product does in this population (referring to all effects and consequences, whether beneficial or undesirable).	Suggest to rewrite: "...how a population uses a product (....) and how the produce affects the population (...).
Section 4.4	Table I Row 1		Burden of disease Disease profiling Case Reports Case Series Cross-sectional studies	Within public health these activities are usually the responsibility of the epidemic intelligence service or equivalent rather than pharmacoepidemiology. The objectives for monitoring the burden & trends in disease are usually much broader than pharmcoepidemiology activities, although evaluation of effectiveness, safety and impact of a drug or intervention on the disease may be an objective within the wider programme of work
Section 4.4	Table I Row 2		Burden of disease Disease profiling Case Reports Case Series Cross-sectional studies	Within public health these activities are usually the responsibility of the epidemic intelligence service or equivalent rather than pharmacoepidemiology. The objectives for monitoring the burden & trends in disease are usually much broader than pharmcoepidemiology activities, although evaluation of effectiveness, safety and impact of a drug or intervention on the disease may be an objective within the wider programme of work
Section 4.4	Table I Row 4		4. Monitor the public health crisis or emergency	Not pharmacoepidemiology - this is incident response and there would be teams of epidemiologists and data scientists working solely on this. The outputs could be used for pharmacoepidemiology studies

Section 4.4	Table I Row		Spontaneous reporting Disease Surveillance Public Health Surveillance	Not pharmaceoepidemiology - firmly within the domain of epidemic intelligence / disease surveillance
Section 4.4	Table I Row		Interpret & communicate the impact of RWE and science in public health crises or emergencies	Should this be "communicate the impact of the medicine/vaccine/intervention in the public health crisis?"