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Overview of comments received on ICH M14 Guideline on general principles on plan, design and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines (EMA/CHMP/ICH/155061/2024)

Please note that comments will be sent to the ICH M14 EWG for consideration in the context of Step 3 of the ICH process.

1. General comments – overview

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AESGP	0	0	Glossary	"The clinical evidence about the usage and potential benefits or risks of a medicinal product derived from analysis of RWD" should strike "clinical". RWE is often developed on data collected outside of a clinical setting.	
AESGP	0	0		AESGP welcomes the opportunity to comments on the ICH M14 Guideline on general principles on plan, design and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines.	
AESGP	0	0		A point could be included to state that before starting any pharmacoepidemiologic study using RWD, a comprehensive review of prior RWD studies in the same topic area should be conducted in order to inform the current study, anticipate challenges (especially with regard to bias and confounding) and to ensure no duplication of effort.	
AESGP	0	0		We would suggest to change "Patient" to "individual" throughout. Vaccine repients are not patients and OTC medications are used outside the supervision of a HCP. "Individual" is a more inclusive term.	
AESGP	0	0		The guideline doesnt really cover the post-study reporting standards. Several good standards already exist in (interventional) clinical studies (e.g. CONSORT, STROBE, STARD) that should be cross-referenced etc to establish an early common ground for RWE studies. If a parallel guidance is in development just for that, it should be made explicit in the current draft that expectations will be to comply with that.	
EFPIA	0	0	0	Our statisticians consider that this document, as its name suggests, is a good guide for the generalities of planning and designing pharmacoepidemiological studies using RWD. The guide does not present specificities or considerations that only apply to safety-oriented questions.	Please clarify if there are any specifics when adressing safety considerations.
EFPIA	0	0	4.2	Discussion of feasibility assumes that the study is being conducted after a product has been marketed in a population.	Authors may consider commenting on the timing of a feasibility analysis when a study question arises when a product is new to market and may not yet have adequate exposure

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EFPIA	0	0	5.2	The practical implications of protocol development and data source feasibility assessments are unclear. Figure 1 provides bi-directional arrows between developing a draft protocol and conducting feasibility assessments, highlighting that protocol development can be an iterative process. Section 5.2 discusses the importance of documenting the data accuracy, completeness, provenance, and traceability within the protocol, which cannot be done if a data source has not been selected. How should the iterative protocol development process be undertaken given the practical considerations regulatory timelines and expectations regarding submitted protocols? Are there suggestions that can be made? For example, data agnostic protocols that include a feasibility assessment as the first objective.	Please consider providing practical suggestions on how to navigate the practical implications of protocol development on regulated times that can be considered by sponsors and regulators.
EFPIA	0	0	5.2	Given that evaluating the suitability of data source becomes easier when the target population is well-defined, we recommend that section 5.2 Data Sources be presented following section 5.3 Target/Study Population.	Move this section after 5.3 for logical flow.
EFPIA	0	0	7.1	Statistical analysis plans may need to be modified if utilization is different than expected in study design	Note the need to reassess analytic plans based on medicine utilization in the real world
EFPIA	0	0	0	The text and the glossary provides a useful overview of terms and key considerations in the planning, designs and analysis of pharmacoepidemiological studies in an accessible manner. The document has very few references included, to help the reader delve more deeply into the various topics it would be helpful if more references to external sources, including the peer-reviewed literature, were inserted into the text.	Some sentences are lacking reference: e.g., on page 1, "Many countries and regions have published guidelines related to general principles of planning and designing such studies mainly for the purpose of safety assessment of a medicine." It would be useful to point the reader to a few examples. More information could be provided on investigating signals (e.g., examining case reports, PM data, conducting a disproportionality analysis)
EFPIA	0	0	11.1	Specific populations in mentioned in this section with an overview of pregnancy studies. We recognize that this is a huge topic which is beyond the scope of the guidelines therefore it would be useful if the reader were directed to other sources which extend the concepts discussed in this section. Also, challenges related to pregnancy studies are briefly identified. It would be useful if some strategies for addressing these or pointing to literature	https://onlinelibrary.wiley.com/doi/10.1002/pds.5711 https://pubmed.ncbi.nlm.nih.gov/34221367/ https://www.mdpi.com/2077-0383/12/22/7033?trk=public_post-text https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119701101.ch12
EFPIA	0	0	6	It would be helpful to include a reminder to confirm a data owner's ability to provide data to regulatory authorities in a compliant format. For example, some data owners cannot allow data to be transferred out of the country. These topics should be discussed with the data owners and regulators prior to selecting a data source for the study.	Add additional text.
EFPIA	0	0	6.2	This section does not differentiate between researchers with access to the data and researchers without access to the data. Some clarification regarding the different types of researchers and how their responsibilities may differ would improve the section.	Add additional text to reflect different types of researchers and differences in responsibilities.
EFPIA	0	0	7	It would be helpful to include information regarding the sample size calculation. The estimated required sample size will help shape the feasibility assessment. The sample size calculation should consider losses to follow-up and potential for misclassification. These considerations can drastically change sample size. It would also be helpful to include language regarding the selection of the detectable measure of association in comparative studies. There is a trade-off between the available sample size and the detectable level of risk.	Add additional text.

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EFPIA	0	0	7	It would be helpful to include considerations for the different analyses that might be done through a products life cycle. For example, what is reasonable to include in an interim report? If a fully powered analysis is possible at an interim report, what considerations should be given to the final report (example: differences between an interim report result and final report result may reflect differences in patient populations and treatment strategies versus a methodological challenge). Some studies are committed to progress reports. Are there recommendations for those. Should outcome information be avoided in reports outside of the interim and final report?	Add additional text
EFPIA	0	0	Applicable from Title and throughout the entire body of this document	-Please consider whether the nomenclature "Pharmacoepidemiological studies... for safety assessment of medicines" should be proposed, on top of all the already existing nomenclatures for such safety studies. Although the Japanese PMDA C173March 2014 guideline used this term, it would be helpful to harmonize this 2024 Harmonization guideline with a more specific nomenclature for non-interventional post-authorisation safety studies (NI-PASS) -In addition, the term “Pharmacoepidemiology” is broad and may include both observational and interventional study designs. In line with this guideline´s objective to focus on non-interventional studies (NIS) it might be clearer to the reader to avoid the broader term of “pharmacoepidemiology".	Proposed nomenclature: - Non-interventional post-authorisation safety studies (NI PASS) or - Non-interventional studies for safety assessment of Medicines/safety NIS
EFPIA	0	0	N/A	Overall this guidelines defiines the principles applying to design and conduct of non-interventional pharmacoepidemiological studies for safety assessment of medicines as stated in section 1.3 .	The title could be simplified and shortened without mention of RWD usages.
EFPIA	0	0		Section 5.2.2. provides a useful overview of the main types of data sources. Advantages are listed for FDNs but not for the other data sources.	There are some nice tabular summaries of advantages and disadvantages of key epi designs elsewhere (NC insert links), it might be useful to include a similar diagram or point the reader to these summaries available elsewhere.
EFPIA	0	0		The recommendations included in this guidance are laudable but represent an ideal that is challenged at several points by the practical reality of regulatory timelines and expectations. Without concrete evaluation of the operational complexities that need to be navigated and solutions to address them, execution of at least some of the best practices outlined in this guidance will remain out of reach. Concrete examples where the recommended practices are applied and the timelines and regulatory interactions described, are urgently needed to complement the thoughtful consideration of study development presented in this guideline. Without that focus on the practical aspects, some suggestions, e.g.,the need to include a plan to map coding changes over the course of a study, reflect poorly on what is otherwise a potentially useful document.	Consider a review focusing on the practical application of each of the recommendations and revise accordingly. Reviewing this document also highlights the urgent need for a practical discussion of how the various updates we all agree are needed to make observational research, especially in a regulated industry environment, more robust, can be implemented in practice. This may highlight the need for some new regulatory pathways or other processes and would be greatfully acknowledged.
EUCOPE	0	0		The use and assessment of controls is minimally addressed in this document. We suggest that the agency expand upon the benefits, limitations, and expectations of control populations.	
Euromedicat Steering Group	0			The text is difficult to read and understand: copy editing by native English speakers with subject knowledge is needed. The target audience should be clarified.	
Euromedicat Steering Group	0			Thank you for the opportunity to comment on this important and interesting document. We have some suggestions to enhance the text and strengthen the evidence. Please contact me if you have any questions.	

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German Rheumatology Research Center | Head of Epidemiology, Prof. Dr. Anja Strangfeld	0	0		The first 50% of the document does not have any added value to existing literature and the content presented is often too undifferentiated and partly incorrect. When comparing this single guideline to the numerous and useful guidelines from ICH to support RCTs, this guideline requires more efforts to be similarly beneficial as the setting of observational studies is considerably more complex than RCTs. EMA should also take a clear position in the discussion of examining causal relationships with observational studies. There are some initiatives that consider that it is possible, for example through the use of DAGs and balancing methods. Perhaps it should be pointed out that causality requires more than an observational design and that the latter can at best provide indications of potential causal relationships.	
H. Lundbeck A/S	0	0	General	We are pleased at the opportunity to provide the following suggestions to the draft ICH M14 guidance. We commend the ICH for progressing initiatives creating more harmonized transparent knowledgesharing around best-practices.	
H. Lundbeck A/S	0	0	Glossary	The definition of Primary Data Collection should indicate that primary data collected is also RWD	Real-world data collected specifically for the purpose of the present study
H. Lundbeck A/S	0	0	Glossary	The definition of Real-World Data (RWD) does not distinguish between primary and secondary data sources	Append the current definition so that RWD includes both primary data collection and secondary data sources
H. Lundbeck A/S	0	0	Glossary	No definition of pharmacoepidemiology is provided	It is encouraged that a definition of pharmacoepidemiology is added to the glossary
IQVIA	0	0	General Comment	We applaud the presentation of a "Framework for Generating Adequate Evidence using Real-World Data" (Section 3) because it seeks to pull together underlying concepts and present a logical flow of activities needed to generate a strong study protocol. We are concerned, however, that stakeholders may interpret Figure 1, which presents the key activities in sequential steps, as required in all cases. While the framework appropriately separates data assessments into an initial scan followed by an in-depth feasibility evaluation, it shows both of these steps completed prior to protocol finalization (i.e., regulatory approval). However, there are scenarios where this would not be realistic.	We recommend Figure 1 be labelled and discussed as a "conceptual" framework and that the text state that sponsors may need to adjust the sequencing of certain activities, especially regarding the evaluation of data reliability, (i.e., accuracy, completeness, provenance, and traceability), depending on the availability of adequate metadata about possible data sources and the availability of data extracts, or the ability of the data holders to program the data and provide reports of key variables for in-depth feasibility assessments. Emphasizing the flexibility of the framework would be consistent with the general principle stated earlier in the guideline that designing a study and selecting data sources should be managed as an iterative process to inform and develop the study protocol, statistical analysis plan, and related materials. We offer the following three examples for your consideration when revising the draft guideline: a.New Drug Scenario. When seeking to use existing data sources for a new drug entering the market, the upfront feasibility will need to determine if potential data sources capture the setting of the expected use of the treatment and whether they capture similar drugs. The actual uptake would be assessed after protocol finalization, and any needed change in the data source would lead to an amendment of the protocol.

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IQVIA	0	0	General Comment	We applaud the presentation of a "Framework for Generating Adequate Evidence using Real-World Data" (Section 3) because it seeks to pull together underlying concepts and present a logical flow of activities needed to generate a strong study protocol. We are concerned, however, that stakeholders may interpret Figure 1, which presents the key activities in sequential steps, as required in all cases. While the framework appropriately separates data assessments into an initial scan followed by an in-depth feasibility evaluation, it shows both of these steps completed prior to protocol finalization (i.e., regulatory approval). However, there are scenarios where this would not be realistic.	b.National Registries. It has become standard practice to publish detailed data catalogues and dictionaries among established national registry programs in Europe and other large registries around the world that provide secondary data for clinical research, as well as to provide certain information about their data collection, transformation, and quality assurance practices. These disclosures enable sponsors to evaluate the relevance of the data asset and certain aspects of its reliability as needed for their fit-for-purpose reviews. When proposing to use such registries it has become customary for sponsors to seek protocol finalization before entering into a contract to access the data and to include detailed steps for assessing the reliability of individual variables in the statistical analysis plan. The initial phase of study execution includes the completion of the reliability evaluations, so that the protocol can be amended, if needed based on this detailed information. In this way, evaluating data feasibility straddles the study planning and the study execution phases.
IQVIA	0	0	General Comment	We applaud the presentation of a "Framework for Generating Adequate Evidence using Real-World Data" (Section 3) because it seeks to pull together underlying concepts and present a logical flow of activities needed to generate a strong study protocol. We are concerned, however, that stakeholders may interpret Figure 1, which presents the key activities in sequential steps, as required in all cases. While the framework appropriately separates data assessments into an initial scan followed by an in-depth feasibility evaluation, it shows both of these steps completed prior to protocol finalization (i.e., regulatory approval). However, there are scenarios where this would not be realistic.	c.Primary Data Collection. If the initial scan to identify potential real-world data sources ultimately leads to the determination that a prospective, primary data collection approach is needed to address the research question -- either to supplement secondary data sources or as the sole source where adequate secondary data are not available -- the in-depth feasibility assessment would need to include considerations pertaining to primary data collection that are not mentioned in Figure 1, (e.g., site selection; expected enrollment based on adequate definition of eligibility criteria, with broad inclusion and few to no exclusion criteria to reflect treatment use under routine clinical practice; data expected to be available as per routine practice to inform underlying variables that will be collected and feed into conceptual and operational definitions of exposure, outcomes, and covariates; downstream considerations regarding data capture including electronic case report forms development within the electronic data capture system). While it would be acceptable to conduct these kinds of feasibility assessment tasks before protocol finalization, in our experience, timeline pressures often necessitate conducting certain activities, particularly related to site selection, afterwards, based on the final protocol.
IQVIA	0	0	Introduction	IQVIA appreciates the opportunity to comment on the ICH publication, General Principles on Plan, Design and analysis of Pharmacoepideiological Studies That Utilize Real-World Data for Safety Assessment of Medicines, M14, Draft Version, (Endorsed on 21 May 2024). IQVIA is a global provider of advanced analytics, technology solutions, and clinical research services to the life sciences industry. With approximately 87,000 employees, we conduct operations in more than one hundred countries.	With the goal of further strengthening this important guidance document, IQVIA is pleased to provide to the European Medicines Agency (EMA) one General Comment and fourteen Specific Comments. We offer these reflections in a spirit of collaboration and hope the Agency finds them useful. IQVIA acknowledges the efforts taken to make this guidance document possible and supports the positive advancement of the application of real-world evidence (RWE) in regulatory decision making. Please reach out to us with any questions you may have, (contact Dan Campion by email Daniel.Campion@IQVIA.com or phone at 617-599-9409).

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ISPE	0	0	0	The ICH M14 guidance is well-written, promoting the harmonization of conducting pharmacoepidemiological studies. The high quality, clarity, and outlined recommendations reflect the hard work and dedication that went into its development. The comprehensive nature of the document, along with its clear, actionable guidance, demonstrates a deep understanding of the complexities involved. This guidance will help sponsors understand expectations for pharmacoepidemiology submissions and facilitate the assessment of the validity of such submissions by scientific reviewers.	
ISPE	0	0	0	In multiple places, the guideline suggests discussing aspects of pharmacoepidemiology safety studies with health authorities without reference to some practical details like a potential regulatory pathway, constraints of regulatory timelines, or specific published guidance that sets expectations. This guideline would be improved and differentiated with the addition of this information at each mention.	When recommending consultation with regulatory authorities as part of the process, please include (1) information regarding regulatory pathways with links to reference documents, (2) acknowledge potential constraints of regulatory timelines that could make scheduling consultations challenging, and (3) any relevant published guidance from health authorities that provide specific details on how/with which divisions to consult. Include practical examples where recommended practices have been applied relative to regulatory timeline constraints. Include further clarification from and/or action by health authorities that may be needed to drive consistently robust, timely observational research that can inform safety decisions.
ISPE	0	0	11.1	Specific populations mentioned in this section included an overview of pregnancy studies. Considering that medication safety during pregnancy is a huge topic which is beyond the scope of the guidelines, it would be useful if the reader were directed to other sources which extend the concepts discussed in this section. It would be useful if some strategies for addressing challenges that were highlighted these were included, including citing relevant literature.	https://onlinelibrary.wiley.com/doi/10.1002/pds.5711 https://pubmed.ncbi.nlm.nih.gov/34221367/ https://www.mdpi.com/2077-0383/12/22/7033?trk=public_post-text https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119701101.ch12
RTI Health Solutions	0	0	0	On behalf of RTI Health Solutions, thank you for the opportunity to comment. We welcome this guidance for pharmacoepidemiology safety studies using real world data and would like to comment on selected topics.	
Syneos Health CRO	0	0	0	To ensure the uniqueness of individuals, rather than just encounters, it would be helpful to understand the regulators' recommendations for identifying and removing duplicates.	
Syneos Health CRO	0	0	0	We recommend that the guideline expand on unstructured data-perhaps by including some of the pitfalls; "black box" and the challenges/risks with using such data. It would also be suitable to include recommendation of how reliable the methods used are for the assessment of the unstructured data.	
Syneos Health CRO	0	0	0	We recommend including considerations on the process for data sharing with regulators and its challenges.	
Syneos Health CRO	0	0	0	We recommend including considerations on multiple studies from real world data perspective and its challenges	
Syneos Health CRO	0	0	0	We would appreciate further clarification on tokenization expectations and how this should be managed overall.	
Syneos Health CRO	0	0	0	We kindly request clarification of whether there will be a separate guidance on how this should be managed with medical devices.	
Syneos Health CRO	0	0	0	We noted that most components of the guideline also seem applicable to efficacy/effectiveness, rather than just safety as it currently reads. We recommend clarifying this.	
Syneos Health CRO	0	0	0	The guideline would benefit from indicating differences in, for example, validation/feasibility assessment/methods to address bias, etc. for non-regulatory vs regulatory and descriptive vs comparative studies.	

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Syneos Health CRO	0	0	0	Quantitative bias assessment – it would be helpful to provide more information on (preferred) methods, references, and (hypothetical) case studies for correct implementation. The same holds for DAGs, high dimensional propensity scores, negative controls, data linkage methods and sensitivity analyses, etc. At a minimum, it would be appreciated if references could be provided.	
VAC4EU	0	0	11		Consider adding specific subsections for paediatrics and rare disorders/exposures, as they may need more strict masking rules, confidentiality issues, data availability or maybe are more prone to contain erlevant information in registries.
VAC4EU	0	0	12	Comment on 'Data Reliability' EMA DQF?	Consider harmonising with other data sources.
VAC4EU	0	0	5.1		Consider adding an explicit reference to the framework of Target Trial Emulation as summarized in the PRINCIPLED paper (Desai et al. PRINCIPLED: considerations from the FDA Sentinel Innovation Center. BMJ. 2024)
VAC4EU	0	0	5.2	'Underlying population' is the term used in the dimension 'inclusion of population' to refer to the population included in the data source: since the target population of any study is necessarily nested within this population, we invite to mention this dimension when describing the concept of target population. 'Prompt' is the term used to refer to the class of events that cause information to be included in the data soure (example: contact with the primary care physician; access to the emergency room; purchase of a reimbursed medicine): no information is available about the study population if the prompts of the data sources are not triggered. The guidance uses the term "settings of care captured", which conveys a similar, slightly more restricted concept: we recommend to replace it with the DIVERSE dimension 'prompt'.	We recommend the reference to the nine dimensions of the DIVERSE framework, in particular to make terminology homogeneous. We recommend to refer to the DIVERSE dimension of 'Healthcare and culture' in the paragraph "Patients, providers, or healthcare systems may have different motivations (…)", that captures precisely that dimension.
VAC4EU	0	0	5.2.4		We recommend to refer to the DIVERSE dimension of 'Prompt' that conveys specifically the notion described in this section.
VAC4EU	0	0	5.2.6		We recommend to refer to the 9 dimensions of the DIVERSE framework.
VAC4EU	0	0		The DIVERSE initiative is a recent initiative funded by ISPE that has identified 9 dimensions needed to characterise a data source repurposed for generation of RWE (Gini et al, Describing diversity of real world data sources in pharmacoepidemiologic studies: The DIVERSE scoping review. PDS 2024). The nine dimensions are: organization accessing the data source, data originator, prompt, inclusion of population, content, data dictionary, time span, healthcare system and culture, and data quality.	We recommend referring to such nine dimensions throughout the document when characterising a data source.

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	2	12		Neither the title of this ICH Guidance nor the text in section 1.1 (objectives) clearly indicate that the guidance focuses on the post-marketing setting, whereas e.g. Figure 1 clarifies that the framework concerns a safety concern or signal requiring further evaluation in the post-marketing setting. Would it be worth to specify the post-marketing focus of this guidance in section 1.1?	

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German Rheumatology Research Center | Head of Epidemiology, Prof. Dr. Anja Strangfeld	2	12	1.1	The mentioned objective of this guideline: "The purpose of this document is to recommend international standards" would be very beneficial, particularly, if as mentioned best practice examples would be added. However, in this section and in none of the following paragraphs it is clear how these standards were selected. In fact, this seems arbitrary and somewhat superficial. For example, one of the internationally accepted standards such as the STROBE recommendations is not mentioned across the entire document. The STROBE recommendations are internationally agreed upon by methodologists and are considered mandatory by many journals for the publication of results from observational studies. Why is such a standard and others missing in this document?	A paragraph 1.5 should be added that entails the methods applied to search for and review international standards.
EFPIA	4	5	1.1	"general principles on planning, designing, and analyzing observations (non-interventional) PE studies...". This is appropriate text, however, this leaves out for example lactation studies that although are intended to be observational, it is not possible to conduct as such and often have to be interventional.	Please consider including all study types as this is a general guidance, and allow all study types to be considered.
ISPE	4	6	1.1	It is unclear if "medicines", defined as drugs, vaccines, and other biologic products, includes medical device products and combination (device delivery for drugs).	If applicable, add "drugs, vaccines, ~~and~~ other biological products, medical device and combination products (device delivery for drugs)".
Cegedim Health Data	5	6	1	"fit-for-purpose data for safety assessment of medicines" : need to specify that the definition of fit for purpose data is included in these guildelines	Footnote referring to part 5.2
EUCOPE	5	1161	1.2	Fit for purpose data appears at least 9 times in this document. It is not well defined and appears to focus on if the data elements may be availbale in the datasources. There should be some description on applicability of data for different geographic regions based on epidemilogy and acceptance of data from one region to another for this purpose given the limitations of data sources	Expand on some of the fit for purpose definitions to discuss epidemiology and patient characteristics and acceptance or consideration of data from different regions. Perhaps expand section in line 579 or 748
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	5	5	1.1	A philosophical comment about equating the term "observational" with the term "non-interventional". Regardless of presence of randomization we are assessing the safety of interventions. So "non-interventional" is an unfortunate misnomer.	Suggest changing of "(non-interventional)" to "(non-randomized)" or "(non-experimental)"
EFPIA	6	6	1.1	There is no mention of combination products (drug-devices)	add whether combination products (drugs-device) are in or out of scope
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	6	6	1.1	Judging by the Glossary definition of medicine, the scope does not include surgical procedures or devices. The definition of medicines also includes substances used in diagnosis. Eg a contrast substance used for visualization would be subject to this document?	If that is intended, could be useful to explicitly clarify the scope.
H. Lundbeck A/S	14	32	1.2	The guidance describes epidemiology studies as a source of data and evidence to support the evaluation of post marketing safety of approved medicines. It also mentions epidemiology studies as a key component in signal detection, hower there is no further discussion of methodological approaches to conducting signal detection by integrating principles of pharmacoepidemiology studies.	1. Provide additional context regarding the use of RWD in signal detection 2. Further discuss methodological approaches to conducting signal detection and integrating these into the conduct of pharmacoepidemiology studies 3. Include ICH definition of a signal in the glossary to ensure consistent interpretation. 4. Revise the statement (…to support the evaluation of post marketing safety of approved medicines) adding '…to support the evaluation of post marketing safety of approved medicines and combination products.
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	14	14		Pharmacoepidemiologic studies are usually not a source of data, just evidende	Delete "data and"
EFPIA	15	15	1.2	"approved medicines" the term is very specific and might leave out of scope medical devices.	Please consider medical devices too.

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EFPIA	16	21	1.2	As we are defining signals, it should be clear what definition of signal is being used. Are we referring to validated signals? or merely data anomalies suggesting a potential safety event?	A clear definition of "signal" should be included or a reference to the ICH glossary to ensure consistent understanding
ISPE	16	16	1.1	The guidleline referes to signals as arising from a wide variety of data sources but there is no defintion of safety signal.	Add a definition for 'safety signal' in Glossary
ISPE	19	19	1.1	The phrase pharmacoepidemiological data is used but not defined, e.g. data generated by a non-interventional observational study design.	Add a definition of pharmacoepidemiological data in the Glossary or revise to RWD.
German Rheumatology Research Center | Head of Epidemiology, Prof. Dr. Anja Strangfeld	21	21	1.2	It should also be mentioned, that pharmaco-epidemiological studies can generate misleading results if conducted inappropriately.	Suggested phrasing: "However, pharmaco-epidemiological studies, if conducted incorrectly, can also generate spurious and erroneous results."
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	22	22		"relies on reliability" sounds redundant	consider rephrasing or using a synonym, perhaps "data quality and fitness for purpose" in combination with sound methods
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	28	32	1.2	(a) I do not understand why the HARPER guidance is beyond the scope of the guideline. The planning and the design of observational studies that utilize fit-for-purpose data for safety assessment of medicines requires a lot of details. It may be not required to repeat all these details in a guideline on general principles. However, it would be more clear, if the documents, in which these details are described, are clearly cited as relevant, rather than saying that these details are "beyond the scope". (b) Why is the FDA Sentinel Innovation Center a "non-governmental group"? (c) A reference to the PRINCIPLED framework is missing.	Replace the sentence "In addition, frameworks for study design and conduct are being developed by non-governmental groups, such as The Sentinel Innovation Center with the PRINCIPLED framework and ISPE/ISPOR's HARmonized Protocol Template to Enhance Reproducibility (HARPER) Initiative, which provide additional detail that is beyond the scope of this guideline [1, 5]." by a statement like this: "In addition, frameworks for study design and conduct are being developed by the FDA Sentinel Innovation Center with the PRINCIPLED framework [REF] and ISPE/ISPOR's HARmonized Protocol Template to Enhance Reproducibility (HARPER) Initiative [1, 5]. These documents contain important additional details which should be taken into account in the planning and the design of observational studies that utilize fit-for-purpose data for safety assessment of medicines". New Reference: Desai R J, Wang S V, Sreedhara S K, Zabotka L, Khosrow-Khavar F, Nelson J C et al. Process guide for inferential studies using healthcare data from routine clinical practice to evaluate causal effects of drugs (PRINCIPLED): Considerations from the FDA Sentinel Innovation Center BMJ 2024; 384 :e076460 doi:10.1136/bmj-2023-07646

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IQWiG	28	32	1.2	(a) We do not understand why the HARPER guidance is beyond the scope of the guideline. The planning and the design of observational studies that utilize fit-for-purpose data for safety assessment of medicines requires a lot of details. It may be not required to repeat all these details in a guideline on general principles. However, it would be more clear, if the documents, in which these details are described, are clearly cited as relevant, rather than saying that these details are "beyond the scope". (b) Why is the FDA Sentinel Innovation Center a "non-governmental group"? (c) A reference to the PRINCIPLED framework is missing.	Replace the sentence "In addition, frameworks for study design and conduct are being developed by non-governmental groups, such as The Sentinel Innovation Center with the PRINCIPLED framework and ISPE/ISPOR's HARmonized Protocol Template to Enhance Reproducibility (HARPER) Initiative, which provide additional detail that is beyond the scope of this guideline [1, 5]." by a statement like this: "In addition, frameworks for study design and conduct are being developed by the FDA Sentinel Innovation Center with the PRINCIPLED framework [REF] and ISPE/ISPOR's HARmonized Protocol Template to Enhance Reproducibility (HARPER) Initiative [1, 5]. These documents contain important additional details which should be taken into account in the planning and the design of observational studies that utilize fit-for-purpose data for safety assessment of medicines". New Reference: Desai RJ, Wang SV, Sreedhara SK, Zabotka L, Khosrow-Khavar F, Nelson JC et al. Process guide for inferential studies using healthcare data from routine clinical practice to evaluate causal effects of drugs (PRINCIPLED): Considerations from the FDA Sentinel Innovation Center. BMJ 2024; 384: e076460.
ISPE	30	30	1.2	The Sentinel Innovations's PRINCIPLED framework is mentioned but not cited.	Cite the BMJ paper describing PRINCIPLED: Desai RJ, Wang SV, Sreedhara SK, Zabotka L, Khosrow-Khavar F, Nelson JC, Shi X, Toh S, Wyss R, Patorno E, Dutcher S, Li J, Lee H, Ball R, Dal Pan G, Segal JB, Suissa S, Rothman KJ, Greenland S, Hernán MA, Heagerty PJ, Schneeweiss S. Process guide for inferential studies using healthcare data from routine clinical practice to evaluate causal effects of drugs (PRINCIPLED): considerations from the FDA Sentinel Innovation Center. BMJ. 2024 Feb 12;384:e076460. doi: 10.1136/bmj-2023-076460. PMID: 38346815.
German Rheumatology Research Center | Head of Epidemiology, Prof. Dr. Anja Strangfeld	33	61	1.3	The phrasing "For the purpose of this guidance, we refer to data collected for the specific study as primary data collection." is inconsistent with the proposed possible data sources discussed in Section 5. Please see more detailed comments below.	Data sources should be specified more precisely and a distinction made between primary and secondary data use. In this context, the objective of this guideline is probably not limited to primary data collections.
EFPIA	34	34	1.3	document refers to "slight differences" between regions - please clarify the exact nature of the difference	add clarification into the glossary text
EUCOPE	34	39	1.3	It's confusing not to mention use of secondary data as the main scope while only mentioning "primary data collection".	Add "secondary use of RWD" for the purpose of safety assessment.
H. Lundbeck A/S	34	41	1.3	It is not clear from the scope what products are covered under this guidance. Only drugs, or are combination products covered under this guidance as well.	Please clarify in the guidance whether combination products are in scope.
Olena Pankova	34	37	1.3.	In the present guideline, the characteristics of data sources have been considered in detail, but additional points should be discussed, particularly the impact of differences in RWD in different regions on research reliability and possible approaches to performing multicentre pharmacoepidemiological studies according to this issue. Taking into account that sources of RWD may be different depending on the region, strategies to mitigate these research limitations should be considered.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
RTI Health Solutions	34	37	1.3	Scope section: it´s not explicit as to whether this guideline is only aimed at studies requested by regulatory authorities, or recommended for any observational safety study for medications already in the market.	Consider specifying this aspect of the scope in the scope section.
EFPIA	35	36	1.3	Intent is non-interventional studies so continue to mention early on. Guidance is not only specific to RWD so other data should be mentioned as well.	Add ".... recommendations for non-interventional studies utilizing RWD and other sources such as primary data collection..."
EFPIA	35	35	1.3	Please consider adding the following to the RWD definition in the Glossary Section "data collected outside of Traditional Clinical Trials" - this aids readers in the understanding of the RWD concept, differentiating it from the data acquired through "Traditional Clinical Trials"	As suggested in the comment. To be added to the Section 12 - Glossary
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	36	37		Term "medicinal products" is used, but the glossary term is "medicine"	Consider using the same consistent terminology throughout the document
EFPIA	37	41	1.3 Scope	This paragraph seems to suggest that RWD is solely based on secondary use of data sources. However, studies based on primary collection of data are also based on "RWD" - RWD sources may provide both secondary use of data AND primary collection of data, Therefore, it might be clearer to write:	To enhance clarity and to better "harmonize" the understanding that RWD consists of data derived from BOTH primary collection of data and from Secondary use data, the following wording is suggested: Non-interverntional post-authorisation safety studies (or if preferred: non-interventional safety studies - safety NIS) may be based on RWD originating form primary collection of data or on secondary use of data, depending on the research question, type/granularity of data needed to address the research question, and availabe data sources providing the required data. At times RWD originating from secondary use of data (e.g. databases, registries) alone may be insufficient to answer the research question. At times, RWD originating from primary collection of data may be inssufficient to achieve requirements such as large sample size for investigatign rare safety risks, representativeness. long follow-up etc. This guideline includes considerations for NI-PASS (or if preferred non-interventional Safety studies - or safety NIS) based on primary collection of data and on secondary use of data.
H. Lundbeck A/S	37	39	1.3	The description of RWD suggests that it only includes secondary data and not primary data collection. This is inconsistent with the footnote for Figure 1, where it can be interpreted that primary data collection is in scope of RWD.	To revise the description of RWD, that which includes both secondary data sources and primary data collection
VAC4EU	38	41	1.3	Primary data or primary data collection can have various meanings, so it is unclear what meaning is being used in this document, as the 2nd sentence seems to be contradicting the first sentence?	
EFPIA	42	43	1.3 Scope	"It is beyond the scope of this document to provide guidance on whether a clinical trial or a pharmacoepidemiological study is the most appropriate approach, nor is it intended as a comprehensive source of knowledge for pharmacoepidemiological methods." The above copied sentence might be misleading, especially because the guideline will not further explain what is meant by "clinical trial" and what is meant by "pharmacoepidemiologic study/methods". The copied sentence seems to indicate that there is a dichotomy of pharmacoepidemiology being synonymous with "real-world" study and that "Clinical trial" is never real-world. As earlier commented, ommiting using the broad term of "Pharmcoepidemilogy" in this guideline might enhance the guideline´s clarity.	Suggest deleting this sentence entirely. However, if it is decided to keep the sentence, to avoid confusion and obtain International Harmonization, it is suggested to introduce and define the terms: - "Low Interventional Clinical Trial/Pragmatic trials as containing Real-world elements together with intervention (e.g. participant randomization at patient level) - Traditional RCTs

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	42	44		The entire sentence can be deleted, as previous section has already narrowed the scope to non-randomized studies (calling them non-interventional)	See suggestion below, possibly redefine the scope.
ISPE	43	43	1	A clarification about how the study type would be judged as more or less appropriate,"…or a pharmacoepidemiological study is the most appropriate approach", should relate closely to the objective of assessing safety.	Revise the sentence to add: "the most appropriate approach to assess the safety of a medicine"
EFPIA	44	45	1.3 Scope	"Rather, the intent is to harmonize regulatory guidance documents for the design, planning and execution of pharmacoepidemiological studies, and to facilitate regulatory review" - The above copied sentence describes a very broad "intent" of this paper; it´s not aligned to this guideline´s title and Objectives (1.1) which are more streamlined and focused on safety studies	Recommended wording: Rather, the intent is to harmonize regulator guidance documents for the design, planning and execution of Non-interverntional post-authorisation safety studies (or if preferred: non-interventional safety studies - safety NIS), and to facilitate regulatory review.
EUCOPE	46	46	1.3	see above	add "primary or secondary" to "pharmacoepidemiological studies"
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	46	48	1.3	I support the reference to non-regulatory guidelines. However, some references are incomplete and the list with only 4 references is very short. We propose to complete the references and to update the list.	See the recommendations below (regarding lines 1144-1153).
IQWiG	46	48	1.3	We support the reference to non-regulatory guidelines. However, some references are incomplete and the list with only 4 references is very short. We propose to complete the references and to update the list.	See the recommendations below (regarding lines 1144-1153).
EFPIA	49	55	N/A	A separate paragraph is provided on patient experience data (rows 56-61), which mentions that regulatory guidances have been developed concerning patient experience data. No additional information (such as the reason why they are not considered suitable or that there are existing guidance documents) is provided for the other study types that are out of scope. It might be worth to mention that there are guidance documents concerning some of these out of scope study types, such as e.g. external comparators derived from RWD used as a control arm for single-arm trials.	
EUCOPE	49	55	1.3	The guideline is clearly focused on safety assessment. We ask that the agency consider whether vaccine effectiveness and PAES are in scope of this document, and if not, to explicity address that these topics are out of scope.	
H. Lundbeck A/S	49	55	1.3	It is not clear which data sources would be out of scope. For example social media sources would not typically qualify as a potential source.	Suggest revising the list to include safety data mined from social media sources, since these sources would not typically support pharmacoepidemiological studies
EFPIA	50	54	1.3 Scope	To enhance clarity, please state that the 3 bulleted study types qualify as Real World studies based on real-world data - but that these are out of scope for the purpose of this guideline.	As recommended in the comment.
EUCOPE	50	51	1.3	This section indicates study types are out of scope such as PV studies using spontaneous report.	There should be a section that describes how these national or global databases can be accessed (and listed as an appendix or linked to another document) and utilized to help formulate hypotheses, complement analyses from RWE data sources
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	50	55		I am not sure why pragmatic trials and external comparator trials are excluded, as they may draw information from databases and thus would be subject to the same requirements. Same goes for studies that collect patient experience data. Hybrid studies that supplement secondary data with additional primary data collection, e.g., review of medical charts, are rather common	Possibly rethink the scope to include any postmarketing safety assessment, regardless of design, that relies on secondary data to define some or all aspects of the study design.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ISPE	51	51	1	Specific examples of PV systems could be added to " …or global databases (e.g.,pharmacovigilance system at national level)"	Add " (e.g. pharmacovigilance system at the national level such as Vigibase, EudraVigilance, FAERS).
VAC4EU	53	53	1.3		Please provide further description of what constitutes patient experience data?
EFPIA	55	55	1.3	Some pharmacoepidemiology studies collect patient experience data	Define what patient experience data refers to
EFPIA	55	55	1.3	clarify if safety data mined from social media sources is in or out of scope	
EFPIA	55	55	1.3	Patient experience data is not known to all	Add 1-2 examples in parentheses
EFPIA	55	55		Clarify and reconsider why patient experience data (PED) is being specifically excluded as it can be primary data, and 'primary data collection' is in scope for this guideline. Likewise, if studies collecting and analyzing PED are out of scope, further clarity is need on whether studies to measures effectiveness of RMMs are also out of scope (eg. surveys among patients or qualitative studies with patients interviews).	
EFPIA	56	61	1.3	This paragraph appears to be redundant as, based on the statement in line 49 this topic already is out of scope. If it is retained then it is recommended that a reference be provided for pharmacovigilance studies (line 50) and studies involving treatment assignment (line 52).	To be deleted text from line 56-61
EFPIA	56	60	scope	patient experience data is out of scope re: "...safety studies to inform on aspects such as notable events, perspectives, needs, and priorities. While a detailed guidance on this is beyond the scope of this guideline, several regulatory guidances have been developed (see Section 13, Regulatory Guidelines Referenced).	please clarify which specific guidances refer to "patient experience data" as the link just goes to the general section and thus it is not clear what exactly is out of scope. For example, are patient surveys that measure the effectiveness of risk minimization measures (module 16) by assessing knowledge, behaviour and understanding considered "patient experience data" and therefore out of scope of this guidance? Please clarify and/or be specific
EFPIA	56	56		Some patient experience studies are requested by Health Authorities to support product registration, not only post-marketing safety studies	"Collecting patient experience data may be a valuable component for product registration and post-marketing safety studies to inform on aspects such as notable events, perspectives, needs, and priorities."
EUCOPE	62	63	1.3	We suggest the agency restructure this sentence for greater clarity.	This guideline does not address the topics of pharmacogenomics, artificial intelligence (AI), and other emerging technologies relevant to the use of RWD given their evolving nature.
European Association of Hospital Pharmacists	62	63	1.3	The guideline explain that they will not address pharmacogenoic, AI and emerging technologies. However, we believe that especially AI and emerging technolgies should be included or have seperate guidelines as soon as possible due to their increasingly growing use to evaluate real-world data. Indeed, while this guideline is well written, due to the exclusion of AI and emerging technologies, they may unfortunatly miss a rapidly growing aspect in the evaluation of RWD and thus may quickly become less applicable.	We would recommend either to include AI and emerging technologies in the current guidelines or to develop some guidelines on the use of AI and emerging technologies in the evaluation of real-world data as soon as possible.
ISPE	65	67	1	Adherence is another non-safety outcome that is relevant to be included in the sentence: "The principles presented in this document provide recommendations….such as utilization and effectiveness studies"	Add "such as adherence, utilization..."
EFPIA	67	67	N/A	The guideline mentions "effectiveness studies". In an extension to the above comment, is it possible to clarify if this refers to knowledge, behaviours and/or outcome studies?	Clarification of what is meant by the term 'effectiveness' study
EFPIA	67	67		Clarify if the term 'effectiveness studies' means 'efficacy studies using RWD' or 'effectiveness of RMMs studies'	
ISPE	69	69	1	To further connect to the safety assessment purpose of the guideline, the sentence"The basic principles presented in this guideline may be relevant to these studies when real-world data elements are included" can be edited.	Add" when real-world data elements are included if safety is being assessed or described".

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	70	91	2	Consideration could be given to including reference to guideline such as FDA draft guidance on Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products; EMA draft reflection paper on use of real-world data in non-interventional studies to generate real-world evidence and EMA: The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 11, 2023).	Please see under comment and rationale
ISPE	72	74	2	Benefit-risk was not defined previous to "Post-approval pharmacoepidemiological safety studies complement other sources of information to provide a better picture of the benefit-risk profile of medicine as used in clinical practice the benefit-risk profile".	Add benefit-risk profile to the Glossary
EFPIA	73	75	2	"Post-approval PE safety studies complement other sources of information to provide a better picture". Other sources is quite vague and abstract in this context, and give that this is a guideline, either bring examples of other sources or specify them in the text.	Please consider to give examples of "other sources"
EFPIA	76	76	2	……the research question……', given the process is iterative, and it is possible to refine/revise the research questions after feasibility assessments, is it appropriate to rephrase to 'initial research question' here in order to differentiate from the 'final research question' after feasibility assessment? Especially if the purpose of the study is to generate hypotheses for future research (as referred in lines 127-128).	initial research question'
EFPIA	76	76	2	Rationale is also important	Add rationale before "research question"
AstraZeneca	79	80		Confounding is one of the three main types of biases in epidemiology. Revise sentence for accuracy. E.g., "considering potential sources of confounding and other biases". Consider calling out the two other overarching types of bias (i.e., selection and information bias), and the importance of evaluating these as overarching concepts.	Revise sentence for accuracy
EUCOPE	80	80	2	We suggest the agency provide additional clarification about the importance of defining the exposure and the outcome. This should be clarified early in this guideline. Ensuring that the outcome is well-defined and that the data sources are fit-for-purpose in supporting data generation for the outcome is critical. This is an important comment which in our opinion needs to be better addressed here and/or in the feasibility section. There is potential for a poorly defined outcome to impact results, or for a potential data source to have incomplete data for appropriate assessment of the outcome.	
VAC4EU	82	83	2	Do you refer to section 4.2 Feasibility assessment?	
RTI Health Solutions	85	85	2	Please list the type submission.	E.g., "submission of study report to regulatory authorities"
EFPIA	88	89	2	"researcher: may be a regulatory agency, sponsor, contract research organization, academic group, or others"	Please consider expanding "others"
EFPIA	89	90		Are we saying that the definition of "sponsor" for this type of studies is the same as outlined in ICH GCP.	
EUCOPE	89	90	2	Original text: "Sponsors of marketing applications and marketing authorization holders are ultimately responsible for all aspects of post-marketing safety studies submitted to regulators." Sometimes PMSS are sponsored and conducted by external organizations, not the marketing authorization holder (MAH). Therefore, we recommend clarifying that this statement is true for those PMSS that are sponsored by MAH.	We recommend the following revision: "Sponsors of marketing applications and marketing authorization holders (MAH) are ultimately responsible for all aspects of post-marketing safety studies submitted to regulators, on behalf of MAH."
EFPIA	92	92	3	The sentence would be clearer if "study-generated evidence" included a hyphen.	Add the hyphen
EFPIA	92	92		States "The strength of the study generated evidence submitted in support of a regulatory decision..."	Could it be clarified in the earlier "scope section" that in scope are RWD studies "...evaluating post-marketing safety of medicinal products' (lines 36-37) for regulatory decision-making? It is still not clear what type of RWD analyses are in scope or out of scope of this guideline

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
RTI Health Solutions	92	92	3	"The strength of the study generated evidence submitted in support of a regulatory decision": hyphen seemingly missing from "study generated"	"study-generated"
EFPIA	96	98		Sometimes researchers may 'have to' align the design to the data source, so this should not be prohibited or discouraged. The guideline should include a note to elaborate on the limitations this requirement imposes and what should be expected from the researcher "Researchers should avoid designing a study that conforms to a specific data source, because a specific data source may restrict the options for study design and limit the inferences that can be drawn."	
EFPIA	97	98	3	Limiting the inferences that can be drawn is not always a limitation. The only inferences that matter are the ones needed to address the research questions. If a study cannot address the research question, it should obviously not be executed but extending inferences is not always a benefit as it may mitigate any risk of Type I errors.	Consider softening or deleting the clause "and limt the inferences that can be drawn."
ISPE	103	103	3	In Figure, Step #3, the phrase "minimum requisite data" is not defined and could be interpreted many ways. It would benefit the readers if a foot note or Glossary entry could be included.	Provide a definition for minimum requisite data in the Glossary
Euromedicat Steering Group	104			Line 104 "adequacy of evidence" should include reference to any differences between the (often very different) contextual variables in the settings where evidence is collected and where it is intended it should be applied. Healthcare delivery standards vary with socio-economic status (Fisher et al 2020).	
EFPIA	107	109	3	There is some discrepancy between the call to assess the adequacy of evidence with pre-specified sensitivity analyses and the sentence that follows, suggesting that quantitative bias analyses may be employed a priori or to facilitate interpretation of study results.	This is all resolved if the "prespecified sensitivity analyses" referred to in the first sentence are clarified to be the quantitative bias analyses referred to in the second. One way to address this: "...and after study implementation with sensitivity analyses pre-specified in the protocol, i.e., quantitative bias analyses (QBA)." but I'm not certain this was the intent. Alternatively, simply clarify what "a priori" refers to: before creation of the protocol, selection of the data source or something else?
ISPE	107	109	3	The description of quantitative bias analysis timing, a priori or post-study conduct, comes before the depiction of research phases in Figure 1, with no cross-referencing to the Figure . This may be more difficult for readers to follow.	Add references to specific Steps in Figure 1 Steps within the QBA description, e.g. a priori application (Figure 1, Step#6), post-study application (Figure 1, Step #8).
EFPIA	108	110	2	We welcome the suggestion on the use of quantitative bias assessments (analyses). We would like to comment though that a priori use of quantitative bias assessments during feasibility may only be possible in data sources to which the researcher has direct access.	
VAC4EU	108	108	3	A priori of deciding which databases are included to answer the research question?	Try to specify this "a priori"
AESGP	112	114	3	Can this "user-generated health data" be considered ancillary to the three main components outlined earlier in this section? If so, see Proposed changes/recommendation.	Studies involving user-generated health data extracted from other sources (e.g., websites, blogs, social media, chat rooms) may not be adequate, but they may be considered ancillary data to generate hypotheses and contextualize the study results
AESGP	112	114	3	Social Media / forums - are important sources of data in niche vigilance areas such as abuse potential of non-prescription / even prescription drugs. A wider net needs to be cast for RWD for non-prescrition drugs. Non-traditional sources such as social media / forums / blogs are helpful and there are advanced methods to ensure validity and integrity of data.	Suggest to reference work by IMI WEB-RADR
EFPIA	112	114	3	Data from Internet sources are not fit-for-purpose and shold not be considered in this context.	Suggest deleting sentence on internet obtained data

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	112	112	3	Is the scope limited to safety studies aimed at addressing regulatory questions? Or perhaps this is intended in a looser sense, referring to studies initiated in response to signals prior to notification of regulatory agencies. This is an important clarification given the increasing use of RWD to assess safety signals during the signal management process. Such work would occur prior to any regulatory request (although it is part of a highly regulated process).	Clarify the scope
Olena Pankova	113	113	3	Mechanisms for the collection of user-generated health data from sources such as social media, chat rooms, blogs, websites etc. need to be clarified, especially with regard to obtaining informed consent and security concerns of data privacy.	
EFPIA	115	116	3	The figure is not really clear.	Suggest changing graphic to a feedback loop
EFPIA	115	115	3	Minor wordsmithery: Fig 1 was undoubtedly the result of careful deliberation. It seems unfortunate to introduce this framework in a sentence that immediately demotes this concise summary of study development.	Consider instead "Figure 1 depicts a linear process for simplicity, but consideration and evaluation ...."
EFPIA	115	116		Further clarification should be provided about the acceptability of the 'iterative' approach.	
ISPE	115	116	3	The guideline acknowledges that Figure 1 depicts a linear process, while consideration and evaluation of evidence that is adequate should be iterative. It would be more instructive to revise the figure to reflect where likely regulatory interactions could occur that would increase the study's probability of success.	Add arrows or other symbols to Figure 1 to denote where in the process (between which Steps/boxes) feedback could be obtained via consultation with health authorities.
EFPIA	117	117	3	"Researchers are encouraged to discuss the attributes of a particular study with the regulatory agency early in the planning process" - it would be helpful to specify the "early" timeframe and also routes to discuss for the major agencies (FDA, EMA) in an appendix. This is not available in any of the guidances, and would be extremely helpul to have this information	
EFPIA	117	117	3	Recent guidances and conference presentations encourage study developers to speak to regulatory agencies early in the plannng process. However, information about the most appropriate way to initiate those discussions is sorely missing: what is the process that should be followed? what types of meetings should be requested? which offices or departments should be present? And how does one even begin to initiate a discussion late in a new regulatory submission (or even during the evaluation of that submission) when a study details must be outlined with a submission or when it represents the only step standing before an approval? While the sentiment is not controversial, the lack of operational clarity on how this can be achieved sorely limits the impact.	Clarity on the mechanism and practical aspects of how those developing a study can discuss the study design with regulators needs to be added.
EFPIA	118	119	3	……validity assessment.' What does this 'validity assessment' refer to? Is it an assessment of 'data validity' or 'study validity', is it for 'internal validity' and/or 'external validity' or 'coding validity'? Is it a specific step associated with a specific template/framework like feasibility assessment?	clarification required on 'validity assessment'
EFPIA	121	122	3	Figure 1 applies to all safety questions using RWD, not only regulatory questions. Therefore, the title can be more general by removing "regulatory" from the title.	Figure 1: A framework for generating adequate evidence using fit-for-purpose real-121 world data to address questions on the safety of medicines
EFPIA	121	122	3	If the guidance can be used for non RWD studies as previously stated, box 3 doesn't need to specify RWD	Substitute data sources for real world data sources in box 3
EFPIA	121	122	3	Consideration could be given to referring to assessment for missingness in Figure 1, lined 196-202 Section 5.2.4	Please see under comment and rationale

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	121	123	3. Figure 1	According to lines 151-154, is it correct that Step 3 should be called Feasibility phase 1? Step 5 is Feasibility phase 2? In general it will be more helpful to align Figure 1 steps (e.g. headings, titles) with the paragraphs in the following texts to elaborate these steps. Otherwise, it is a bit confusing when there are different steps/titles in the text below which are different from those included in the graph. In lines 209-213, it is mentioned 'feasibility assessment' of primary data collection, need to clarify (maybe in notes underneath the graph) that 'feasibility assessment' in step 3 and 5 is different from 'feasibility assessment' for primary data collection?	update Figure 1, and streamline sections below, and clarification required on 'feasibility assessment'
EFPIA	121	123	Figure 1	Clarify that the framework shows a sequence of steps linked to text in Section 3	see comments below
EFPIA	121	123	Proposed flowchart	We are proposing a flowchart that highlights the steps that are listed from lines 125-142 to help further refine the research question (including how to address the unknowns): for this flowchart, we propose to expand the diagram in Fig 1 by adding conditional statements (IF: diamond shape): 1a) IF "unknowns are highlighted" (then/Yes) or (else/No) 1b) iF "feasibility assessment already conducted or not needed" (then/Yes) or (else/No) 1c) NOTE: such IF (conditional statements) create iterations (loop back) to improve refinment of the research questions (1a) and refinement of the study protocol (1b) 2) The diagram (flow chart) in Fig 1 is called only in the Chapter 3, although it is not described in Chapter 3. However, some of the steps in Fig 1 are mentioned/presented in the Chapters 4-5.	Framework with iterations and conditional statements (draft) https://docs.google.com/document/d/1ccZuXabRI9DPj_xrXi-qjZX-uoRgBOGhERFKAWBwczM/edit?usp=sharing
EUCOPE	121	123	3	Original text: 1.Identify safety concern or signal requiring further evaluation in the post-marketing setting To be consistent with the terminology used in pharmacovigilance (see EMA's guideline on good pharmacovigilance practices: Module IX), we recommend using the term "validated signal" instead of just "signal."	We recommend the following revision: 1.Identify safety concern or validated signal requiring further evaluation in the post-market setting
EUCOPE	121	123	3	It would be helpful for the agency to include an explanation for the use of quantitative bias analysis mentioned in Steps 6 and 7. This will clarify how quantitative bias analysis works in those steps and how it benefits the study design.	
EUCOPE	121	123	3	Original text:4. Develop study draft protocols/synopsis describing study design.. Etc	4. We recommend including ''database strengths and limitations''
H. Lundbeck A/S	121	123	3	Framework for generating adequate evidence using real world data: Figure 1 seems to be one directional when in reality there should be bidirectional feedback at almost all steps due to the interative nature of the process.	Suggest updating Figure 1 to account for the iterative process evidence generation. Specifically there should be a feedback loop in most steps with ability to go back to the previous steps based on information emerging in subsequent steps
IQVIA	121	123	3 Framework for generating adequate	Figure 1, Box 5 should list other data source characteristics that need to be assessed as part of study feasibility, (i.e., in addition to representativeness, exposure, outcome and covariates), such as data access, lag, linkage potential, and use rights.	We recommend including other operational aspects of RWD that should be addressed as part of the feasibility assessment, including data access, lag, linkage potential, and user agreements.
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	121	123		Figure 1: the feasibilty assessment should also identify data source that adequately identifies the study population, e.g., patients with the target condition or patients within the target demographic. Eg, PEDIANET database may have great data on all study variables, but it cannot be used to study adults because it is restricted to children	Adjust Figure 1 to include identification of the study population in the feasibility assessment. It is invoked in section 4.2, so should be harmonized.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	122	123	3	An intent shared in the document is to harmonize regulatory guidance documents for the design, planning, and execution of pharmacoepidemiology studies, and to facilitate regulatory review. A particularly important gap in many guidances is an acknowledgement of the time it takes to properly identify data sources and perform feasibility assessments. The time it takes to perform activities is outlined in guidances is often mismatched with the time regulators allow for those activities. Time is a missing aspect in Figure 1. Without better alignment on time, there is a larger risk of designing a study to conform to a specific data source, a practice that should be avoided.	Please consider adding a time element to the figure. It can be a range of time. For example, how many months might one expect to perform a wide scan assessment to identify a prioritized list of potential data sources. How long might a feasibility assessment be expected to take?
EFPIA	122	123	3	Step 1. It is unnecessarily restrictive to limit this step to evaluation of medicines in the post-marketing setting. While secondary data, representing the most commonly used RWD, must necessarily be collected in thecourse of routine care, this step seems to imply safety concerns about a medicine will only be evaluated using postmarketing data about that medicine. Safety concerns or signals may also arise prior to approval of a medication for a specific indication. This may require evaluation of the issue in the indicated population based on medications in the same class or, when the medicine is already available on the market for other indications, potentially based on exploratory evaluation of off-label use.	Replace "in the postmarketing setting" with "using RWD" or delete it
EFPIA	122	122	Figure 1 (step 6)	The term study is unclear	To avoid misunderstanding, pls state that this refers to the study protocol
EFPIA	122	122		A priori 'specification' of Quantitative Bias Analysis (QBA) is reasonable, and the approach should be included in the protocol, but the conduct of QBA should be expected to be conducted 'after' study implementation often in the form of sensitivity analyses. Consideration should be given to whether QBA - on 'interim' findings enhances confidence - or somehow jeopardises credibility of the findings if the iterative conduct of analyses is perceived as some form of data dredging	
ISPE	122	123	3	Step 1. Is the scope deliberately limiting this step to evaluation of medicines in the post-marketing setting? While secondary data, representing the most commonly used RWD, must necessarily be collected in thecourse of routine care, this step seems to imply safety concerns about a medicine will only be evaluated using postmarketing data about that medicine. Safety concerns or signals may also arise prior to approval of a medication for a specific indication. This may require evaluation in the indicated population based on Standard of Care/medications in the same class or, when the medicine is already available on the market for other indications, potentially based on exploratory evaluation of off-label use.	If pre-authorization safety assessments are in scope, replace "in the postmarketing setting" with "using RWD" or delete it.
ISPE	122	123	3	The guideline outlines a purpose of harmonizing regulatory guidance documents for the design, planning, and execution of pharmacoepidemiology studies, and to facilitate regulatory review. A particularly important gap in many guidances is an acknowledgement of the time it takes to properly identify data sources and perform feasibility assessments. The time it takes to perform activities in outlined in guidances is often mismatched with the time regulators allow for those activities. Time is a missing aspect in Figure 1. Without better alignment on time, there is a larger risk of designing a study to conform to a specific data source, a practice that should be avoided.	Add a time element to Figure 1. For example, how many months (range) might one expect to perform each Step and generate the necessary information to inform decisions about data source fitness-for-use and operational feasibility given a specific study design to accomplish the safety-related research question(s).
EFPIA	123	123	4.2.	Box 5 of Figure 1 needs to be modified to clarify that data quality needs to be as well assessed upfront during feasiblity assessment.	Consider adding in Box 5 of Figure 1 "and realiable" as follows: 5.Conduct feasiblity assessment to determine which data* are fit-for-purpose (assessing patient count and whether exposure, outcome, and covariates are relevant and reliable, operational, accurate)
VAC4EU	123	123	3	Comment regarding figure 1, step 3.	Consider adding "(…) minimum requisite data on selection of study population, exposure (…)"
VAC4EU	123	123	3	Comment regarding figure 1, should exposure and outcomes be labelled as exposure(s) and outcome(s), also no mention of potential confounders and effect modifiers?	
RTI Health Solutions	125	142	4.1	At the time the research question is formulated, investigators should be explicit whether the study has descriptive or causal (inferential) objectives. The guidance differentiates between descriptive and inferential studies in sections 1.2 and 7, and refers to the target trial emulation framework for causal inference in section 4.1, but it is important to explicitly differentiate between these two aims when specifying the research question, as this will drive design and analysis.	Insert in L139: Researchers need to be explicit whether goals are descriptive or casual, and about the principled framework for study design and estimation of the risks of a medicine.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	126	127		Are there different expectations, or should there be, on studies testing hypotheses, vs those generating hypotheses - some guidance on this is warranted particularly if an 'iterative' approach to the study conduct is seen as jeopardising its credibility.	
RTI Health Solutions	126	139	4.1	Studies conducted to meet requirements from regulatory agencies have their research questions determined by the regulatory request; studies not requested by regulatory agencies can mold their question addressing gaps in the literature more easily. Please see question on scope of this document. Epidemiology and statistics are moving away from the framework of hypothesis testing (eg, ASA on p-values, https://www.amstat.org/asa/files/pdfs/p-valuestatement.pdf); most studies intend to estimate a range - Also consider language similar to that used in the EMA refelection paper which distinguishes "between NIS having descriptive objectives and NIS having causal objectives".	Remove or replace sentence in lines 126-128. Consider rephrasing this section to address more closely research as it is currently designed, conducted and published
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	126	142	4.1	Good idea to emphasize the importance of the research question, however, the provided text seems a bit generic and coming from any epidemiologic textbook.	Consider tailoring this section specifically to the research questions related to safety of medicines, e.g., making the research questions specific in terms of population of interest (e.g., pregnancies), source of the safety concern (e.g., pregnancy signal originating from TIS may be subject to selection bias). Also a research question may be that of adherence to risk minimisation measures. Consider providing an example of a good research question in postmarketing safety studies.
ISPE	128	129	4.2	An addition is recommended for the statement:"The research question may be formulated by use of the population, intervention (exposure in the case of non-interventional studies), comparator, outcome, and timing (PICOT) template", in order to take into account the healthcare setting in which the medicine was prescribied/used.	recommend use of "PICOTS" to also include Setting within the research question
IQWiG	129	131	4.1	It is mentioned that prior to a formulation of an adequate reserach question, a literature review should be conducted This is an important issue to avoid research waste. Therefore, a systematic review of the literature should be performed.	Add the word "systematic" before "review of the literature" in line 131 to emphasize the importance of the review.
EFPIA	130	131	4.1	Delete "In the case of non-interventional studies,'intervention' can be …." as it is redundant with the parenthetical statement in the previous sentence.	See comment
Euromedicat Steering Group	130			Line 130 treating an intervention as an exposure in observation studies is inappropriate, and will lead to confusion when assessing studies' risk of bias: ROBIN=I and ROBIN-E differ in several parameters. This should be acknowledged or the sentence removed.	
ISPE	130	131	4.1	A recommended edit for clarity of language.	Move "exposure" first in the following sentence: "In the case of non-interventional studies, "exposure" can be considered the same as an "intervention"
EFPIA	131	133	4	The specific question should be formulated after a review of the literature…'. Does it need to be systematic literature reviews (SLRs)? Is there a preference of SLR over other types of literature reviews?	Clarification is needed: if there is a preference of different types of literatures? Or the choice of literature reviews should be context based and justified?
EFPIA	131	133	4.1	"The specific questions should be formulated after a review of the literature to identify and understand any knowledge gaps..." Literature is not the only source of information that will be used to formulate a research questions.	Please consider adding another possible source other than literature to identify and understand any knowledge gaps such as a final study report can be the source of a new research question., etc.
EFPIA	131	132	4.1 Research Question	"The specific question should be formulated after a review of the literature to identify and understand any knowledge gaps, strengths and weaknesses of prior studies, the expected magnitude of effect, and important confounding factors." Pleae acknowledge that this is not always possible, e.g., newly launched first-in-class drug.	Recommendation: Initiate the sentence with wording such as "When possible/applicable…
EUCOPE	132	132	4.1	Original text: strengths and weaknesses of prior studies	change into 'prior published studies'
EFPIA	136	139	4.1	It seems we can refine research question after feasibility assessment, so the process should be iterative, rather than linear as per above figure 1: research question - feasibility - study design - protocol - analysis - results	Consider update and keep consistent of the Figure 1 and following texts to demonstrate the 'iterative process'

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	136	139	4.1	The sentence "Careful formulation of the research question will highlight unknowns that will need to be addressed through information derived from the feasibility assessment and this information may further refine the question and drive protocol 138 development." is not presented in Figure 1.	clarify figure 1
EFPIA	137	137	4.1	In the sentence 137, the term “highlight unknowns” needs additional clarification.	add clarification for the term
EUCOPE	137	137	4.1	Original text: unknowns	change into 'evidence gaps'
ISPE	139	142	4.1	Suggest stronger emphasis on the recommended use the “estimands” framework approach, especially for comparative studies with effect measures, exposures, and outcomes that directly emulate experimental designs.	Suggested edit: "Researchers should consider a principled framework for study design… …for which the target trial and estimands framework are recommended…”
RTI Health Solutions	139	142	4.1	References 3 and 5, cited here, may not be the intended references for this section.	Please confirm the references; as a reader, one could expect a reference to a seminal publication on target trial emulation and to one on the estimand framework.
EFPIA	140	141	4.1	……the estimands framework……'. Which framework to use and/or preferred: PICOT or ESTIMANDS? Is it case by case decision?	If the framework is assessed on a case by case basis, clarification required whether researchers need to justify the framework choice or whether it is ok to use any?
RTI Health Solutions	140	141	4.1	We are concerned by the reference to the ICH E9 (R1) Addendum on Estimands […] . We support the specification of the estimand as part of the design of a noninterventional study, but we disagree with the use of the ICH guidance “E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials” as a valid guidance for such specification. We were surprised that the ICH guidance, which was developed for the analysis of randomized trials, is recommended in this reflection paper for noninterventional studies. The ICH guidance introduced new terminology that undermined precision (e.g., both the use of rescue medication and death are grouped into “intercurrent events,” when they are events that require completely different methodological approaches), defined irrelevant estimands (e.g., “while on treatment” and “principal stratum”) and generally failed to provide guidance on how to define causal contrasts that go beyond the intention-to-treat effect. We recommend against extending the use of the ICH guidance to noninterventional studies where literature on how to analyze sustained treatment strategies is abundant (the target trial emulation framework mentioned in Lines 140-141 and other relevant frameworks).	Remove estimand framework
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	140	142	4.1	Regarding the invocation of the TTE, it looks like this document is closely related to this EMA paper https://www.ema.europa.eu/en/reflection-paper-use-real-world-data-non-interventional-studies-generate-real-world-evidence-scientific-guideline. The reflection paper, section 4.4, uses a stronger language "The target trial emulation (TTE) framework should be considered as a strategy that uses existing tools and methods to formalise the design and analysis of NIS using RWD with causal objectives."	Should this paper (currently under public consultation as well) also be cite and connected to this document? Also consider using stronger language for use TTE for causal inference.
EUCOPE	141	141	4.1	Original text: design	change into 'study design'
EFPIA	143	233	4.2	Feasibility assessment is important and this section needs structure. Although feasibility is always study specific, more direction and structure in this section would be helpful	Add a table with potentially important factors to assess for feasibility

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	143	169	4.2	Comprehensive assessment of the feasibility of (a) data source(s) before deciding to use it for a study is optimal, however, this approach is fraught with practical complexity. Simple feasibility assessments, i.e., a count of people with a given relatively simple-to-define exposure or variable, can be obtained fairly easily from multiple data sources whether they are readily available (licensed in-house) or accessed through a vendor. Evaluation of variables defined with more complex algorithms or -- worse yet -- based on patients who will accumulate in the data in the future is more complicated / infeasible. Comprehensive investigations of feasiblity may require licensing of data through execution of contracts -- typically requiring weeks of discussion -- and are frankly not possible in the timelines available to industry to (a) develop study outlines for inclusion with a submission, (b) respond to regulatory requests during evaluation of a submission, or (c) even during the typical time (usually 6 months, but regulators often press for more rapid development) allowed for development of a PASS protocol. Efforts to develop study protocols (for studies that would not initiate for at least a few years based on reaching target numbers of exposued patients) agnostic of data source at the time of submission -- so that the most appropriate source could be selected at thet ime market uptake reached higher levels, an approach that might have allowed more thorough fit-for-use asssessment -- have not been acceptable to regulatory agencies. Without operational solutions to fit such assessments into the regulatory timelines provided for study development, feasibility assessments will remain limited to what can be gleaned from study-agnostic understanding of data sources or simple queries of the data through a vendor concurrent with protocol development. If these laudable, if challenging, assessments are to be adopted, regulatory processes, expectations, and timelines must adapt to allow them.	Consider reviewing the recommendations with a focus on practical application and revise as needed. I aIt would be helpful to at least acknowledge that some of these recommendations may be challenging to achieve in practice.
Euromedicat Steering Group	143			Feasibility Assessment – Substantial details are provided on the process of identifying fit-for-purpose data according to specified characteristics. However, a vital part of the use of RWD is to collaborate with people who have been involved in its original data collection or who have experience of analysing it and have lived in the area for considerable time. There is no section including advice to form such a collaboration before deciding on the relevant data sources.	
Euromedicat Steering Group	143			Consideration of issues concerning small number suppression – what the precise restrictions are and who judges whether they have been complied with or not.	
Syneos Health CRO	143	233	4.2	Feasibility assessments should also include a data governance component: access to data (e.g., will the data holder analyze the data and can data leave the location) and ethical requirements in each country included to (re)use the data.	
EFPIA	144	146	4.2	A feasibility assessment is a…..' Is this definition only specific to M14? has this been aligned across other guidelines?	Consider add reference or context of this definition
EFPIA	146	149	4.2	This statement only applies to studies that do not have pregnancy outcomes.	A feasibility assessment for pregnancy exposed safety studies, outcomes may be evaluated.
IQVIA	146	146	4.2 Feasibility Assessment	The term “treatment arm” is typically used in the context of randomized study designs and seems out of place in this discussion of safety assessments relying on non-interventional approaches.	We recommend rephrasing the sentence as follows: “A feasibility assessment is a systematic process to identify fit-for-purpose data to address a specific research question and to obtain information on the statistical precision of a potential study without evaluating outcomes for treatment arm associated with the medicine under evaluation.”
ISPE	148	148	4.2	Clarify language in recogniztion that evaluation of outcomes can occur in feasibility assessments (e.g. characterizing the frequency of outcome measure within population, over time, etc.).	Replace “without evaluating outcomes” with “without evaluating exposure or intervention effects”.
EFPIA	151	154	4.2	Feasibility phases to be linked to the Figure 1? See comments on Figure 1 above	Revise Figure 1 to align feasibility phases

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	151	157	4.2	We welcome a description of the feasibility assessment process in order to identify fit-for-purpose data. From how the feasibility assessments are structured (two-phase process), it is clear that there is a heavy reliance on the Gatto 2021 SPIFD framework, which is also cited as a reference. We have also identified some differences, including some omissions, from SPIFD. For instance, there are critical supporting documentation mentioned in Gatto (e.g., data dictionary) that are universally required for "understanding (of) RWD source characteristics (line 157)" and for ultimately specifying the minimum criteria needed to address design elements for the research question. We thus suggest a direct reference to SPIFD, as well as specific elements of SPIFD, to help guide the process of feasibility assessments.	Feasibility assessments should be structured in at least two phases [2]: - An initial scan to determine whether data are available, likely sufficient, and to narrow down data source options; and - A subsequent, more comprehensive feasibility assessment of the candidate data sources. After the research question and design elements are established, researchers should specify the minimum criteria required to address the key design elements specific to the research question. This task will require an understanding of RWD source characteristics (e.g., using key supporting documentation such as the RWD source data dictionary and entity-relationship diagrams) and the clinical context.
EFPIA	151	154	4.2	"Feasibility assessments should be structured in at least 2 phases: 1. initial scan to determine whether data are available, likely sufficient, and to narrow down data source options". This example does not include all possible scenarios such as the rare diseases and rare outcomes for instance. For example, some data sources are not directly accessible by industry. In these situations it might be necessary to join a consortium. It would be helpful to add considerations of alternate ways to access data versus direct access.	Please consider to add exceptions for rare diseases or outcomes or situations of consortiums were several data sources are pulled together.
EFPIA	157	157	4.2.	The content of the feasiblity is geared towards design aspects (enough study size, enough follow-up, etc) and less towards RWD source data quality, which is an important aspect of feasiblity. It is suggested to add the fact that data quality is part of the feasiblity, as specified later in the ICH M14 guideline (During development of the protocol, as informed by the feasibility assessment(s)). As written now, it seems that first the feasiblity checks the design aspects and that data quality dimensions are only cheked at a later stage (in the discussion of the protocol) rather than much earlier.	Consider adding wording as follows: This task will require an understanding of RWD source characteristics, including RWD data quality, and the clinical context
EFPIA	158	165	4.2	Access and format of the data (e.g., aggregate data in Sentinel, common data model) can also drive design/methods	Add sentence on data format and access
EFPIA	158	158	4.2 Feasibility Assessment	Additional Design elements to consider: - Index time (time zero) - Look back period before Index date - Inclusion period	As listed in the Comments column
EUCOPE	159	159	4.2	Original text: Data needed to understand and define the study population, exposure, comparison groups, outcomes and covariates	add 'study objectives'
EUCOPE	159	160	4.2	We suggest the agency consider additional clarification and text related to defining the exposure and outcome.	
Euromedicat Steering Group	159			Line 159 includes design elements to consider. I would suggest that the motivation for data collection should also be included here as it will influence the type and accuracy of data collected.	
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	159	165	4.2	In the listed design elements the important issue of the start of follow-up (time zero) is missing. This should be added.	Between lines 160 and 161 add the design element ""Start of follow-up (time zero)" as second important design element.
IQWiG	159	165	4.2	In the listed design elements the important issue of the start of follow-up (time zero) is missing. This should be added.	Between lines 160 and 161 add the design element ""Start of follow-up (time zero)" as second important design element.
EFPIA	161	161	4.2	Minimium length of follow-up should be assessed in an individual; a population may have a long follow-up, but individual people may contribute a short window of time	clarify follow-up is relevant to the individual's person-time contribution

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	161	161	4.2	We agree that length of follow-up is important to observe outcome(s). Additionally, having a clear start (and end) of follow-up is equally important. In cases where patients are treated, the start of follow-up is often clear as the time they started treatment. However, if aiming to compare to untreated patients, it becomes more challenging to define time zero.	Change bullet to “Ability to assess start (index date) and end of follow-up, and availability of minimum length of follow-up to observe outcome(s);”
AstraZeneca	162	162		Because this is a guideline for RWD, the focus should be expected effect size and minimal sample size needed to achieve desired power and precision instead of 'targeted sample size'	Revise for accuracy. Cite Ken Rothman's paper on estimating sample size.
EUCOPE	164	165	4.2	When feasible, information about the health care system including method of diagnosis, preferred medicines, formulary coverage and prescribing practices	Suggest adding “over time” at end of the sentence
ISPE	164	165	4	Clarify the following sentence to also account for missing data: "When feasible, information about the health care system including method of diagnosis, preferred medicines, formulary coverage and prescribing practices"	Add: "and any data that might be missing due to out of network or in- or out-patient healthcare"
Euromedicat Steering Group	165			Line 165 et seq When selecting data sources, ‘context, including GDP per capita’ and ‘current guidelines’ should be considered.	
EFPIA	167	169	4	If 3rd party agreements cannot be obtained, we suggest incorporating an addiitonal interaction with the regulatory agency to discuss what would be acceptable in terms of data sharing	Add: "If third party ageements are difficult to be obtained, additional discussions with the regulatory agency are encouraged to find possible solutions under the available data sharing agreements."
EFPIA	167	169	4.2	For the avoidance of doubt it should be clarified that any need to submit patient level data is determined by indiviudal jurisdictions.	Sponsors should obtain any required third-party agreements to access relevant patient-level or analytic data that may ~~will~~ be required by the regulatory authority for submission, based on applicable regulatory requirements.
EFPIA	167	168	4.2	Clarification is needed for the statement "Sponsors should obtain any required third-party agreements to access …." Should this be patient-level or analytic data that will be required *by the study*? If this is truly intended to refer to obtaining agreements to share patient-level data with regulatory agencies, it is not realistic to consider that this activity can be executed concurrently with development of a study. Providing patient-level data to regulatory authorities is not routine and there are no standard paths currently that facilitate this. Data owners are highly sensitive to the idea of releasing their data to an entity who can be required to turn it over to a third-party, i.e. through a FOIA request - regardless of how unlikely such a scenario might be. Privacy consultations are time-consuming and development of the specific solutions that each data owner requires to address privacy and legal concerns has been unique to each data owner. Even the process for delivering the data to the regulatory agency may be challenging, not to mention the challenge of how RWD can be formatted to meet regulatory submission requirements -- which I believe is an external undertaking that is not yet complete. It is difficult to imagine that a plan to achieve all of this could occur within the current timelines at the same time that a study is designed.	Consider how this could be applied and add language to recognize the current state of data provision to regulators. It may also be useful to point to FHIR and any others making efforts to create formatting standards for RWD (this would be invaluable!).
ISPE	167	168	4.2	Clarification is needed for the statement "Sponsors should obtain any required third-party agreements to access …." Providing patient-level data to regulatory authorities is not routine. Privacy consultations are time-consuming and development of the specific solutions that each data owner requires to address privacy and legal concerns has been unique to each data owner and region. Even the process for delivering the data to the regulatory agency may be challenging combined with the challenge of formatting RWD to meet regulatory submission requirements simultaneous to meeting timelines for study design and data source fitness-for-use assessments.	Add language to recognize the current state of data provision to regulatory authorities. Mention ongoing efforts by FHIR and any others to create formatting standards for RWD that would facilitate this process.
EFPIA	168	169		Other provisions need to be considered as acceptable, where the MAH cannot provide the IPD. Such arrangements maybe for a 3rd party to provide access, either directly, or as analysis behind the firewall (as with DARWIN EU).	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ISPE	169	169	4	Recognizing additional documentation related to data reliability and provenance is recommened following "for submission".	"for submission as well as data handling documentation that pertains to data reliability and provenance"
EFPIA	170	173	4.2	Other important factors such as whether medication data are dispensings vs orders; whether patients can be identified and contacted for additional data collection	Consider adding these examples
EFPIA	170	174		Provisions need to be made in case these elements aren't accessible by the sponsor	
EFPIA	174	174	4.2	Existing validated algorithms still needs to be assessed to determine whether they fit the purpose of the intended study. The time, country, population, and the results of the validation should also be part of the consideration for feasibility assessment	Revise the bullet point to evaluate whether an existing algorithm is suitable for the intended study as part of the feasibility assessment
ISPE	177	177	4	It is recommended to include health insurance claims data as an important source for linkage"...link data sources to other types of data (e.g.,vital records, cancer registries, vaccine..."	Add: "(e.g., vital records, ...health insurance claims")
ISPE	178	178	4	It needs to be acknowledged that not all of the mentioned information will be possible to identify for all data sources.“	Substitute "should" for "will": "it ~~will~~ should be possible"
EFPIA	184	184	4.2	"…an in-depth feasiblity assessment should be conducted." Please see previous comments. How is such an assessment to be completed with the currently avaiable timeline for development of a study?	
EUCOPE	185	186	4.2	Potential studies that would be included might be broader than just 'databases'. We suggest the agency consider changing to 'data sources' to be consistent with language elsewhere.	In some instances, fit-for-purpose data will be identified during the initial feasibility scan, in which case the detailed step will apply to the data sources under consideration.
ISPE	186	188	4	The concept of data completeness is mentioned but has not been previously defined: " In the detailed feasibility step, the researcher can verify that the specific data needed for the key design criteria are available and that there is sufficient evidence of validity and completeness"	Bold data completeness and add definition to the glossary
RTI Health Solutions	186	186	4	There is inconsistency in the use of "data source" and "database".	Please assess whether consistency is needed throughout the document - beyond this specific page range. The following publication (supplementary material 1) provides a glossary of terms relating to data sources (including the terms, "data source", "database" and "data bank", which may be useful as reference). doi: 10.1002/pds.5871
EFPIA	187	189	4.2	We welcome the statement around the possibility for performing verification during the detailed feasibility step that is provided in this section. We suggest providing more clarity and context on what verification entails, which may be particularly useful in some data access models (as illustrated in the example below). In some RWD sources where researchers do not have direct access to patient-level data (e.g., patient registries), current processes and tools (e.g., Appendix 1. Checklist for evaluating the suitability of registries for registry-based studies of the EMA Guideline on Registry-Based Studies.) for establishing fitness-for-purpose still have limitations. For instance, when considering the design elements of targeted sample size / event rate, variable validity and completeness are evaluated using several sections of the EMA Guideline checklist (2.3. Patient population covered; 2.4. Data elements; 2.6. Quality requirements). From experience, unless analyses are performed on the study population, results from the feasibility assessment may not be representative of the true validity or completeness of variables in the data source. Data holders do not always allow such verification to be performed at feasibility stage, and thus an ICH guideline that encourages verification will be valuable in increasing general data quality.	In the detailed feasibility step, the researcher can verify that the specific data needed for the key design criteria are available and that there is sufficient evidence of validity and completeness of the minimal design elements in the specific data source. Should direct access to patient-level data not be possible, it is important that the researcher can have qualitative and quantitative verification (e.g., through a small exploratory analysis) of the validity and completeness of the minimal design elements.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	190	190	4.2	In selection of data sources, ease of access to the data, population covered and how the data are generated (e.g., claim vs vs medical record) are important factors in selecting data in addition to whether subjects can be identified and contacted.	Add the additional points mentioned i "other factors in data source selecction": such as population, how data are generated, whether data can be linked and/or patients contacted, and ease of access to the data
ISPE	190	191	4.2	"When selecting a data source, data recency, frequency of data refresh, completeness of follow up from exposure to outcome should be considered." it is important to consider observability in baseline window, average observable time for patients in the data, or observability/feasibility in linked assets (e.g. EHR-claims) as part of the process.	Provide more discussion of observability at baseline and overlapping observable time within the context of multiple linked data sources as part of a feasibility assessment that can inform on fitness for use for the specific safety assessment.
EFPIA	191	193	4.2	For the avoidance of doubt it should be clarified that any need to submit information to the regulatory authority is determined by individual jurisdictions. Please note that clarification of the term "data files" would be welcome e.g. patient level data, etc.	In addition, the possibility to submit data files generated during conduct of the study to relevant regulatory agencies may need to be determined, based on applicable regulatory requirements.
ISPE	191	191	4	Include another option for regulators to all access a secure server where data are stored in addition to: ", the possibility to submit data"	Add: or all regulators access a secure environment containing the data
ISPE	191	192	4.2	There is not clear guidance about the need for a separate protocol for feasibility assessments, including if the feasibility assessment should be made public to provide a rationale for the study design.	Provide more detail on the expected specifications for (e.g. template) and communication beyond sponsor-regulatory authority regarding feasibility assessments.
EFPIA	193	195	4.2	The reality is that experience with the data (and especially with the parties who provide and/or execute the analyses) is likely one of the top 3 considerations in the selection of data, due to the primacy of timeliness in the trenches of industry study development and the importance of working with entities who reliably deliver on regulatory timelines.	
Euromedicat Steering Group	193			Line 193 Researchers are advised to choose data sources (from scans of all sources) that funders or researchers know best to expedite data analysis. This risks selection of a convenience sample of well-funded data sources, leading to findings unrepresentative of the whole population and irrelevant to the populations represented by data sources that are less known or less convenient. Excluding these less affluent populations risks the 'All's well' bias (Sackett 1979): adverse drug reactions are more common in less affluent populations (Payne et al 2013, Khezrian et al 2020, Mur et al 2022).	
VAC4EU	193	195	4.2	Prior experience with data of similar size than the current project? even having previous experience timelines may change a lot depending on the variables to be extracted.	
ISPE	196	206	4.2	There are various techniques to address missingness or missing variables to improve the feasibility of using fit-for-purpose data	Add: clarification of whether additional primary data will be collected from a subsample of the cohort on which the fit-for-purpose data is based or a different but similar population to augment the fit-for-purpose data
EFPIA	203	206	4.2	This type of detailed request will require full execution of a contract with the data holder, a process that can easily require weeks of time. As a regulated industry, work cannot be requested, let alone conducted, prior to execution of such a contract ….expending limited time to develop the study protocol. (Penalties for not delivering a protocol on time could be substantial, disagreement or lack of information on feasibility will lead to a request for revision.) As it is, there is already limited time to discuss questions about the data, scientific methodologies to be implemented, write the protocol, and conduct the necessary internal and external reviews. It is difficult to see how estimation of incidence rates and generation of additional descriptive results on covariates -- particularly for a complex outcome, exposure, or covariate -- could be accommdodated. Without solutions or examples that describe how such an assessment can be achieved, it does not seem feasible that such an assessment can be executed at all or at least well, except in the most straightforward cases.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ISPE	203	206	4.2	This type of detailed request for feasibility assessments to address all of the critical data elements in context of the specific research question(s) will require execution of a contract with the external data holder, a process that can easily require weeks. Readers seeking guidance will appreciate solutions or examples that describe how such an assessment can be achieved within typical regulatory timeframes.	Acknowledge challenges to completing detailed feasibility studies that amount to separate descriptive studies predicated on initial searches for appropriate sources and contracts with data providers. Further mention of the uncertainty at time of planning, e.g. extent of market uptake, availability/pricing of alternative treatments, etc that can require adjustments to final study design or data sources.
ISPE	204	204	4	Clarify that the incidence rate of the outcome would be generated without regard to prior treatment exposures that may be compared in the proposed safety study.	Add: "incidence rate of outcome... without regard to treatments that may be compared in the eventual study"
VAC4EU	204	206	4.2	The concept of 'data holder' is underspecified for this task. The DIVERSE framework distinguishes two relevant types of institutions that can provide information on the data: data originators, who have information on how the data is generated, but do not necessarily have expertise or even awareness on how data can be repurposed for RWE generation; and research organizations, that have access to the data for the purpose of generating RWE, and have internal expertise. Research organizations that historically use a specific data source are sometimes termed Data Access Partners for that da asource (e.g., in the MINERVA project on metadata collection on data sources that advised on the HMA-EMA Catalogues of studies and data sources, see Pajouheshnia et al. MINERVA: Development and Pilot of a Metadata List and Catalogue in Europe. PDS 2024) and may be the ideal target for such requests. The MINERVA commentary (Gini et al, MINERVA: Lessons Learnt From the MINERVA Project in Europe. PDS 2024) specifically expresses concerns around the calculation of quantitative metadata, such as "incidence rate of outcome to conduct sample size calculations", and invites to caution in requesting such information to institutions that lack epidemiological expertise.	We invite to rephrase this recommendation to convey this specification.
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	204	204	4.2	Often researchers with expertise know data better than data holders	Replace "from the data holder" with "from the data holder or an expert data user".
EFPIA	207	210	4.2	The document specifies a sequential series of steps to identify the right data source including a primary data collection. In the case of rare disease or paediatric areas, primary data collection may be the only option available.Please mention this	add information for rare and paediatric diseases
EUCOPE	207	210	4.2	After the detailed evaluation is complete, the data sources are compared, and a data source(s) 207 can be selected for the study. Occasionally, at any of the steps, it will be apparent that a specific 208 data source is not suitable to address the research question. In these circumstances, the 209 researcher may conduct a feasibility assessment for primary data collection	We should also explore quasi studies where we identify the patients using real world data sources and follow the patients longitudinally into the future for the outcomes. These studies reduce the cost and timelines as we can get most of patients history/comorbidites from available data sources
EUCOPE	207	208	4.2	This sentence does not read well due to inconsistent tense. We suggest the agency consider alternate language for greater readability.	After the detailed evaluation is complete, the data sources can be compared. From here, a data source(s) can be selected for the study.
EFPIA	209	213	4.2	In these circumstances, the researcher may conduct a feasibility assessment for primary data collection'. This is a different 'feasibility assessment' as the ones mentioned in the Figure 1 and above paragraphs, usually in such primary data collection studies, we call this 'feasibility assessment' as 'feasibility study' as it is quite substantial and much more detailed than 'feasibility assessment' referred in paragraphs above.	Consider change 'feasibility assessment' to 'feasibility study'
EFPIA	209	210	4.2.	The guideline proposes to use primary data collection when RWD sources cannot be identified. However, primary data collection is not the only approach. As an example, a chart review (which is considered secondary use of data) might be possible. The current text present the options as binary, i.e. RWD sources or primary data collection) and seems to exclude other options. It is proposed to edit the text to acknowledge that other design possibilities exist.	Consider rephrasing the sentence "In these circumstances, the researcher may conduct a feasibility assessment for primary data collection. This assessment typically.... " as follows: "In these circumstances, the researcher may conduct a feasibility assessment for other data collection options, including primary data collection. The assessment of primary data collection typically ...."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	210	216		Note primary data collection should also be considered to reflect extraction of data previously collected, but not in a readily accessible 'secondary-use' form of data, such as is the case when original medical charts are reviewed and extracted to a CRF. Many of the requirements for ethics approval, site selection, physician/site queries, source-data verification also apply, yet the study does not create 'new' data per se.	
EUCOPE	210	213	4.2	Many studies may not have active enrollment. We ask the agency consider replacing the word 'enrolled' with the word 'included'.	This assessment typically includes physician and site queries, including information about the patient population, to determine if a sufficient number of participants can be included and followed for the appropriate timeframe to yield meaningful answers to the research question.
EFPIA	212	212	4.2	It can be difficult to 'read the tea leaves' for one of the most critical and high-profile study types, the post-authorization safety study, and ensure that a sufficient number of participants will be enrolled. Many factors that are unknown at the time of study development can influence market uptake (e.g., availability of alternate new medications, changes in formularies, safety concerns related to uncommon adverse events, etc) and derail sample size expectations.	Acknowledge it may not be possible to address all of these recommendations for all studies. If desired, post-authorization safety studies could be explicitly referenced as an exception.
AstraZeneca	213	216		Sometimes this timing may not fall within specified regulatory timelines. It would be helpful if the guideline provides guidance on how to proceed in such situations. E.g., 'researchers should work with health authorities to amend or optimize regulatory timelines'	The guideline should provide guidance on how to proceed when timelines are not optimal. E.g., 'researchers should work with health authorities to amend or optimize regulatory timelines'.
EFPIA	213	215	4.2.	The sentence "whenever primary data collection, ….." raises awareness about time to set-up a primary data collection study. The fact that ICH M14 only mentions time aspects for primary data collection can be perceived as RWD source are faster and this is not the case for many RWD sources, in particular patient-registries. There are several use cases in which agreement with registries has taken up to 1 year which is longer to site initiation in a primary data collection study. It is suggested to include wording about time aspects when using RWD source studies	Consider adding in Line 216 the following sentence: "Likewise, when using RWD sources, the researcher should consider the time to set up the study agreement, data holder governance approvals, and data permit applications, to ensure that data is available in a timely manner"
Euromedicat Steering Group	216			L216 Volunteer cohorts are vulnerable to volunteer selection bias and collider bias. Discussion of these problems is important, as it is difficult to account for collider bias post hoc. Accounting for collider bias rests on untestable assumptions, and it is better to avoid this problem by analysing unselected populations (Griffith et al 2020). If the whole population is not included, the limitations of potential selection and collider biases must be addressed (Elwert & Winship 2014). This has implications for all studies not based on the whole population.	
EFPIA	217	224	4.2	Appropriate comparator group is mentioned but additional details are in 5.1	Refer reader to section 5.1 for more information
EFPIA	223	224	4.2	Please provide links to the regulatory guidances provide additional information on the characteristics of an appropriate comparator.	add links to main document or glossary
EFPIA	223	223	4.2	Please cite the regulatory guidances that provide information on the characteristics of an appropriate comparator.	Add a citation.
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	223	224	4.2	It is described that regulatory guidances provide additional information on the characteristics of an appropriate comparator. I propose to add guidelines as well as systematic reviews of clinical studies (aggregated evidence) in the present therapeutic indication as information sources.	Replace the sentence "Regulatory guidances provide additional information on the characteristics of an appropriate comparator" by a statement like this: "In determining an appropriate comparator therapy, regulatory guidances, as well as current guidelines and systematic reviews of clinical studies in the present therapeutic indication should be taken into account."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IQWiG	223	224	4.2	It is described that regulatory guidances provide additional information on the characteristics of an appropriate comparator. We propose to add guidelines as well as systematic reviews of clinical studies (aggregated evidence) in the present therapeutic indication as information sources.	Replace the sentence "Regulatory guidances provide additional information on the characteristics of an appropriate comparator" by a statement like this: "In determining an appropriate comparator therapy regulatory guidances, as well as current guidelines and systematic reviews of clinical studies in the present therapeutic indication should be taken into account."
ISPE	223	223	4.2	It would be helpful to readers if the regulatory guidances that provide information on the characteristics of an appropriate comparator could be specifically highlighted to help increase the likelihood of a successful study design.	Add a citation that describes appropriate comparator definition/selection (clinically and empirically).
EFPIA	226	227	4.2	There is currently no path or requirement for the submission of a feasibility assessment report as a standalone document. Some description of the process to submit such a report is needed. Some regulators frequently do not provide review comments for protocols themselves, how likely is it they would comment on a feasibility assessment report...and if and if it will not receive a review, what is the advantage of submitting it as a standalone document prior to submission of the protocol or even final study report? Further, how would this feasibility report be evaluated? Practically, it is unlikely that a feasibility assessment report would be submitted as a standalone report for a typical post-authorization safety study. Perhaps under very specific circumstances where discussions with regulatory agencies are possible and necessary, e.g., submission of a sponsor-initiated request for a label update based on RWE, this might be reasonable. If that was the intention, these scenarios should be described.	
ISPE	226	227	4.2	We are not aware of any requirements for the submission of a feasibility assessment report as a standalone document. Some description of the process to submit such a report is needed.	Provide additional detail on scenarios where a feasibility assessment standalone report would be submitted with feedback provided to sponsors prior to protocol submission.
EFPIA	227	229	4.2	Consideration should be given to the basic/essential elements of a feasibility report i.e. what content must be addressed at a minimum	
AstraZeneca	231	233		Are there any particular frameworks/templates that the ICH recommends/endorses?	
EFPIA	231	233	4.2	Detailed frameworks, template, …' Does this mean submitter could use any templates/frameworks for feasibility assessments as long as it is justified? Or is there a preferred or recommended list of these frameworks, templates, checklists, etc.	Clarification required: if there are any recommended frameworks, templates, checklists, or if anything can be used as long as it is justified
ISPE	231	233	4.2	There are no citations for this concluding sentence: "Detailed frameworks, templates, and checklists for conducting feasibility assessments are available in 232 scientific publications."	Add relevant citation, e.g. Wang SV, Schneeweiss S. Data Checks Before Registering Study Protocols for Health Care Database Analyses. JAMA. 2024 May 7;331(17):1445-1446. doi: 10.1001/jama.2024.2988. PMID: 38587830.
Euromedicat Steering Group	232			L232 Please specify which 'scientific publications' offer the recommended checklists. Summary bullet points for section 4.2 Feasibility Assessments would be helpful.	
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	233	233		It would be helpful to end this section with a short summary of what specific things make a data source NOT feasible. We see a lot of examples of sponsors knowing data limitations but still moving forward with bad studies.	
IQVIA	235	248	5 Protocol Development	The draft guideline discusses the need to involve subject matter experts to address a range of issues when designing and conducting pharmacoepidemiological safety studies.	We recommend adding an additional area where essential input is needed as follows: "Review of biostatistical methods to assure the suitability of study methods and to reflect current research and practice in statistical analysis."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	237	238	5	Adding a description of the expertise and credentials of study team members would trigger updates of a protocol every time a study member changes, creating an additional burden of work given the regulated processes required. Any bio would also need to be heavily redacted before release to comply with privacy regulations, rendering the addition of limited value. It is already required practice, for audit purposes, that regulatory protocols in pharma companies and their contracted organizations maintain descriptions of the training and experience of all participants leading, directing, and executing a study. Adding a bio to the protocols is not a practical option.	Consider revising or deleting the suggestion to add descriptions of the qualifications of each study member to the protocol.
Euromedicat Steering Group	237			L237 Please define 'appropriate expertise' e.g. qualifications, number of publications, community links.	
ISPE	237	238	5	Adding a description of the expertise and credentials of study team members over the course of the study would trigger updates of a protocol every time a study member changes. Any bio would also need to be heavily redacted before release to comply with privacy regulations, rendering the addition of limited value. It is already required practice, for audit purposes, that regulatory protocols in pharma companies and their contracted organizations maintain descriptions of the training and experience of all participants leading, directing, and executing a study.	Revise or delete the suggestion to add descriptions of the qualifications of each study member to the protocol; a generic statement of what skills/experience for required roles could be sufficient to ensure quality while maintaining privacy and reducing undue burden when inevitable changes occur.
EUCOPE	240	248	5	Original text: "These personnel provide essential input in a number of areas, including:" The bullets that mention essential inputs should have safety related bullet point.	We recommend adding the following text as a new bullet point: •Understanding safety profile of the product, including background on the safety concern or validate signal in this research question
VAC4EU	240	240	5		Consider adding "Development of *inclusion/exclusion criteria,* exposure (…)"
EFPIA	243	244	5	A study might not use electronic health care data. It would be helpful to include "if applicable" to this bullet.	Please consider adding "if applicable" to this bullet.
EFPIA	245	245	5	"Disease area billing and coding practices" - this won't apply to all sources of data. It would be helpful to include "if applicable" to this bullet.	Please consider adding "if applicable" to this bullet.
EFPIA	245	245	5	clarify that guidance is for RWD and non RWD non interventional studies. Propsed rewording: disease area billing and coding practices to identification of key data elements such as diagnoses and medication use within specified data source.	Proposed re-wording of bulleted point in line 245
Euromedicat Steering Group	245			L245 Please define 'area billing'.	
EFPIA	246	246	5	A study might not use primary data collection. It would be helpful to include "if applicable" to this bullet.	Please consider adding "if applicable" to this bullet.
EFPIA	246	246	5	Please clarify what characteristics or types of characteristics these might be	
ISPE	246	246	5	Please clarify what characteristics or types of characteristics these might be. A study might not use primary data collection.	Add: "Specific characteristics around primary data collection, if applicable
EFPIA	247	247	5	Given the potential for a requirements that data be shared with regulatory agencies, this bullet might also include "…data privacy and security concerns raised when accessing and sharing (as relevant) health care data."	Please consider adding " "…data privacy and security concerns raised when accessing and sharing (as relevant) health care data." to this bullet
EFPIA	249	253	5	Certain elements listed here are bette suited for the feasibility assessment. Researchers could only select the a data source(s) for the study if they can manage to access.	Move the applicable element for selected data source to feasibility assessment
EUCOPE	249	253	4.2	Given that all real-world data sources have limitations, we ask that the agency please consider whether to further discuss the importance of prioritization of the data that are critical for a given study as compared to lower priority data.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
VAC4EU	249	249	5		Consider adding “in the assessment of *inclusion/exclusion criteria,* exposure (…)”
Syneos Health CRO	254	280	5.1	In section 5.1: it would be helpful to add to this section what regulators generally prefer in terms of population of interest (e.g., new users, active treatment comparator vs placebo).	
Medicines for Europe	255	255	5.1	Addition of "prevalance" word along with "incidence" is suggested. The pharmacoepidemiological study not only estimate the incidence but also prevalance of outcome of interest.	"incidence and prevalance" - Additional word proposed.
EFPIA	258	261	5.1	According to the guide, a feasibility assessment of the available data should have already been conducted during the question definition. Therefore, in the paragraph discussing the selection of the most appropriate study design, it is worth considering the types of available data as one of the factors to be taken into account for choosing the best design.	Please add a sentence califying this point.
EFPIA	261	261	5.1	The question of biologic plausibility is currently considered for the purposes of selecting an appropriate study design. Biologic plausibility should be considered earlier to determine whether a pharmacoepidemiology is needed. Perhaps this was intended to capture what is known about the mechanism of action and pathophysiology. For example, thresholds of exposure needed, latency, etc.	Please consider removing biologic plausibility and replacing with more relevant considerations for study design.
EFPIA	262	268	5.1	This paragraph addresses the identification of the appropriate comparator, which is actually a component of defining the research question rather than study designing . Section 4.1 recommends using the PICOT strategy for question formulation. It is important to note that a thorough understanding of the comparator is essential in conducting a feasibility assessment before aproaching the study.	we suggest relocating this paragraph to section 4.1
EFPIA	262	268	5.1	The choice of comparator is not only a design decision but should follow from identifying the main target causal contrast of interest as a study objective (using for example PICOT or the treatment attribute in the Estimand framework).	Please add a sentence or two emphasizing the importance of alignment of design to the research question (cross-reference to Section 4.1). That is, for a given PICOT, one is limited to particular comparators to be used in the design and therefore a specific type of confounding. Conversely, by choosing a specific comparator to reduce confounding by indication, one may be targeting a different PICOT than first intended. For example, “The research question (Section 4.1) determines many design elements, including the choice of comparator, as the design needs to align to the research question of interest. Conversely, after feasibility and assessment of bias, one may find that the set of comparators in the research questions may be refined, for the design to be feasible and the analyses to be meaningful.”
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	262	264	5.1	In line 264 historical controls are listed as example for comparators. However, in lines 53-54 trials with external comparators are described as out of scope. This should be clarified.	Either delete "trials with external comparators" in lines 53-54 or delete "historical controls" in line 264.
IQWiG	262	264	5.1	In line 264 historical controls are listed as example for comparators. However, in lines 53-54 trials with external comparators are described as out of scope. This should be clarified.	Either delete "trials with external comparators" in lines 53-54 or delete "historical controls" in line 264.
EFPIA	265	265	5.1	For comparator selection, how a study will deal with patients treated with medicines that become available during the course of the study is an important consideration. Post-authorization safety studies, even those relying on secondary data sources, are subject to the tidal forces of new drug approvals and market uptake. New drug approvals are sometimes known or expected at the time of study development, though, and should also be considered in general, regardless, especially when 'standard of care' is chosen as the comparator. Secular changes occurring outside the study can post substantial challenges to an ongoing study.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ISPE	265	265	5.1	For comparator selection, how a study will deal with patients treated with medicines that become available during the course of the study is an important consideration. Post-authorization safety studies, even those relying on secondary data sources, are subject to the tidal forces of new drug approvals and market uptake. New drug approvals are sometimes known or expected at the time of study development, though, and should also be considered in general, regardless, especially when 'standard of care' is chosen as the comparator. Secular changes occurring outside the study can pose substantial challenges to an ongoing study.	Add sentence to indicate that Research has shown that a comparator of non-users can introduce bias, and that the use of the new user, active comparator mitigates potential confounding bias.
AstraZeneca	266	268		The comparability of exposed and comparator population goes beyond confounding by indication.	The sentence should be revised for completeness (accuracy).
EUCOPE	266	268	5.1	Original text: Considerations for comparator selection may include the specific indication within a disease, contraindications, disease severity or comorbidity, and the treatment sequence. It is important to maximize and evaluate the comparability of the exposed and comparator ICH M14 Guideline populations to reduce issues related to confounding by indication	Researchers should define appropriate statistical designs to ensure reliability and validity of the comparator arms
EFPIA	270	271	5.1	A graphical diagram on the study design does not necessarily clarify the analysis plan. It clarifies only the study design and the different assessment periods.	Replace “analysis plan and time components” in the sentence with “the study design and assessment periods for design elements”. Proposed revision: Researchers should also consider developing graphical representations (such as a study design diagram) to clarify the analysis plan and time components study design and assessment periods for design elements such as inclusion period, lookback period, follow-up period, overall study period.
EFPIA	271	272	5.1	It may be worthwhile to clarify the difference between time related to study elements, i.e., lookback periods, follow-up since cohort entry, etc. vs the calendar period when eligible people will be identified. These are often two distinct concepts that are sometimes conflated, leading to confusion.	
EUCOPE	272	272	5.1	Original text: 'inclusion period'	Change to cohort identification period
RTI Health Solutions	272	272	5.1	A key element of study design is to align at time zero: 1 - study eligibility criteria, 2 - start of therapy, and 3 - start of follow-up, to prevent faulty designs prone to time-related and other biases.	At the end of line 272 and prior to discussing Visualization (line 273, ADD: "The start of eligibility, start of treatment, and start of follow-up should be aligned to prevent the occurrence of time-related bias"
RTI Health Solutions	273	274	5.1	"Visualization of design details helps to clarify and communicate the study design to a broad audience of decision makers [3]": the updated version of this work could also be referenced	Consider adding as a reference DOI: 10.2147/CLEP.S358583
EFPIA	274	275	5.1	Please see earlier comments about the impracticality of discussing proposed study designs for post-authorization safety studies that become commitments at the time of regulatory approval for NDA/BLA, etc. Such consultation would ideally resolve many questions and concerns from sponsors and regulators, but current regulatory timelines do not support these types of interactions except for the most basic of written question and answer. Even outside of submissions, when the intent may be to cede on all but scientifically unsound requests, the structured nature of regulatory interactions does not facilitate discussion. It can be challenging to confirm understanding of epidemiological concepts or requests through written interactions with regulators - likely on both ends. Unless a pathway is created to support this, calls for discussion of study designs with health authorities prior to finalization will remain largely aspirational for all except very specific types of studies, i.e., sponsor-initiated studies that are not regulatory commitments.	
ISPE	275	275	5.1	More guidance is needed to explain when and by what mechanism a sponsor can seek feedback through a discussion"early in the process".	Add more specific guidance on what 'early' means and the specific mechanisms by which this discussion can take place: "The proposed study design should be discussed with health authorities early in the process through mechanism XYZ…
Euromedicat Steering Group	276			L276 Whilst discussions with health authorities may be useful at the study design stage, constraining researchers this way will obstruct academic freedom and innovation. Suggest remove the sentence.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	277	278	5.1	After initial feasibility analyses,….. should be prespecified'. How to deal with the post-hoc analyses that are not pre-specified?	Clarification needed on how to deal with the situation of post-hoc analyses that are not pre-specified?
EFPIA	277	278	5.1	The document states that "after initial feasibility analyses, all essential elements of study design, analysis, conduct, and reporting should be prespecified" - what is the proof needed for pre-specification? Should the study be registered or it is sufficient to share with regulators?	add clarification on proof for pre-specification
Syneos Health CRO	277	280	5.1	Clarification would be appreciated on whether it is always required to provide a separate protocol for validation studies.	
EFPIA	278	278		Guidance indicates that everything should be 'prespecified' after initial feasibility analyses. Further guidance is needed on what constitutes feasibility vs pre specification. "After initial feasibility analyses, all essential elements of study design, analysis, conduct, and reporting should be prespecified. For each study element, the protocol and final study report should describe how that element was ascertained from the selected data source in studies utilizing secondary data, including applicable validation studies"	
EFPIA	281	515	5.2.	Section related to data source could be moved earlier as a separate section within section 4. Initial design and feasiblity as per Figure 1	Move section related to Data Source (moving lines 281 and 515 sections 5.2.1 to 5.2.5) within section 4.
VAC4EU	283	283	5.2	"(..)the data are fit-for-purpose (…)" and relevance, reliability, and also representativeness?	
German Rheumatology Research Center | Head of Epidemiology, Prof. Dr. Anja Strangfeld	286	288	5.2	Regarding the phrasing: "and the term reliability includes data accuracy, completeness, provenance, and traceability." This section employs disparate aspects of data quality and inappropriately aggregates them under the rubric of reliability. This terminological and conceptual ambiguity is unsuitable for a guideline and has long been overcome in current research. One illustration is the completeness or missingness of data; if data are missing entirely at random even with a greater extent, the data can still be highly reliable. Conversely, it is simple to utilise complete but completely unreliable data if the incorrect instruments or an inadequate study design are employed.	Reliability of data is one of several aspects of data quality, such as accuracy, completeness, provenance, and traceability.
EFPIA	287	288	5.2.	This section refers to accuracy, completeness, provenance, and traceability and specifies that the protocol should provide discussion and documentation of these key data characteristics. However, there are other study documents in which all these aspects can be documented with more granularity. In some studies, complexity deserves having separate plans and in others the full assessment of this elements is not complete at the protocol level (e.g., traceability). In that sense, Figure 2. Landscape Assessement Insight Pillars of the recently available Transcelerate Audit REadiness (see link: https://www.transceleratebiopharmainc.com/wp-content/uploads/2023/12/Assuring-Audit-and-Inspection-Readiness-Considerations-for-the-use-of-RWD-and-RWE-in-Regulatory-Decision-Making_12.11.23.pdf) provides suggestions on how to document each of these characterstics. It is suggested to add a clarification to acknowledge that these data characteristics can be included in other documents to avoid susbtantial amendments updates and lessen flexibility in the study documentation.	Consider adding wording as follows: "The protocol should provide discussion and documentation of these key data characteristics or refer to the appropriate study document that provides such data characteristics (e.g., data management plan...)"
EUCOPE	287	287	5.2	Original text: 'protocol'	Protocol should have clearly defined table shells and codes as an appendix
EFPIA	289	289	5.2 Data Sources	"Several data source characteristics need to be considered in pharmacoepidemiological studies, as they may affect the study design and the interpretation of the results." The use of "pharmacoepidemiological" in this context seems to apply strictly to "secondary use of data"	Recommendation: In this context we recommend using "in safety NIS (or if preferred Non-interverntional post-authorisation safety studies or non-interventional safety studies) based on secondary use of data"
VAC4EU	290	292	5.2	Not only in coding systems but also the semantics these codes reflect can be different across healthcare sysrtems.	Consider including this aspect somewhere in this guidelines.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Cegedim Health Data	293	293	5.1	"(monetary, social or otherwise)": the most important one seems to be missing: medical (for data extracted from electronic medical records)	"(medical, monetary, social or otherwise)"
EFPIA	296	296		Recognizing that the authors may have deliberately elected not to include some examples of federated data networks, nonetheless a brief list or reference with example would increase the value of this document	Add some examples of federated data networks
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	296	301	5.2	It is mentioned that researchers should consider the steps taken to harmonize data across institutions or data sources. We propose to move up the cross-reference "see Federated Data Networks" from line 299 to line 296 and to change the sentence order.	Change the order of the sentences from: "In recent years, federated networks of RWD sources have been developed in various regions. When utilizing multiple data sources, either as a network or through data linkage, researchers should consider the steps taken to harmonize data across institutions or data sources (see Federated Data Networks). Some of these networks have been specifically designed to support scientific evaluations and regulatory decision-making, allowing a growing number of studies to include data from these federated networks, often from different countries." to: "In recent years, federated networks of RWD sources have been developed in various regions (see Federated Data Networks). Some of these networks have been specifically designed to support scientific evaluations and regulatory decision-making, allowing a growing number of studies to include data from these federated networks, often from different countries. When utilizing multiple data sources, either as a network or through data linkage, researchers should consider the steps taken to harmonize data across institutions or data sources [NEW REFERENCE]." Add NEW REFERENCE: Fortier I, Raina P, Van den Heuvel ER et al. Maelstrom Research guidelines for rigorous retrospective data harmonization. Int J Epidemiol 2017; 46(1): 103-105. (See also the last recommendation [regarding lines 1144-1153] on adding references.)

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IQWiG	296	301	5.2	It is mentioned that researchers should consider the steps need to be taken to harmonize data across institutions or data sources. We propose to move up the cross-reference "see Federated Data Networks" from line 299 to line 296 and to change the sentence order.	Change the order of the sentences from: "In recent years, federated networks of RWD sources have been developed in various regions. When utilizing multiple data sources, either as a network or through data linkage, researchers should consider the steps taken to harmonize data across institutions or data sources (see Federated Data Networks). Some of these networks have been specifically designed to support scientific evaluations and regulatory decision-making, allowing a growing number of studies to include data from these federated networks, often from different countries." to: "In recent years, federated networks of RWD sources have been developed in various regions (see Federated Data Networks). Some of these networks have been specifically designed to support scientific evaluations and regulatory decision-making, allowing a growing number of studies to include data from these federated networks, often from different countries. When utilizing multiple data sources, either as a network or through data linkage, researchers should consider the steps taken to harmonize data across institutions or data sources [REF]." New Reference: Fortier I, Raina P, Van den Heuvel ER et al. Maelstrom Research guidelines for rigorous retrospective data harmonization. Int J Epidemiol 2017; 46(1): 103-105. (see also the last recommendation [regarding lines 1144-1153] on adding references)
Euromedicat Steering Group	299			L299 and L417. We are pleased to see mention of Federated Data Networks. EUROmediCAT is one such network. We note that the only model referred to is the distributed database model. EUROmediCAT has a distributed database, but also a central database to which many partners contribute. This model should also be included. E.g. Dolk et al 2022.	
EUCOPE	301	301	5.2	Original text: 'different countries'	Different countries have their own regulations in accessing RWE data. For example, RWE data sources in USA need to be HIPPA compliant. It is important to understand these regulations and receive appropriate permissions prior to using the data. Study timelines need to be adjusted accordingly.
EFPIA	303	329	5.2.1	This is a helpful summary. It is more relevant to feasibility/choosing fit-for purpose data - suggest move and merge with Section 4.2 on Feasibility assessment	Consider a way to integrate much of this section in with feasibility as these are the factors that drive Feasibility assessments
RTI Health Solutions	303	303	5.2	Appropriateness of Data Sources does not discuss primary data collection. Primary data collection are referred to only later when discussing dissemination and record retention	A new subsection is needed for primary data collection.
Euromedicat Steering Group	304			Line 304. “Researchers should demonstrate an understanding of the data source(s) and its appropriateness to address specific research questions” Insert: It is helpful if Federated Data Networks include researchers with specific experience of each data source to be accessed, their strengths and limitations.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	308	312	5.2.1	A prioritized description of what is essential to evaluate may be helpful to support practical evaluation of the recommendations in the bullets. Not all data sources have all of the information listed (e.g., socioeconomic status is not available in most US data) and not all information may be available at the tme of study development (i.e., formulary decisions and market uptake). The degree of completeness of any but essential and simple variables will also not be evaluable at the time of studydevelopment for reasons stated previously. Availability and access to data prior to initiating study development / execution is a major difference between epidemiology work in industry and academia. The requirement to fully document any analyses of the data, other than simple feasibility counts, is another difference between industry and academia which imposes additional resource burdens on study development in industry. Ultimately, what can be implemented is based on a priori knowledge of the data type (the sponsor's or the immediate vendor contracted for protocol/study development) and source and evaluation of key variables that rely on simple algorithms. Any in-depth evaluation could require negotiation of timelines with regulatory agencies which would be subject to internal agreeement to request amendment to an agreed timeline.	
IQVIA	312	329	5.2.1	Appropriateness of Data Sources. Whether data elements are captured in structured vs. unstructured fields can have a big impact on data quality; however, this factor is not listed among the "key aspects of the proposed data source(s)."	We recommend adding a bullet to describe how the data are captured, in terms of structured fields, unstructured notes, or other kinds of artifacts like imaging and pathology reports.
VAC4EU	312	313	5.2.1	It is important to note that the data source does not capture study elements. Data are prompted into existence in the data source due to its primary purpose, and are then repurposed for the study via algorithms (often referred to as 'phenotypes') that mimic the collection of the study variables. Such process generates variables that may have imperfect validity, e.g., have false positives, or false negatives, or delay in recording of true positives (this in fact motivates the next point in this list, about validation).	We recommend to specify the notion of algorithm/phenotype, to avoid confusion.
EUCOPE	314	315	5.2.1	The items listed under 'other key study elements' are significant and should be emphasized. We ask that the agency consider creating separate bulleted lines for validation of each exposure, key covariates, and inclusion/exclusion criteria similar to outcome.	• The capability to validate the outcome; • The capability to validate exposures; • The capability to validate key covariates; • The capability to validate inclusion/exclusion criteria);
VAC4EU	314	314	5.2.1		Please clarify what is meant by outcome validation and capability to validate in this context, or link the section to case validation further in the document?
AstraZeneca	316	319		Historical experience with use of similar data sources to the selected data source should be considered relevant as well.	
VAC4EU	316	319	5.2.1	We wonder if ICH considers it appropriate to indicate as an example of source where this information can be easily retrieved the HMA/EMA Catalogues of studies and real world data sources	
EFPIA	320	321	5.2.1	Propose adding the following bullet "Availability of interim data," which could be key to monitoring the progress of the (likely lengthy) study	•Time to data availability, frequency of data refresh; •Availability of interim data
EUCOPE	320	320	5.2	Original text: 'data'	Change into 'data adjudication'
EUCOPE	326	326	5.2	Original text: 'The key patient characteristics which might act as potential confounders, including age, 326 socio-economic status, health conditions, risk factors for the outcome, health system 327 (e.g., private or public/governmental healthcare)'	add gender, race, region,
ISPE	326	327	5.2.1	Expand the list of "The key patient characteristics which might act as potential confounders, including age…"	Add lifestyle factors: "The key patient characteristics which might act as potential confounders, including age,... lifestyle factors, etc.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	329	329	5.2.	There is an increase of multi RWD studies to increase study size or to increase generalizability of results. However, this comes with heterogeneity that is observed and that limits the interpretation of results. It is important to understand the origin of heterogeneity and potential sources of heterogeneity that need to be anticipated in the study protocol together with its management. Heterogeneity is to be tackled at the design stage (feasibility assessment) and not at the analyses or discussion of reports. This relevant point is missing in the list of bullet points and it is suggested to be added. In addition, the recent "Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence" includes a section dedicated to "heterogenety, and adding this bullet point will increase consistency across documents.	Consider adding a new bullet point dedicated to heterogeneity in multi RWD source studies as follows: "In multi RWD source studies, potential sources of heterogeneity across RWD sources need to be anticipated at the protocol stage and ist managed presented"
EUCOPE	329	329	5.2	Original text: 'limitations'	including strengths
Euromedicat Steering Group	329			L329 Please add to the bulleted list: 'co-exposures, such as substance or alcohol misuse' and medicines or conditions known to pose considerable risk for example, type 1 diabetes.	
EFPIA	330	330	5.2.2	This section is specific as to what should be included in the protocol with regards to describing the chosen data for the study.	this section should be focused on that to include in the protocol once the data has been selected
German Rheumatology Research Center | Head of Epidemiology, Prof. Dr. Anja Strangfeld	330	340	5.2	From this point onwards, the guideline does no longer fit the purpose and fails to meet the aforementioned objective of dealing with "primary data collections" in order to address pharmacological issues. It is evident to any experienced researcher that EHR data and claims data are in no sense "primary data collections" in the context of scientific research. Such data are of administrative nature only, and the researcher has no influence on the scope and depth of the information. The use of EHR and CLAIMS is frequently appropriate though. However, this represents a secondary use of data, with all the associated advantages and disadvantages from an epidemiological perspective. For example, primary data collections, as such derived from cohorts, are designed to advance scientific understanding and encompass, inter alia, patient-reported outcomes (PROs). Administrative data collections are not focused on scientific enquiry and they do not include (PROs).	The guideline misses a clear differentiation of data sources
Syneos Health CRO	330	330	5.2.2	Major Data Sources: We would recommend adding a section on laboratory data, the current scope is too limited and the text need to elaborate of the use of data. Very often the collaboration for 2nd data is done directly with the lab vendor so this needs to be included.	
Medicines for Europe	335	335	5.2.2	Please elaborate abbreviation of "EHR'. As this is the first mention of EHRs.	Replace EHR with "Electronic Health Records"
AESGP	341	364	5		Recommendation to add a sentence highlighting the importance of adhering to local health information privacy policies (i.e. Health Information/Insurance Portability and Accountability Act [HIPAA] in the U.S.). More specifically, the de-identification (anonymization) of patient health data before it can be used for research purposes should be highlighted.
Cegedim Health Data	341	364	5.2.2	This section is uncomplete and should mention that exists initiatives (of data providers) to offer EHR with a long follow-up of patients and already following a CDM even mapped to OMOP and including clinical variables or claims in some case.	Nevertheless it exists in Europe initiatives that offer already access to European EHR following a CDM and already mapped to OMOP CDM which represents a gain of time. This RWD may includes clinical variables, and can offer a consistent follow-up over time.
Euromedicat Steering Group	342			Line 342 on EHR data - Somewhere need to mention difficulty in obtaining data on medications prescribed during in-patient stays which is frequently not included in EHR data.	
ISPE	346	346	5.2.2	"...standardization of data formats is often a major issue in a study when integrating data from multiple institutions…." Possibly through a common data model (bolded)	Add sentence that Consideration should be given to variables in the common data model and how they may differ in collection, implementation and interpretation among different institutions

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
AstraZeneca	355	358		This recommendation is best suited for documentation in the statistical analysis plan. Most of these information are not readily available at the protocol development phase. A similar conflict is seen in lines 755 - 757.	Revise sentence to suggest documentation in the statistical analysis plan as recommended in lines 575 - 576.
EFPIA	355	358	5.2.2	While it is important to harmonize data that will be analyzed in a single dataset, another valid approach would be to analyze data from different institutions separately and combine using meta-analysis.	Consider noting that this is one approach and other methods may be available.
EUCOPE	356	356	5,2,2	Original text: 'such as'	add procedures
EUCOPE	365	378	5.2.2.	Mentioned briefly elsewhere, but(agency wording) importance of understanding whether data exists which would validate claims when compared to EMR data.	
Cegedim Health Data	366	378	5.2.2	This section is uncomplete and should mention that Claims data by essence don't give access to clinical data nor biological results nor diagnosis which represents a limitation in the analysis. Also usually process to get access to these data could be long depending on country procedure and could be updated once a year (again depending on country procedure) so generating a potential additional time lag for new products launched.	Nevertheless Claims data by essence don't give access to clinical data nor biological results nor diagnosis which may represent limitations in the analysis. Please note also that process to get access to these data could be long and could be updated once a year (again depending on country procedure) so generating a potential additional time lag for new products launched.
ISPE	366	378	5.2.2	It is important to recognize that claims data are differentiated in juisdictions with publicly funded healthcare systems vs private.	Add: "In jurisdictions with publicly funded health care systems, public administrative claims data are characteristically available across a wide range of publicly funded health encounters and services. It is feasible to track individuals who utilize these services across contacts and service delivery continuously over relatively long periods of time."
Euromedicat Steering Group	380			L380 Registries	
Euromedicat Steering Group	380			From the OED, which is academia's standard, 'registry' is 'a repository where registers are kept: a registry office' https://www.oed.com/dictionary/registry_n?tab=meaning_and_use#26215891 . Therefore, Anglophones would expect 'register' here: ' any of various records kept listing details of names, events etc. A book or volume in which important items of information of a particular kind are regularly and accurately recorded; a collection of entries so created; a written record or account (…)' https://www.oed.com/dictionary/register_n1?tab=meaning_and_use#26208244	
EFPIA	383	385	5.2.2	Consider whether registries based on non-drug exposures need to be added. These are often employment-based exposures, but can be based on others, e.g., Agent Orange.	See comment
EFPIA	389	389	5.2.2 Registries	"If a study makes secondary use of registry data,…" - not very celar	Suggestion: If a study is based on secondary use of registry data..
EFPIA	398	401	5.2.2 Registries	"...linkage to external data sources or supplemental data collection through other means should be explored" To further aid the reader, we recommend adding "(e.g., primay collection of data)".	As suggested in the comment column.
EFPIA	406	406	5	Data from DHTs may require additional regulatory approaches	Add language on potential regulatory considerations governing the use of DHTs

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IQVIA	409	410	5.2.2	Characteristics of Major Data Sources: Digital Health Technologies. Digital health technologies (DHTs) not only comprise or are used as a component of medicinal products (devices, drugs, and biologics), but are increasingly used as part of healthcare delivery enhancements, opening up additional data reliability concerns.	We recommend broadening the discussion to state that DHTs are also used in the healthcare setting to monitor the compliance and enhance the consistency of clinical care of patients, such as sensors worn by hospital staff and/or patients to improve healthcare delivery, monitor movements or emergency alerts.
VAC4EU	416	416	5.2.2		The term "data source maturity" would need definition.
EUCOPE	417	449		While the advantages of federated data networks are described, it would be appropriate for the agency to also consider the disadvantages of working in data that have been transformed into a common data model, which may result in loss of resolution on granular detail not captured in the data model and increase data lags due to the need for transformation.	
H. Lundbeck A/S	417	449	5.2.2	This section describes the major characteristics and possible advantages of federated data networks and common data models. However, there remains a need for guidance on how to evaluate the feasibility and fit-for-purposeness of federated data network/common data model multi-database study versus executing separate database studies.	The guidance should recommend when it would be favorable to use federated data network multi-database studies.
IQVIA	418	423	5.2.2	Characteristics of Major Data Sources: Federated Data Networks. The draft guideline provides a high-level description of federated data networks (FDNs), which enable distributed analyses among multiple databases. Given the growing role of FDNs in the development of reliable and reusable RWD sources, it would be helpful to provide more details, including best practices demonstrated by leading FDNs.	We recommend listing the following attributes of FDNs: •Use of common data model and guidelines to drive consistency in transforming data into a common format. •Use of standard data quality reporting guidelines. •Use of standardized ontology / terminology. •Use of standardized, verified, and validated analytic methods, which can be adapted per use case. •Maintenance of a central coordinating center to facilitate and govern FDN.
RTI Health Solutions	421	421	5.2	We would like to suggest including the option of conducting analysis using original data not transformed into CDM, but where a common protocol and SAP are used to guide harmonization of data required for the study across data sources	Insert in L421 after (CDMs), "or harmonization based on a common protocol and SAP that can be used to provide a standard structure for sharing and analyzing data"
Medicines for Europe	423	423	5.2.2	Please provide few examples for operational aspects.	
EUCOPE	425	425	5,2,2	Original text: 'from multiple databases'	When combining data from multiple data sources, researcher need to make sure the patients claims are not duplicated.
Cegedim Health Data	430	433	5.2.2	This section is uncomplete. It does exists European clinical RWD which are mapped to CDM which have a patient care focus by design and give access to original records thanks to proprietary ETL process.	Nevetheless it exists in Europe initiatives that offer to data mapped to CDM which have a patient care focus by design and give access to original records thanks to proprietary ETL process.
Euromedicat Steering Group	433			L433 et seq: CDM-driven protocols may exclude key information if not all sources in a consortium have the data. These omissions might be mitigated by ensuring that all covariates can be tested in at least one member of the consortium.	
EFPIA	434	449	5.2.2	FDN have numerous strengths described here and limitations described throughout the remainder of the document. One limitation to consider adding is the additional time it may take to coordinate an analysis within an FDN	Add caveat to consider additional time in study planning stage

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	434	434	5.2.2	There are also some important disadvantages of Federated Data Networks that have not been considered, e.g., heterogeneity due to underlying differences in original data sources/ healthcare systems, etc; operational complexity, and lack of access to industry(Sentinel and Darwin). At least some of the platforms that make those data available also allow individual data owners to opt out for any reason. That's not unreasonable, but can make it difficult to achieve sample sizes needed for analysis or predict what will be feasible prior to engaging with the FDN. Also, unless such networks themselves generate the information needed for fit-for-use evaluation of each data source, it is hard to imagine how any one sponsor would be able to conduct such an assessment for every data source from an FDN that would be included in a study.	
EFPIA	434	435		"FDNs can provide unique advantages that can assist with addressing drug safety questions, such as..."	When providing benefits of FDNs (or any of the described RWD sources) can also disadvantages (especially operational) be described? This will enable readers to understand full context of RWD options for a given situation.
ISPE	434	434	5.2.2	There are also some important disadvantages of Federated Data Networks that have not been considered, e.g., heterogeneity due to underlying differences in original data sources/ healthcare systems, etc; operational complexity, and lack of access to industry(Sentinel and Darwin). At least some of the platforms that make those data available also allow individual data owners to opt out for any reason which can make it difficult to achieve sample sizes needed for analysis or predict what will be feasible prior to engaging with the FDN data partners. Until there are coordinating centers that can efficiently perform the feasibility assessments on behalf of sponsors, it could be a slow process to complete assessments one partner at a time from a contractual standpoint.	Include some current limitations of FDNs that are relevant to steps outlined in the guidance.
Euromedicat Steering Group	447			Line 447. Insert “ascertainment of outcomes and exposures”.	
EFPIA	450	450	5	Data linkage is not inherently part of the "characteristics of major data sources," as indicated in the text. Furthermore, it can be utilized in databases that are not classified as major data sources. Therefore, we recommend allocating a separate section, such as 5.2.3 Data Linkage. Tokenization as part of data linkage should be added..	Add a separate section on data linkage. Add tokenization as part of data linkage.
Euromedicat Steering Group	450			L450 Linkage. Linking of data often imposes much greater restrictions on the use of such data (for example small number suppression may be imposed or a much more limited time period of data access)	
IQVIA	450	467	5.2.2	Characteristics of Major Data Sources: Data Linkage. When linking identifiable data (e.g., EDC data) to de-identified data (e.g., claims), other critical considerations include data privacy, de-identification issues, and the potential benefits of tokenization.	We recommend adding considerations around data privacy, re-identification risk determination (RRD), and the potential need for tokenization and separation of environments when linking primary and secondary data.
Syneos Health CRO	450	467	5.2.2	Tokenization of patients: We recommend adding linkage to increase patient population. Currently the draft guideline only reflects linkage to increase patient journey.	
EUCOPE	460	462	5,2,2	Original text: 'If the study involves a data linkage, the 460 protocol should describe each data source, the information that will be obtained, linkage 461 methods, and the accuracy and completeness of data linkages over time'	To identify same patients from multiple databases, we can do either Proablistic linkage (based on certain demigraphic variables such as age, gender, region, plan type) or deterministic linkage using SSN/government issued IDs.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IQVIA	469	490	5.2.3	Data Standardization. The draft guideline describes several challenges to data standardization in the context of FDNs and multi-database studies, however, additional concerns include the validation of the standard itself and ensuring that each data source is following the same standardization guidelines. For example, in the OMOP CDM standard, a patient record showing an injection of a drug should be transformed to both the drug-exposure and the procedure-occurrence tables. This allows the information about the drug and the physical procedure to be captured. Unless all data sources used in the study follow this guideline (e.g., only add record to the procedure table), then the analysis would likely result in missing patients.	We recommend adding a new paragraph after Line 483 as follows: "Data standardization of RWD may generate incorrect results if the data sources selected do not follow the same standardization guidelines. It is essential to perform verification and validation of the data standardization to ensure consistency between all data sources used in the study.
RTI Health Solutions	469	478	5.2.3	While many aspects of study implementation can be standardized across data sources in a federated network or multi-database study, some inherent aspects of diverse data sources cannot per se be standardized (ie transformed in some way to be more similar or comparable) but are fundamentally different, including differences in the event(s) that prompt the recording of the data in data sources, and differences in the underlying heathcare system and/or culture of the area where the data source is generated. Such differences instead need to be carefully described and considered when interpreting the findings of the study, and can offer opportunities to address the research question across different contexts (eg, populations or healthcare systems).	Consider including the following after the bullet point list in section 5.2.3: "Some aspects of data sources, such as differences in the events that prompt the recording of data, and differences in the underlying heathcare system and/or culture cannot be standardized but remain fundamentally different. This can provide opportunities to examine the research question under different contexts, and such differences should be carefully described when interpreting the findings of a study."
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	471	471	5.2.3	In EU, different languages provide additional challenge. Please also consider that diversity of data sources should be embraced in the spirit of triangulation.	
EUCOPE	476	478	5,2,3	Original text: 'Differences in healthcare systems, such as business processes and local healthcare practice patterns, database structure, vocabularies, coding systems, and deidentification methodologies used to protect patient data when shared'	Suggest adding “variable definition” after “coding systems”
EFPIA	480	481	5.2.2	Please describe what is expected as a plan for mapping coding systems as they evolve or change. Beyond a statement that changes in coding practice that may occur over the course of a long study will be accounted for, this plan is out of scope of what an industry observational study will be able to do. Such a plan requires an enterprise-level effort and including this without any detail about how this might be included in a protocol is not helpful.	Please describe what is expected in terms of the scope of the plan or delete this recommendation.
ISPE	480	481	5.2.2	Please describe what is expected as a plan for mapping coding systems as they evolve or change. Beyond a statement that changes in coding practice that may occur over the course of a long study will be accounted for, it is unclear what would be in scope to include in the protocol/SAP to manage these potential changes.	Add detail on what is expected in terms of the scope of the plan or delete this recommendation.
EFPIA	481	481	5.2.3.	ICH M14 states it is relevant to provide the plans to mapping coding systems as they evolve over time and this point is welcome. Nevertheless, it is also relevant to specify how the mapping will be performed (manual, automated) and what are the limitations.	Consider adding a sentence as follows: "The approach used to map codes (automated, manual) should be fully described and ist limitations acknolwedged in the limitation section of the protocol"
EFPIA	484	490	5.2.2	It's unclear why this text is italicized.	Remove italics
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	484	490	5.2.3	It is unclear why these lines are formatted in italic. Probably, normal formatting should be used.	Delete the italic formatting in lines 484-490.
IQWiG	484	490	5.2.3	It is unclear why these lines are formatted in italic. Probably, normal formatting should be used.	Delete the italic formatting in lines 484-490.
RTI Health Solutions	484	490	5.2.3	Text is in italics; it is unclear why	Please clarify or remove the italics for lines 484-490.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
RTI Health Solutions	484	509	5.2.5	There is inconsistency in the use of pharmacoepidemiologic, pharmacoepidemiological (eg, "pharmacoepidemiological study", "pharmacoepidemiologic study", "pharmacoepidemiologic data")	Please assess whether consistency is needed throughout the document - beyond this specific page range.
EFPIA	487	490	5.2.3	Improvement: Although this text is relevant, we do not believe it belongs in section 5.2.3 Data Standardization. Additionally, it is unclear why this text is in italics.	Delete text
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	491	503	5.2.4	No consequence is described for the case that data are not intended to be collected in the data source and therefore are not available. It should be added that if any of the specified required variables (exposure, comparator, outcomes, covariates) is completely missing, the corrsponding data source is not fit-for-purpose and cannot be used for the desired safety assessment.	Add in Section 5.2.4 that the consequence of the second szenario has the consequence that the considered data source is not fit-for-purpose and cannot be used for the desired safety assessment if the completely missing data correspond to one of the specified required variables (exposure, comparator, outcomes, covariates).
IQWiG	491	503	5.2.4	No consequence is described for the case that data are not intended to be collected in the data source and therefore are not available. It should be added that if any of the specified required variables (exposure, comparator, outcomes, covariates) is completely missing, the corrsponding data source is not fit-for-purpose and cannot be used for the desired safety assessment.	Add in Section 5.2.4 that the consequence of the second szenario has the consequence that the considered data source is not fit-for-purpose and cannot be used for the desired safety assessment if the completely missing data correspond to one of the specified required variables (exposure, comparator, outcomes, covariates).
EFPIA	499	499	5.2.4	add the word dispensed to bullet 2 on line 499, so it appears as "..may have been ordered but not conducted or dispensed"	"..may have been ordered but not conducted or dispensed"
Euromedicat Steering Group	502			L502 Perhaps add another reason for missing data: Data may be missing because the data controllers consider it unduly sensitive and redact. For example, data on sexually transmitted diseases and miscarriage are redacted in some data sources.	
EFPIA	504	504	5.2.5	Integral to feasibility work	Refer this section back to feasibility
German Rheumatology Research Center | Head of Epidemiology, Prof. Dr. Anja Strangfeld	504	515	5.2	Thus far, this document has suggested that questions pertaining to study design and aspects of data quality are independent of the data source. This is, in fact, a gross oversimplification. This can be demonstrated by the example of data quality alone, which is presented incorrectly in this context. Keller et al. (https://doi.org/10.1097/BRS.0b013e3181cd656f) have demonstrated that the concepts of data quality vary according to the type of information collection. Designed and primary data collections have distinct approaches to data quality, with their own conceptual frameworks, e.g. Schmidt et al. (https://doi.org/10.1186/s12874-021-01252-7). This is different from concepts pertaining to EHR or claims data, e.g. Weisskopf et al. (https://doi.org/10.5334/egems.218).	For the purpose of representing a beneficial guideline, extensive efforts should be made to meet the current scientific status quo. In the present version the guideline appears superficial, kind of arbitrary in selecting standards, and flawed in concepts and recommendations.
EFPIA	507	507	5.2.5 Data Quality	What is meant by "pharmacoepidemiologic data"?	Again, we recommend to remove the term "pharmacoepidmiologic from this guidelie in favor of using more precise nomenclature. In this instance, simply deleting the word "pharmacoepidemiological" would suffice.
EUCOPE	516	529	5.2.6	Claims data can be variable on how well they capture medical outcomes (due to coding issues or lack-thereof.) We ask that the agency consider mentioning the importance for sponsors in understanding how well a claims-based algorithm performs when interpreting relevance of findings.	
EFPIA	519	520	5.2.6	(e.g. anatomical therapeutic chemical (ATC), International Classification of disease (ICD)) is not fully including all known possibilities such as READ or ICPC	Please consider to add ICPC, READ, etc...
ISPE	520	520	5.2.6	Expand to cover computable phenotypes for defining the target population, medicine exposures and outcomes.	Add: "any methods used for data linkage.. and algorithms implemented to better identify population, exposures and outcomes."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Syneos Health CRO	530	542	5.3	We recommend medication adherence to be mentioned in this section.	
RTI Health Solutions	532	532	5.3	The unit of years was missing from ages "e.g., children aged 12-16 with attention deficit hyperactivity disorder".	Please add units, eg, "12-16 years"
EFPIA	541	542	5.3	No mention of validated algorithms to define	Add e.g., references for validated algorithms.
EFPIA	541	542		(see Error! Reference source not found.).	reference missing
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	541	542	5.3	There is an incorrect cross-reference in line 542.	Correct the cross-reference in line 542.
IQWiG	541	542	5.3	There is an incorrect cross-reference in line 542.	Correct the cross-reference in line 542.
EFPIA	542	542	5.3	on page 18, the hyperlink is not working for the reference under 5.3 Target/Study population	
EFPIA	542	542	5.3	Reference is missing (see Error! Reference source not found.).	Provide cross- reference (external or within the same document).
EFPIA	542	542	5.3.	Minor: the reference needs to be fixed as it appears as "(see Error! Reference source not found.)."	Typo
EFPIA	542	542		Hyperlink reference is broken	
EUCOPE	542	542	5.3	Reference source not found	Reference source not found.
Medicines for Europe	542	542	5.3	Please re-add reference. This seems to be a technical error.	
RTI Health Solutions	542	542	5.3	Reference was listed as "(see Error! Reference source not found.)"	Please update.
VAC4EU	542	542	5.3		Check this error.
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	542	542		Broken link	Update the link
EFPIA	546	568	5.4	The paper suggests that the conceptual definition should start at the time of initial database selection. However, it seems that a conceptional definition should be available prior to database selection and should be used during the landscape and feasibility assessment. Without a conceptual definition, it will be difficult to determine whether a data source can be considered "fit for purpose." Part of selecting the appropriate database will be determining whether the exposure/outcome/covariate operationalization adequately captures the conceptual definition. Additionally, the paper outlines that the protocol should comment on whether the operational definitions and performance characteristics are adequate in the chosen data source. By virtue of having a selected data source, wouldn't the adequacy already have been determined? If it was considered inadequate, then the data source would not have been selected, correct? Perhaps it would be better stated that the protocol should contain justification regarding the appropriateness of the operational definition. It would also be valuable to clarify that if the operational definition cannot be justified, then perhaps the chosen study design is not appropriate.	Please consider whether the conceptual definition should be developed prior to selecting the database. Consider whether the bullets started on line 563 are considerations that should be made before the final data is selected.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ISPE	546	568	5.4	The guideline suggests that the conceptual definition should start at the time of initial database selection. However, it seems that a conceptional definition should be available prior to database selection and should be used during the landscape and feasibility assessment. Without a conceptual definition, it will be difficult to determine whether a data source can be considered "fit for purpose." Part of selecting the appropriate database will be determining whether the exposure/outcome/covariate operationalization adequately captures the conceptual definition.	Clarify whether the conceptual definitions should be developed prior to selecting which databases to include in the feasibility assessment.
EFPIA	553	557	5.4	The operational definition for code-based algorithm should include additional details such as position of diagnosis, such as place of service, quantity and frequency of the code where applicable, particularly in claims data. Differences across EHR systems should also be considered when applying the same code-based algorithms.	
ISPE	554	555	5.4.1	The intent of the objective of operational definition in the following sentence is perhaps unclear: “An operational definition should be developed based on the conceptual definition to extract the most complete and accurate data from the data source”	Recommended revision “An operational definition should maximize construct validity by representing the conceptual definition as closely as possible through derivation from identified available data elements”.
Medicines for Europe	558	558	5.4	Addition of "or structured data such as standardized guidelines at global level, relevant high indexed publications" is suggested. Because the operational definitions can be derived not only from unstructured data but also from structured data	unstructured "or structured data such as standardized guidelines at global level, relevant high indexed publications". - Additional text is proposed.
EFPIA	569	571	5.4	We welcome the guidance on when and how conceptual and operational definitions are defined. We would like to note, however, that the term "phenotype" / "computable phenotype" for the conceptual definition is not widely used, and may cause confusion for some readers.	The conceptual definition may be referred to as the phenotype. The protocol should include a detailed description of the operational definition, sometimes referred to as the computable phenotype (including the coding system and rationale) and the associated limitations…
ISPE	569	569	5.4	Computable phenotype may not be a universally familiar term.	Suggest to include a reference for the use of 'computable pheontype'
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	569	576		"The protocol should include a 569 detailed description of the operational definition..." the PASS protocols usually only need high-level definitions, the detailed phenotypes are usually given in Analysis Plans	I strongly suggest no requiring including a fully detailed operational definition in the Protocol, because things change between protocol development and study implementation. The full definition should be given in SAP. Protocol can provide high-level definition, e.g., data provenance and type of vocabulary used (e.g., ICD-10 codes from primary diagnosis fields at inpatient stays), while details should be fleshed out in SAP. The protocol can also specify whether a given agorithm has been validated and cite the relevant validation studies.
EFPIA	575	576		It is of note, the operational definitions may be pre-specified, but may also emerge during the conduct of the analysis, where unexpected patterns in the data, indicate or imply an inherent bias that must be further adjusted for - such emerging issues may be adjusted for, but their remediation should not jeopardise the study, through lack of detailed pre-specification. Guideline should clarify that such analytical adjustment should not be mistaken for data-dredging	
EUCOPE	577	581	5.4	These should be some consideration on epidemiology of rare conditions and the operational challenges of using any of these RWE databases and limitations for assessing these elements in extremely rare medical conditions or disorders.	Describe limitations based on epidemiology incidence and prevalence and limitations based on these considerations.
German Rheumatology Research Center | Head of Epidemiology, Prof. Dr. Anja Strangfeld	600	630	5.4	This section differentiates some exposure definitions, however, implications of those definitions should be mentioned depending on the type of the outcome. For example, is it useful to consider an ever exposed approach with regard to serious infections?	
Medicines for Europe	612	612	5.4.1	Please provide details about the excipient used for drug administration and device details.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCOPE	613	613	5,4,1	Original text: "[…] (e.g., for a medicine with the same active substance name made by different manufacturers)." The sentence should include biosimilar to make it complete, so include it.	We recommend the following revision: "(e.g., for a medicine with the same active substance name or a medication that is highly similar to an already approved original biologics made by different manufacturers)."
EFPIA	617	630	5.4.1	EMRs generally have orders and not dispensings. There is no mention of orders in this section and how they differ from dispensings with regards to strengths and limitations.	Add strengths and limitations of medication orders from EMRs.
Gesellschaft für Phytotherapie (GPT)	617	633		The dosage form must be clearly described as it is key for understaning and using the data. Therefore, chapter 5.4.1 needs to be respectively amended (see next column).	In general, it is essential to capture for all medicines the information needed to doubtlessly identify them and their active ingredients, formulation and dosage form. The information needed for that purpose is different for different medicinal products. There are resp. standards which can be followed : Butcher NJ, Monsour A, Mew EJ, Chan AW, Moher D, Mayo-Wilson E, Terwee CB, Chee-A-Tow A, Baba A, Gavin F, Grimshaw JM, Kelly LE, Saeed L, Thabane L, Askie L, Smith M, Farid-Kapadia M, Williamson PR, Szatmari P, Tugwell P, Golub RM, Monga S, Vohra S, Marlin S, Ungar WJ, Offringa M: Guidelines for Reporting Outcomes in Trial Reports: The CONSORT-Outcomes 2022 Extension. JAMA. 2022;328: 2252-2264 Cheng CW, Wu TX, Shang HC, Li YP, Altman DG, Moher D, Bian ZX: CONSORT-CHM Formulas 2017 Group. CONSORT Extension for Chinese Herbal Medicine Formulas 2017: Recommendations, Explanation, and Elaboration. Ann Intern Med. 2017 ;167:112-121 Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C: CONSORT Group. Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement. Ann Intern Med. 2006;144:364-7
EUCOPE	625	625	5,4,1	Original text: Exposures that are not captured in the data source such as samples, low-cost medicines, non-prescription medicines, and immunizations offered in the workplace; and	adding "over the counter drugs" to the sentence
EFPIA	626	626	5.4.1	re-wording proposed on bulleted point on "coding systems used to identify exposures" - reword exposures to make it specaific to medications	Change to "coding systems used to identify medicines" to make it specific
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	626	626		ATC is not mentioned, it is most frequently used in Europe.	Add ATC.
ISPE	627	630	5.4.1	Provide a concrete rationale for the provided example of the importantce of considering multiple types of exposure settings/health system contacts.	"[exposures] may be administered [across multiple settings], so setting and treatment patterns should be considered in terms of potential requirements for data linkage to avoid exposure misclassification."
Medicines for Europe	627	627	5.4.1	Re-phrasing of text is proposed.	"setting of treatment administration" is proposed instead of "setting of administration".

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Koop Phyto	630	630	36986	It is key for the usefulness of any pharmacoepidemiological study that the intervention is decribed in a way allowing a clear identification by the reader. This applies especially for pharmaceutical products with their multitude of APIs, formulations, dosage forms etc. Tho warran this, the resp instructions in the guideline would need to be more explicit (see text proposal). It will be helpful to also add references to key publications in the field: - Butcher NJ, Monsour A, Mew EJ, Chan AW, Moher D, Mayo-Wilson E, Terwee CB, Chee-A-Tow A, Baba A, Gavin F, Grimshaw JM, Kelly LE, Saeed L, Thabane L, Askie L, Smith M, Farid-Kapadia M, Williamson PR, Szatmari P, Tugwell P, Golub RM, Monga S, Vohra S, Marlin S, Ungar WJ, Offringa M. Guidelines for Reporting Outcomes in Trial Reports: The CONSORT-Outcomes 2022 Extension. JAMA. 2022 Dec 13;328(22):2252-2264. doi: 10.1001/jama.2022.21022. PMID: 36511921. - Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C; CONSORT Group. Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement. Ann Intern Med. 2006 Mar 7;144(5):364-7. doi: 10.7326/0003-4819-144-5-200603070-00013. PMID: 16520478. - Cheng CW, Wu TX, Shang HC, Li YP, Altman DG, Moher D, Bian ZX; CONSORT-CHM Formulas 2017 Group. CONSORT Extension for Chinese Herbal Medicine Formulas 2017: Recommendations, Explanation, and Elaboration. Ann Intern Med. 2017 Jun 27;167(2):112-121. doi: 10.7326/M16-2977. PMID: 28654980	When the conceptual definition is translated into the operational definition, the information required to uniquely identify the medicinal product, its active substance, its formulation and its pharmaceutical form must be recorded for all medicinal products. The availability of the information depends on the type of medicinal product. This should be based on appropriate standards, for example the CONSORT statement, including adaptations for special groups of medicinal products such as herbal medicinal products.
VAC4EU	631	633	5.4.1	Many reseach questions can be addressed without this granularity.	We suggest to replace with "For vaccines, *it may sometimes be useful* to have granular information on brand, dose schedule, coadministration with other vaccines, and sometimes batch number or administration route and site."
Euromedicat Steering Group	635			L635 Exposure. The half-life of the medicine of interest should also be considered when determining the exposure window of the medication. Information on half life should be made available for neonates (particularly pre-term neonates), pregnant women, individuals with extreme BMI, older adults and those with severe illness.	
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	635	636		"The exposure (i.e., dose, dosage regimen) to the medicine of interest should be well-defined and measured". This rarely happens in RWD. Most data sources do not record the prescribed dose or regimen, and those need to be defined using assumptions.	Consider rephasing, acknowledging the cited limitations.
EFPIA	649	662	5.4.2	No mention of clinical experts	Add this should be done in consultation with clincal experts.
Euromedicat Steering Group	650			Line 650 and elsewhere. We support separating conceptual and operational definitions of outcome. No change.	
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	658	662	5.4.2	Due to the high relevance of patient-important outcomes, we recommend that diagnostic criteria for defining clinical outcomes should include information about whether an outcome was symptomatic or not. In the same sense, it is highly important and common standard to classify safety outcomes according to their seriousness. This should be already mentioned here.	Add at the end of the paragraph: "It is essential to define and to describe whether a clinical outcome was symptomatic, serious, or both."
IQWiG	658	662	5.4.2	Due to the high relevance of patient-important outcomes, we recommend that diagnostic criteria for defining clinical outcomes should include information about whether an outcome was symptomatic or not. In the same sense, it is highly important and common standard to classify safety outcomes according to their seriousness. This should be already mentioned here.	Add at the end of the paragraph: "It is essential to define and to describe whether a clinical outcome was symptomatic, serious, or both."
Euromedicat Steering Group	662			L662 Where possible, outcomes should be verified from >1 source. Primary care providers do not record all problems, and their data can usefully be combined with hospital admissions data to obtain a more complete picture.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EUCOPE	664	664	5,4,1	Original text: An operational definition is one that can be implemented independently using the data available	adding “or algorithm” after “an operational definition”
ISPE	664	665	5.4.2	The topic of operationalization of follow-up for outcome occurrence (e.g., start and end date definitions) was missing from the section.	Add guidance for defining start and end date defintions to clarify when participant is eligible for outcome identification.
VAC4EU	664	664	5.4.2	What is meant by implemented independently?	
ISPE	665	665	5.4.2	"..in the proposed study with acceptable performance" -- What is the definition of acceptable performance, is it sensitivity, specificity, positive predictive value)?	Add a definition of acceptable performance
EUCOPE	669	669	5,4,1	Original text: (e.g., physician’s encounter notes, radiology, or pathology reports), or measurement tools such as questionnaire scales	adding “(e.g. numerical pain scale)” after questionnaire scales
EUCOPE	669	670	5,4,1	Original text: Consideration for changes in coding or the underlying EHR systems over time is essential	when adding multiple data sources, researcher need to consider the general equivalence mapping between various medical coding systems. It can be a forward mapping converting local codes to standardized vocabulary or vice versa (backward mapping).
EUCOPE	673	673	5,4,1	Original text: Single appearances of a diagnosis code may indicate a rule out diagnosis	to rule out data error, the best practice is to conisder atleast 2 diagnoses within the study period with a gap of atleast 30 days in between.
ISPE	682	682	5.4.2	Further addition to clarify caveats re: cause of death information after"Linkage to external vital statistics resources may be necessary" --	Clarify that Where date of death is available or can be linked, cause of death is not always available or reliable.
EFPIA	683	692	7	incorporate sensitivity analyses to ensure you have the best PPV as part fo the outcome definition	incorporate sensitivity analyses to ensure you have the best PPV as part fo the outcome definition
EFPIA	705	705	5.4.3	DAGs can be very useful when deciding on covariates	Consider mentioning directed acyclic graphs in this section.
H. Lundbeck A/S	706	723	5.4.3	The guidance supports the conceptual definition and operationalization of covariates, however there remains a need for additional guidance to support the identification of confounders relevant to the research question. In this context, directed acyclic graphs (DAGs) can be applied for identifying variables that, if controlled for in the design or analysis phase, are sufficient to eliminate confounding and some forms of selection bias.	The guidance could offer suggestions for a framework to support the identification of confounders relevant to the research question.
ISPE	723	723	5.4.3	Causal language is used in some parts of document, "counterfactual", "causal pathway", but DAGs were not mentioned as a recommended part of the protocol development process.	Addition: Consider the use of DAGs to aide in identifying sources of bias for addressing in study design, analysis, and quantification.
EFPIA	724	728	5.4.3	The majority of this text focuses on the operationalization of covariates rather than their conceptual definition.	
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	725	296	5.4.3	It is described that researchers may consider whether proxies for a missing covariate are appropriate. The simple consideration is insufficient. If a proxy variable should be used for a missing covariate a clear reasoning is required that it is appropriate to use the proxy instead of the missing covariate. The consequence should be added that the considered data source is not fit-for-purpose if a covariate is missing and no appropriate proxy is available.	Add in line 278 after "… whether proxies for the covariate are appropriate" a statement like this: "A clear reasoning is required that it is appropriate to use the proxy instead of the missing covariate. Without such a clear reasoning the considered data source is not fit-for-purpose and cannot be used for the desired safety assessment if a covariate is missing and no appropriate proxy is available.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IQWiG	725	296	5.4.3	It is described that researchers may consider whether proxies for a missing covariate are appropriate. The simple consideration is insufficient. If a proxy variable should be used for a missing covariate a clear reasoning is required that it is appropriate to use the proxy instead of the missing covariate. The consequence should be added that the considered data source is not fit-for-purpose if a covariate is missing and no appropriate proxy is available.	Add in line 278 after "… whether proxies for the covariate are appropriate" a statement like this: "A clear reasoning is required that it is appropriate to use the proxy instead of the missing covariate. Without such a clear reasoning the considered data source is not fit-for-purpose and cannot be used for the desired safety assessment if a covariate is missing and no appropriate proxy is available.
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	732	734	5.4.3	It is described that covariates are typically identified and assessed during the period before the start of the exposure of interest (baseline). Instead, it should be stated that possible covariates must be systematically identified and prespecified. Otherwise, it cannot be assessed whether all relevant covariates are covered by the selected data source.	Replace the sentence "Covariates are typically identified and assessed during the period before the start of the exposure of interest (baseline)." by a statement like: "The relevant covariates must be systematically identified and prespecified in the necessary depth of detail. Otherwise, it cannot be assessed if all relevant covariates are covered by the considered data source. If that is not the case, the data source is not fit-for-purpose and cannot be used for the desired safety assessment." Then continue with: "Covariates are typically assessed during the period before the start of the exposure (baseline) [...]."
IQWiG	732	734	5.4.3	It is described that covariates are typically identified and assessed during the period before the start of the exposure of interest (baseline). Instead, it should be stated that possible covariates must be systematically identified and prespecified. Otherwise, it cannot be assessed whether all relevant covariates are covered by the selected data source.	Replace the sentence "Covariates are typically identified and assessed during the period before the start of the exposure of interest (baseline)." by a statement like this: "The relevant covariates must be systematically identified and prespecified in the necessary depth of detail. Otherwise, it cannot be assessed if all relevant covariates are covered by the considered data source. If that is not the case, the data source is not fit-for-purpose and cannot be used for the desired safety assessment." Then continue with: "Covariates are typically assessed during the period before the start of the exposure (baseline) [...]."
EUCOPE	735	735	5,4,3	Original text: The length of this lookback period is selected by considering factors such	include data availability
Euromedicat Steering Group	735			L735 The length of lookback should be carefully evaluated using different time periods in order to identify the optimal time period, it is hard to predict by just considering the relevant factors listed in lines 735 onwards	
EFPIA	737	737	5.4.3	There is a typo in the second sentence: "Covariates and may also be assessed…."	Remove the "and" after the word "covariates"
EFPIA	737	737	5.4.3	Typo	"Covariates and may also be assessed during…"
EUCOPE	737	738	5,4,3	Original text: Covariates and may also be assessed during the observation period	name it as coexisting conditions
VAC4EU	737	737	5.4.3	Covariates sentence not reading well.	
EFPIA	744	744	5.5	Channeling bias can be important in safety studies	Add channeling bias

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Medicines for Europe	744	744	5.5	Addition of "recall Bias" is proposed. Details about "Recall bias" need to be mentioned as this is a most common bias seen in control group or placebo group which may not provide relevant information about exposure status and outcome. This can be handled with choosing an appropriate control group.	
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	744	764	5.5	Confounding IS a form of bias.	Consider renaming this section to 5.5 "Systematic error" or "Bias" and revise the entire section for this terminology
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	745	746		"To obtain a valid and precise estimate of the effect of exposure on the outcome of interest, studies must address two sources of error": given the title of the section, the reader may think that by 2 sources of error you mean bias and confounding.	Rephrase to read "To obtain a valid and precise estimate of the effect of exposure on the outcome of interest, studies must address two sources of error: the random error and the systematic error."
EFPIA	759	759	5.5	Not all types of bias, particularly in studies that use RWD, can be controlled; sometimes, we can only attempt to assess their effect on the results.	The proposed data source should be evaluated to determine whether it is adequate to capture information on important factors so that bias and confounding can be adequately controlled or assessed.
IQVIA	765	775	5.1	Selection Bias. The section states that "[d]ifferent forms of selection bias may be addressed in either the design (preferred) or analysis stages, however, it would be challenging to address selection bias post-design phase. One can use quantitative bias analysis to estimate the potential impact of selection bias on the estimates but cannot "adjust" for it. The section also lists "loss to follow-up" as a form of selection bias, but it is "differential loss to follow-up" that would result in selection bias. The section only describes prevalent user bias, but not other forms of selection bias. In addition, the last statement in the subsequent section on Information Bias (Lines 784-787), which discusses the development of a plan to use quantitative bias analysis, also pertains to Selection Bias.	We recommend clarifying that selection bias should be addressed primarily during the design phase and explaining other forms of selection bias, particularly due to differential loss to follow-up. We also recommend adding a statement about including Selection Bias in the overall plan to use quantitative bias analysis, as discussed in other sections of the draft guideline.
RTI Health Solutions	767	767	5.5.1	"loss to follow-up (time-related bias)". It is unclear why the parenthetical clause appears there.	conbsider to replace "loss to follow-up (time-related bias) with "censoring bias" or "differential loss to follow-up".
Euromedicat Steering Group	775			L775 it would be useful to include 'volunteer bias' here.	
EUCOPE	777	778	5,5,2	Original text: Information bias arises when misclassification of binary or categorical variables or mismeasurement of continuous variables exists	clarify on the top that Information bias is a one type of Misclassification bias
EFPIA	788	793	5.5.3	The definition of immortal time bias seems to be incomplete. We would appreciate if more detail can be added, given that this is a common bias with RWD sources and should be accurately identified.	
ISPE	788	791	5.5.3	Immortal Time Bias. The first sentence should probably omit "bias": "Immortal time refers to a period of cohort follow-up time during which an outcome of interest cannot occur. " The key aspect that translates into biased estimated effects is that outcome eligibility is imbalanced across comparison groups.	Revise: "Immortal time bias results from unequal eligibility for the outcome of interest over [one or more periods of] follow-up across comparison groups"
EFPIA	789	790	5.5.3	The current definition is immortal time but not necessarily immortal time bias.	Reword to "immortal time bias a distortion of results from the misclassification or exclusion of immortal time"
RTI Health Solutions	792	792	5.5	Immortal Time Bias and other time related biases can be prevented through alignment at time zero of time of eligibility, start of therapy and start of follow-up. Refer to comment for line 272.	If text proposed for line 272 was not added, please include in this section

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	795	807	5.5.4	It is described that it is typically impossible to capture all potential confounders that are relevant to a research question. Nevertheless, for a valid analysis all relevant confounders are required. It should be added that it is required to define clearly which confounders are mandatory and have to be included in the analysis in order to minimize bias. Again, the consequence should be added that the considered data source is not fit-for-purpose if a mandatory covariate is missing.	Add in line 796 after "… or residual confounding a statement like this: "Therefore, it is essential that it is clearly defined which confounders are mandatory and have to be included in the analysis in order to minimize bias. If a mandatory covariate is missing the considered data source is not fit-for-purpose and cannot be used for the desired safety assessment."
IQWiG	795	807	5.5.4	It is described that it is typically impossible to capture all potential confounders that are relevant to a research question. Nevertheless, for a valid analysis all relevant confounders are required. It should be added that it is required to define clearly which confounders are indispensable and have to be included in the analysis in order to minimize bias. Again, the consequence should be added that the considered data source is not fit-for-purpose if a relevant covariate is missing.	Add in line 796 after "… or residual confounding a statement like this: "Therefore, it is essential that it is clearly defined which confounders are indispensable and have to be included in the analysis in order to minimize bias. If an indispensable covariate is missing the considered data source is not fit-for-purpose and cannot be used for the desired safety assessment."
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	795	807		Confounding by indication or severity should be mentioned in this specific document	Define confounding and specifically confoudning by indication and severity
IQWiG	804	805	5.5.4	DAGs are state-of-the-art in planning non-randomized studies and should be used to describe the researchers' causal assumptions (see e.g., Rodrigues et al. Int J Epidemiol, 2022).	The setentence should be changed: "Directed acyclic graphs should be used to understand the relations between the … [REF]". New Reference: Rodrigues D, Kreif N, Lawrence-Jones A et al. Reflection on modern methods: constructing directed acyclic graphs (DAGs) with domain experts for health services research. Int J Epidemiol 2022; 51(4): 1339-1348.
Euromedicat Steering Group	807			L807 Pharmacovigilance studies should attempt to guard against confounding by ensuring that none of the potential confounding variables is absent from all included data sources.	
EFPIA	808	835	5.6	Would the authors be able to provide recommendations when validation is not possible to conduct as described? Guidance on the use of surrogate markers to prove validity will be welcome.	
IQVIA	808	835	5.6	Validation. Where data are collected from electronic health care data sources, additional wording is needed regarding the use of validated electronic systems as well as confirming databases are operating in a validated state.	In Line 816, following the sentence starting "Validation efforts should be commensurate with the level of evidence required….," it would be useful to add a new sentence to the effect, "Where data are collected from electronic healthcare data sources, sponsors should assure validated electronic systems are in use."
ISPE	808	835	5.6	It would be helpful to include citations that provide more context and detail related to the topic of validation of outcomes in real world databases. This paper could fit well at line 825.	cite:Weinstein EJ, Ritchey ME, Lo Re V III. Core concepts in pharmacoepidemiology: Validation of health outcomes of interest within real-world healthcare databases. Pharmacoepidemiol Drug Saf. 2023;32(1):1-8. doi:10.1002/pds.5537
Medicines for Europe	808	808	5.6	Information about external validity should be considered in this section. Details regarding generalisability of study results.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
RTI Health Solutions	808	808	5.6	Validation efforts may be conducted to validate an algorithm (eg, to validate an outcome-identifying algorithm, in order to determine whether the algorithm can be used in a study) or to validate the actual events (so that the confirmed status of each event can be used in a study). When validation efforts are conducted, it is important to note how the information obtained will be used in the analysis.	Please consider adding the possible uses of validation and requesting that protocols mention how the validation results will be incorporated in the analysis (in the parent protocol or in the validation protocol)
Euromedicat Steering Group	809			L809 'accurately' is normally associated with reliability. Would 'cogently, and congruous with real-world experience' be better?	
Euromedicat Steering Group	810			L810 needs a reference and page number for the definitions.	
RTI Health Solutions	810	811	5.6	In addition to validating the presence/absence of an event (eg, exposure, condition or characteristic), it is often of value to validate the date when the event happens, or the presence/absence of the event at a certain point in time.	Please consider clarifying this.
RTI Health Solutions	813	814	5.6	"These may include complete verification, partial verification": it is unclear what is completely or partially verified. For example, does this refer to the complete pool versus a part of the pool of potential cases identified by an algorithm?	Please clarify this.
EFPIA	820	821	5.6	The suggestion that sponsors should have early interactions with regulatory authorities to discuss and agree upon study design is quite common across a variety of opinion papers, draft guidances, and guidelines; however, the practical aspect of how to accomplish this is never addressed. Suggestion for the regulatory pathway to use for such discussions would help align sponsors and regulators and would set this paper apart from the many that are already available.	Please provide practical guidance on accessing regulatory pathways for initiating the suggested discussions.
EFPIA	820	822	5.6	It should be clarified that the need to discuss the proposed approach with regulatory authorities is determined based on applicable regulatory requirements in individual jurisdictions and/or at the discretion of the sponsor.	It is recommended that sSponsors should have early interactions with regulatory authorities (based on applicable regulatory requirements) to discuss and agree upon a proposed validation approach, such as partial vs. full, or adoption of definitions validated previously
EFPIA	826	826		The rational for validation (studies) to be managed under a separate protocol is unclear. In this case, presumably there are no restrictions placed on the use of the same study dataset for such validation efforts. In such instances, guideline should clarify whether it is sufficient to consider this a step in the same protocol or not.	
EUCOPE	826	826		We ask that the agency reconsider the statement that validation should be conducted under a separate protocol. Although the items that are listed for characterization of validity of an algorithm are fully appropriate, there are many instances in which it is both efficient and desirable to conduct outcome validation in the context of the study in which the algorithms will be used. This is operationally efficient and ensures that the algorithm is suitably tailored to the study population, maximizing the applicabilty of estimates of positive predictive value when this is the selected metric.	
EFPIA	828	828	5.6	Kappa statistic is often biased and insufficient	Consider adding PABAK and ICC to list of metrics to be reported
VAC4EU	829	831	5.6	To support internal validity of the database or of the operational definition?	
ISPE	831	832	5.6	Add additional example of how the validation would occur (through chart review or clinical review / adjudication using pertinent data).	Add how: "For instance, when cases are rare, one may need to select highly sensitive operational definition and then validate all potential cases through chart review or clinical review / adjudication using pertinent data"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	834	835		The guideline should provide discussion on considerations for separating design-phase 'analyses' from study analyses. For example, ICH could provide further assurance by stating analyses may be performed in a 'blinded' manner to address all manner of design questions, and then with what ever adjustments implemented, the hypotheses are tested formally on the unblinded data - with no concerns about the integrity of the study are expressed even though there may have been iterative explorations on the same dataset prior to the hypothesis test step.	
EFPIA	837	864	6	Review the numbering of this section and ensure it is consistent with the style used in other sections. It is unclear why "Data Management Plan" and "Quality Assurance and Quality Control" are not numbered. On the contrary, "Data Holder" and "Researchers" seem to be subsections within the QA and QC section.	Check formatting.
EFPIA	845	850		Guideline should provide additional data consideration - for example from FDN - which can never be 'provided' as datasets for submission. Further, such datasets may not even be preserved entirely by the FDN, where such datasets 'evolve' within new patients entries and some patient exits (eg. Changing insurance plan). Consequently, the only information likely to be available / submitted is the codes used to examine data in the FDN. Is this not sufficient, assuming the Regulator would be afforded equal 'remote' access to use the submitted code? Would this not apply to analyses conducted via the DARWIN-EU network too?	
Medicines for Europe	858	858	6	Data protection/privacy should also be maintained and mentioned in this section.	
EFPIA	871	892	6.2	We would like to request more clarity on the role of researchers in secondary data use registry-based studies. The current descriptions of the roles and responsibilities of researchers in the current document are more appropriate in RWD sources where the researcher has direct access to patient-level data, and can perform analysis on the data. In some registry-based studies, registry governance does not allow data transfer to third-parties, and a marketing authorization holder may not be able to fulfill all the roles and responsibilities defined in section 6.2. For instance, responsibility for the "management and quality assurance of all data cleaning, processing, and analytic datasets" is still under the control of the data holder.	We would suggest the addition of a subsection that describes roles and responsibilities of data holders that perform analyses on behalf of researchers, with examples of use cases / data access models that warrant this model.
ISPE	871	892	6.2	This section does not differentiate between researchers with access to the data and researchers without access to the data. Some clarification regarding the different types of researchers and how their responsibilities may differ would improve the section.	Add additional text to reflect different types of researchers and differences in responsibilities.
EFPIA	899	902	7	We agree that the SAP concept needs to be concurrently developed with the protocol. However, for certain RWD use cases, it may be challenging to provide and submit the SAP concurrently with the protocol. A specific example would be the use of patient registries for a post-authorization safety study (PASS) of a first-in-class treatment. In such a case, most natural history registries may require an augmentation of both the data collection infrastructure and processes to accomodate treatment-related safety data collection. While knowledge of the data collection infrastructure and processes permit researchers to identify potential biases and limitations from the data source, a full evaluation of the analyses that are ultimately possible can be gleaned once the data starts being collected. In such a case, the SAP may co-evolve with the study. In such cases, we would welcome an allowance for a staged development of the SAP, rather than a concurrent development and submission with the protocol. Finally, we would welcome suggestions for a SAP template for RWD studies.	An overview of the *statistical analysis plan (SAP)* should be provided in the protocol. Where possible, the complete SAP should be provided as a standalone document, or as a detailed section of the protocol.
EUCOPE	899	900	7	We suggest that the agency consider clarifying that the statistical analysis approach should be outlined in the protocol, and the details of the plan should be spelled out in the SAP.	An overview of the statistical analysis approach should be provided in the protocol. A complete statistical analysis plan (SAP) should be…

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
RTI Health Solutions	901	901	7	To this point, the document mostly emphasizes estimation rather than testing. We consider this to be a strength of the document. We think that it is important to clarify proactively, early in the critical areas of the Analysis section for the appropriate planning and interpretation of statistical analyses.	Insert in L901 after "section of the protocol" : "The SAP should include all the contrasts between exposures and outcomes, and within subgroups. The SAP and report of the study should elaborate on the full set of contrasts planned and undertaken so that readers understand the universe of statistics from which the reported results emerged and its sequence, before or after reviewing study results. Statistical significance testing, and statistical significance-like interpretation of confidence intervals, and mechanical adjustments for multiple comparisons (such as Bonferroni adjustments) are not recommended because these interpretations lack nuance and lead to errors."
EFPIA	903	904	7	The document states that "the SAP should provide sufficient detail to allow replication of the study to help ensure confidence in the results". It is unclear whether the analytic codes also be submitted in the completed SAP or in the QC documentation?	clarify where the analytic codes should be submitted to ensure that the study can be replicated
EFPIA	911	913		This 'timeline' approach to the analytical trial is a useful protection and should be encouraged in the context of 'design-level' analytics, vs a priori and post-hoc analyses as distinguished in the analysis section.	
EFPIA	918	936	6.2	Estimands are mentioned on line 140 and 951, consider also addressing Section 7.1 Statistical analysis (line 918 and below).	Please see under comment and rationale
Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University	918	959	7.1	The subsection Missing data seems to be out of place here.	The section should have subheadings "Descriptive analyses", "Primary analyses", "Secondary analysis", "Exploratory analyses", "Sensitivity and post-hoc analyses".
EFPIA	919	935	7.1.1	Add recommendation regarding justification of methods. For example, the use of matched PS vs IPTW	Add examples of methods and, if needed, suggestion for justification
ISPE	919	930	7.1	It would be helpful to include information regarding the sample size calculation. The estimated required sample size will help shape the feasibility assessment. The sample size calculation should consider losses to follow-up and potential for misclassification. It would also be helpful to include language regarding the selection of the detectable measure of association in comparative studies. There is a trade-off between the available sample size and the detectable level of risk.	Revise to include more guidance on sample size calculations relative to minimal detectable risk, including considerations of loss to follow-up and potential misclassification.
EFPIA	920	921	7.1.1	Based on the ICH-E9 principles, one should consider the full estimand (population, treatment(s), variable, intercurrent event, and summary measure) as a target of the analysis, not only the summary measure. This statement holds true for the primary and secondary analyses.	Rephrase to "Each analysis should be directed towards the unbiased estimation of its target estimand of interest. That is, the estimation with different analyses should align with the research question (Section 4.1)". This sentence should be moved to above section 7.1.1 as it is a governing principle for all analyses, and not only primary analyses.
IQVIA	924	924	7.1.1	Primary Analysis. The draft guideline states, "The following aspects and elements may be considered for inclusion…" This is a robust list of elements that should be considered imperative for the sponsor to consider.	We recommend changing the "may be" to "should."
EUCOPE	925	929	7.1.1	In Section 7.1.3 below, sensitivity analysis is mentioned as a separate section. We ask that the agency consider whether the contents related to subgroup/sensitivity analysis should be consolidated under the sensitivity analysis section rather than being included in both the primary analysis section and sensitivity analysis section.	
Medicines for Europe	929	929	7.1.1	Mention of "Type II error" is proposed here.	
RTI Health Solutions	929	929	7	Refer to comment and proposed text in line 901, with respect to the emphasis of estimation over statistical significance/hypothesis testing	Remove "type I error control (e.g. for sequential analyses)"

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
RTI Health Solutions	933	933	7.1.1	"Whether the algorithm was supervised (i.e., using input and review by experts) or unsupervised": this is not the standard definition of a supervised algorithm. Consider this definion from and FDA-issued document "Machine learning can occur using two different methods—supervised or unsupervised. In supervised learning, the data is labeled and tells the machine what patterns it should identify. Most ML applications use supervised learning which require a training dataset for which the outcome variable (e.g., disease state) is known. Unsupervised learning does not have labeled data, so the goal is to infer the natural structure present within a dataset." Source: https://www.fda.gov/media/151482/download	Please revise the text, removing the terms supervised and unsupervised, as follows, "...whether the algorithm received input or was reviewed by content (eg, clinical) experts, and specify the input or review process,…"
IQVIA	940	943	7.1.2	Missing Data. The draft guideline states, "Descriptive analyses should be included to characterize missing data." However, it is unclear what information is intended. It may be useful to explain that a systematic count of the number of missing data poin	We recommend clarifying what kinds of descriptive information are needed to characterize missing data.
Euromedicat Steering Group	946			L946 should add: Where missing data have been imputed, a sensitivity analysis without imputation should be reported.	
EUCOPE	954	959		It could be advantageous for the agency to broaden the scope of the QBA section of the guidance to acknowledge methods such as the e-value rather than approaches dependent on assumptions around prespecified parameters alone. We ask that the agency expand upon QBA analyses and their purpose.	
EFPIA	960	971	8.1	It is recommended that guidance be provided on the reporting of AEs under competing risk events e.g. if death occurs or withdrawal from the study (a short follow up), etc.	Please see under comment and rationale
EFPIA	961	971	8.1	It is not clear how this section is linked to the scope of this document. How or why would adverse events (AE), adverse drug reactions (ADR), or similar events be identified in this type of study, particularly when such variables were not mentioned in the variables of interest in previous sections? There is a lack of clarity in this regard. Providing some examples might help researchers understand whether they need to include a section to review these events within their study or if they should conduct an active search in the database for event outside the research question.	Please add an illustrative example.
H. Lundbeck A/S	961	971	8.1	Reporting and Submission: It is unclear how this section is relevant to the scope of this document and how adverse events (AE), adverse drug reactions (ADR), or product complaints and similar events should be identified in an observational study.	The draft guidance should include some examples of when an AE might be generated during primary data collection versus when they cannot be identified. This would help researchers understand whether they need to include a section in their study to review and summarize these events.
EFPIA	963	964	8.1	Propose amending the sentence to ensure 'special situations' are accommodated in the text	Adverse events, adverse drug reactions, special situations with or without an AE and product quality complaints identified during the conduct of a study…
EUCOPE	963	964	8	Original text: "Adverse events, adverse drug reactions, and product quality complaints identified during the conduct of a study may require reporting to the relevant regulatory authority."	Recommend the following revision: "Adverse events, adverse drug reactions, other observations and product quality complaints identified during the conduct of a study may require reporting to the relevant regulatory authority."
VAC4EU	963	963	8.1		Please clarify how product quality complaints would be identified in RWD studies?
EFPIA	974	976	8.2	There are many published guidelines regarding the format and content of study documents. For example, PASS information for the EU: https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/post-authorisation-safety-studies-pass. It might be better to suggest that teams consider published information before consulting with regulators. As it is currently written, the discussion with regulators is the first suggestion.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
H. Lundbeck A/S	974	979	8.2	In the absence of specific formatting and content required by regulators, it is suggested that sponsors may utilize frameworks developed by the scientific community as a guide for document development and reference is made to HARPER as an example. However, the HARPER protocol template was intended is for secondary data database studies, not for primary data studies.	The guidance should provide reference to a framework for formatting of study documents pertaining to studies with primary data collection.
EFPIA	975	979	8.2	As written the text could imply that individual regulators within a given jurisdiction determine submission requirements. It should be clarified that such requirements are determined a priori based on applicable regulatory requirements.	These documents may vary by regulator based on applicable regulatory requirements, can include the feasibility assessments, protocol, analysis plan, and interim In the absence of specific formatting and content required by regulators based on applicable regulatory requirements, sponsors may utilize frameworks developed by the scientific community as a guide for document development, such as ISPE/ISPOR's HARmonized 978 Protocol Template to Enhance Reproducibility (HARPER) [1, 5].
EFPIA	976	979	8.2	We welcome the suggestion of using HARPER as a guiding framework. However, depending on the scientific question, modifications may need to be made to this framework. We have noted for instance, that ENCePP is not fully integrated with HARPER. Would it be possible to have clarity on whether the ICH workstream compared across available protocol templates?	
EFPIA	983	985	9	Statistical analysis plans are typically submitted/posted at the end of the study with the results on most registries.	Proposed revision: "It is encouraged that the protocol ~~and statistical analysis plan~~ be made publicly available in appropriate registers before study initiation and study reports *and statistical analysis plans* upon completion."
EFPIA	983	985	9	Discussions about transparency are not considered to be within the scope of ICH guidelines. Note that while we agree that research transparency is important for good science and to support the credibility of RWE beyond statutory requirements, such disclosure is voluntary. Although the guideline states that such disclosre is encoraged rather than being mandatory, for clarity, this should be emphasised in the text.	It is encouraged that the protocol and statistical analysis plan be made publicly available in appropriate registers before study initiation, and study reports upon completion. However, beyond statutory requirements such disclosure is determined at the discretion of the sponsor.
EFPIA	983	985	9	Consider adding that publicly posted documents should be redacted to remove confidential information. Also consider that a SAP might not be finalized prior to study start. For example, there are cases where regulators request SAPs. In those cases, the study often starts before the SAP is finalized.	Add additional text
EFPIA	983	987		We support public disclosure, but guidance should indicate that protocol/SAP may evolve during the 'design-phase' exploration of the data source, so publishing the protocol/SAP may in fact be more 'contemporaneous' with the conduct of the study - rather than 'before' initiation - a phrase that is somewhat unhelpful since 'initiation' is even prior to the protocol being reviewed and approved let alone the SAP which may be 'tailored' specifically in light of emerging data understanding. The timelines are more compressed with RWE, since prospective studies afford time for protocols to be finalised and published before patients enrol, and usually several years can go by before analysis and study reports are available. RWE studies are more compressed in time, and subject to evolution as data are employed in the feasibility and then hypothesis testing phases - all of which may be within weeks of one-another precluding the ability to 'published' sufficiently in 'advance' of starting.	Perhaps a high-level protocol/SAP might be communicated, or even just the Research question and basic provisions of the datasource timelines etc. Protocols/SAPs should be documented and date stamped prior to unblinded analysis, and study reports should capture all the twists and turns - with dates - that have ensued.
EUCOPE	983	985	8	Original text: It is encouraged that the protocol and statistical analysis plan be made publicly available in appropriate registers before study initiation, and study reports upon completion.	It would be helpful to provide examples of registers for making the protocol and statistical analysis plan publicly available (e.g., HMA-EMA Catalogue of RWD studies).
Euromedicat Steering Group	983			L983 I suggest public availability be 'mandated', rather than 'encouraged'.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
ISPE	983	985	9	It is important to consider that publicly posted documents should be redacted to remove confidential information. Further, a SAP might not be finalized prior to study start (e.g. when the first phase of a study is simple descriptive exposure monitoring) and depending negotiations with health authorities.	Revise text to acknowledge importance of redaction prior to protocol posting and some instances of expected lag in SAP finalization/posting relative to study start.
EFPIA	997	1001	9		Proposed revision: "Results of the research should be communicated to the study participants (for example, via the participating research sites when primary data collection is used. The lay language results should also be made available to the public, and patients via posting in public registries, so that they may be aware of and understand the study results and their implications. The lay language result Communications should include a factual summary of the overall study design and results in an objective, balanced and nonpromotional manner., including relevant safety information and any limitations of the study.
Euromedicat Steering Group	997			L997 – If results are based on studies using population-based RWD, then it is more difficult to disseminate the study findings. Also, if publishing results of a potential signal based on one study, need to include statement saying that the results need to be confirmed in an independent dataset.	
Medicines for Europe	999	999	9	Information on "Potential conflict of interest" is missing in this section.	
EFPIA	1004	1007	10 Study Documentation	"Key principles for studies utilizing RWD in post-marketing safety studies are similar to those for GCP (especially for primary data) and Good Pharmacoepidemiological Practice (especially for secondary use of data)." - Suggest stating this at the begining/Intro of this guideline, since this information is applicable to all sections - not only documentation and record retention - Also, since this is an international Harmonization guideline, suggest including the GVP module VIII as refence in several applicable sections of this guideline.	As suggested in the Comment Column.
EFPIA	1023	1025	11	Propose including "patients with severe renal / hepatic impairment" as they are also common excluded from pre-approval clinical trials	Specific (special) populations are often not enrolled in pre-approval clinical studies and include pregnant and lactating people, infants, children, adolescents/young adults, older adults, immunocompromised patients, patients with severe renal/hepatic impairment, and people with disabilities and/or rare disorders.
Euromedicat Steering Group	1033			Line 1033. Include ConcepTION D1.2 Core data elements in references.	
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	1033	1066	11.1	It is unclear for us why in a guideline "on general principles" the specific challenges of pregnancy studies are described. It should be considered to delete this section.	Please consider to delete Section 11.1 on pregnancy studies.
IQWiG	1033	1066	11.1	It is unclear for us why in a guideline "on general principles" the specific challenges of pregnancy studies are described. It should be considered to delete this section.	Please consider to delete Section 11.1 on pregnancy studies.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
RTI Health Solutions	1033	1066	11.1	In Obstetrics, gestational age is measured from the first day of the last menstrual period (not from conception). The clinical definition of a preterm or term delivery is counted from LMP. If one were to count from conception, the threshold for preterm delivery should be 35 weeks from conception instead of the universally accepted 37 weeks from LMP. The standard duration of pregnancy would need to be stated as 37/38 weeks from conception instead of the universally accepted 39/40 weeks from LMP. Lines 1043/44 state "measurement of both conception and pregnancy start dates". This text indicates that conception is not pregnancy start. For consistency of pharmacoepidemiologic studies with Obstetrics, pharmacoepidemiologic studies should also use LMP as the pregnancy start date. Which concept is used as pregnancy start date (eg, LMP, conception) should be stated in the protocol. Sources: ACOG - https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2013/11/definition-of-term-pregnancy RCOG - https://www.rcog.org.uk/for-the-public/a-z-of-medical-terms/ FIGO - https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/ijgo.15113 EMA - Guideline on the exposure to medicinal products during pregnancy: need for post-authorization data (Annex 4), 2005, https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-exposure-medicinal-products-during-pregnancy-need-post-authorisation-data_en.pdf EMA - HMA-EMA GVP module III, 2019, https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-good-pharmacovigilance-practices-product-or-population-specific-considerations-iii-pregnant-and-breastfeeding-women_en.pdf	Please replace "conception" with "last menstrual period", “LMP” or "first day of last menstrual period" in this section.
H. Lundbeck A/S	1034	1066	11.1	Pregnancy Studies: This section acknowledges the inherent challenges of conducting a pregnancy registry study including recruitment challenges and retention of paticipants. However, there is no discussion or guidance provided to industry on acceptable innovative ideas/solutions to ensure successful and timely completion of these studies. Given the methodological challenges associated with conducting pregnancy studies (selection bias in relation to enrollment and retention, long study duration) and the desire to obtain safety data on preganancy exposure quickly to guide prescribers decision making, the guidance is recommended to include examples of innovative scientific approaches which may address these challenges, incl. addressing challenges on selection bias.	The guidance is recommended to provide alternative innovative scientifically sound proposals for approaches that could potentially be acceptable to health authorities within regulatory boundaries, while protecting the study data integrity.
EFPIA	1036	1036	11.1.	Outcomes in pregnancy safety studies are mentioned but "pregnancy safety outcomes" (e.g. spontaneous abortion) are missing. Consider adding them to the enumeration.	Consider adding pregnancy outcomes as follows:"…. , and maternal, pregnancy, and infant outcomes"
Euromedicat Steering Group	1038			Line 1038. Insert “and birth defect registries”.	
IQVIA	1038	1040	11.1	Pregnancy Studies. The draft text describes pregnancy registries as being challenged by enrollment, retention, and selection issues and discusses the frequent need to link existing data sets, within the data source (e.g., mother-child link) and/or with complimentary data sets (e.g., birth registries). It does not explain, however, that registries used for assessing product safety in regulatory decision-making often require primary data collection to provide sufficient details pertaining to selected diseases or drug classes.	We recommend describing how pregnancy registries often need to include primary data collection in order to obtain sufficient details, especially with regards to selected diseases or drug classes.
Euromedicat Steering Group	1045			L1045 – consideration should also be given to the type of birth (live birth, foetal death or termination of pregnancy for foetal anomaly). Also, gestational age would normally be recorded in maternity data.	
Euromedicat Steering Group	1045	1046		Line 1045-6. “A valid estimate of gestational age, from which a conception date may be estimated, is critical for determining the timing of exposure and may require availability of linked data such as ultrasound or laboratory data”. Insert “gestational age at birth”. This does not require linkage with ultrasound or laboratory data, but instead with maternity data.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	1046	1047	11.1.	The sentence “may require availability of linked data such as ultrasound or laboratory data” may be misleading because it suggests that linkage is the solution but in fact, the relevant part is that US or laboratory data is available, through linkage or not. Estimates based on foetal biometric measures from ultrasound scans (USs) are increasingly used to estimate gestational age. It is suggested to clarify this in the text.	Consider replacing “may require availability of linked data such as ultrasound or laboratory data” by “May require availability of foetal biometric measures from ultrasound scans (USs) or from laboratory data. Such US or laboratory data might be obtained through linkage with other RWD sources and can used to confirm or adjust date of Last Menstrual Period (LMP).”
EFPIA	1049	1050	11.1.	The sentence “Exposure information in the time period just before pregnancy is often also important, especially for products with a long half-life” is not completely correct. A drug with a short half-life taken closely to date of start of pregnancy can be also harmful. Some more detail about how to calculate the risk window before pregnancy is appreciated.	Consider replacing the sentence “Exposure information in the time period just before pregnancy is often also important, especially for products with a long half-life” by “The risk windows prior to pregnancy might vary according to the medicine and it is influenced by the elimination half-life of the medicine. This parameter allows to estimate the exact duration of the exposure (which usually corresponds to the period of the medication intake + the 7 elimination half-lives that are necessary to eliminate 99% of the dose) (Dasgupta, 2020). Potential metabolites along their half-lives have also to be considered” Complete reference is: Dasgupta, A, Krasowski, MD. Pharmacokinetics and therapeutic drug monitoring. Therapeutic Drug Monitoring Data. 4th edition. Elsevier, 2020: 1–17.
EFPIA	1051	1052	11.1.	Relevant pregnancy outcomes are missing in the list. Spontaneous abortion is listed as stand-alone but it is a pregnancy outcome. Ectopic pregnancy is also relevant. Stillbirth is not mentioned and it is assumed that it is included in birth outcomes. Considering adding pregnancy outcomes (sponatenous abortion, ectopic pregnancy), birth (stillbirth, livebirth), neonatal outcomes,...	Consider replacing "spontaneous abortion, birth/neonatal" by "pregnancy outcomes (spontaneous abortion, ectopic pregnancy), birth (stillbirth, livebirth, preterm birth, small for gestational age), neonatal,..."
IQVIA	1053	1056	11.1	Pregnancy Studies. This section states that definition of outcomes should include disease severity, however, it should also include the dimension of granularity, which is dependent upon sample size, (e.g., stratification, splitting, grouping).	We recommend adding granularity to the definition of outcomes (i.e., organ specific major congenital malformations [CMs], or any major CMs; preterm birth or split into different gestational groups).
EFPIA	1056	1056	11.1.	The guideline states that ". The protocol should state a priori criteria for defining the outcomes of interest, including their severity (e.g., major birth defect)," but the example of congenital anomalies deserves some more detail. As specified in the Postapproval Pregnancy Safety Studies Guidance for Industry, Criteria for defining birth defects as major should be clearly stated. Similarly, criteria should be established for abnormalities that will be excluded from the definition of outcomes (e.g., those that are minor, transient, chromosomal abnormalities, genetic syndromes, positional defects, prematurity related) (Holmes and Westgate 2011). This is really important and in many protocols it is not clear what exactly how major congenital anomalies are defined and what is excluded.	consider adding : "Criteria for defining birth defects as major should be clearly stated as well as those abnormalities that will be excluded from the definition of this outcome (e.g., those that are minor, transient, chromosomal abnormalities, genetic syndromes, positional defects, prematurity related) (Holmes and Westgate 2011). Complete reference: Holmes, LB and Westgate MN, 2011, Inclusion and Exclusion Criteria for Malformations in Newborn Infants Exposed to Potential Teratogens, Birth Defects Research (Part A), 91:807–812.
Euromedicat Steering Group	1062			Line 1062. Replace “elective terminations” with “terminations for fetal anomaly”.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Euromedicat Steering Group	1062			L1062 – If a pregnancy was terminated due to a CA, ICD does not have specific codes to classify these CAs in the mother's record. Also, if a pregnancy was terminated due to a CA, the foetus will not have a health record number in healthcare databases in order to be identified. Ability to identify TOPFA is essential for pharmacoepidemiologic studies in pregnancy; therefore specialist data sources such as EUROmediCAT are required to identify TOPFA cases (Garne et al 2022, Bakker et al 2023) these.	
EFPIA	1063	1063	11.1	Many infant outcomes beyond MCMs may be recorded in either or both mother and infant records. All infant outcomes should be assessed in feasibility analysis to ensure the data are extracted from the best source	Consider stating "MCMs and other infant outcomes may be recorded…"
Euromedicat Steering Group	1065			Line 1065. Confounding by indication is not specific to pregnancy studies, but a general consideration in all pharmacoepidemiology.	
Euromedicat Steering Group	1066			L1066 add 'co-exposures', including substance or alcohol misuse.	
Medicines for Europe	1067	1067	12	Please consider to add data protection/data privacy, data validity (external).	
VAC4EU	1067	1067	12		Would a section summarising the overall document be an appropriate conclusion before the Glossary?
EFPIA	1070	1071	12	Definition of Bias: This definition is unclear and not consistently applied throughout the document. What does "deviation" or "the truth" mean in this context? Are we putting emphasis on testing rather than estimation? The wording deviation and distortion encompasses changes in mean and uncertainty. Note that the proposed definition are biases related to internal validity rather biases related to external validity.	We recommend using one of the following definitions and cross-references to examples of bias discussed in the document. The ICH E9 definition ("Bias describes the systematic tendency of any factors associated with the design, conduct, analysis, and interpretation of the results of clinical trials to make the estimate of a treatment effect deviate from its true value") the Robins'I tool definition "Systematic deviation or distortion of the estimated treatment effect from its true (estimand) value."
EFPIA	1070	1071	12	Definition of Estimand: The term 'estimand' is used in and can be defined in observational studies, but because the definition reported in the glossary is from clinical trials, it is not immediately clear how it applies to ICH-M14. We also note that this term appears only 3 times in the document when it is the target of the inference driving the data selection, feasibility, study design, and analyses.	Provide a definition that can be applied to observational studies. For example, in Chen, J., Scharfstein, D., Wang, H., Yu, B., Song, Y., He, W., … Lee, H. (2023). Estimands in Real-World Evidence Studies. Statistics in Biopharmaceutical Research, 16(2), 257–269. https://doi.org/10.1080/19466315.2023.2259829
EFPIA	1070	1071	12	Definition of Confounding: The definition is not precise, it could apply to a common cause of exposure and outcome (confounder) or a common consequence of exposure and outcome (and conditioning on that would lead to selection bias).	Suggest considering the non-technical definition by the journal of clinical epidemiology "Confounding bias is The distortion of a measure of the effect of an exposure on an outcome due to the association of the exposure with other factors that influence the occurrence of the outcome. Confounding occurs when all or part of the apparent association between the exposure and the outcome is in fact accounted for by other variables that affect the outcome and are themselves not affected by the exposure." (reference: Bours, Martijn JL. "A nontechnical explanation of the counterfactual definition of confounding." Journal of Clinical Epidemiology 121 (2020): 91-100.)

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	1070	1071	12	Definition of Target Trial: A common citation from the literature is missing from this document.	Consider including the following citation: Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016 Apr 15;183(8):758-64. doi: 10.1093/aje/kwv254. Epub 2016 Mar 18. PMID: 26994063; PMCID: PMC4832051. Or more recently MA Hernán (2021) Methods of Public Health Research – Strengthening Causal Inference from Observational Data. N Engl J Med 2021;385;1345-1348. DOI: 10.1056/NEJMp2113319 MA Hernán, W Wang, DE Leaf (2022) A Framework for Causal Inference from Observational Data. JAMA 2022;328(24);2446-2447. DOI: 10.1001/jama.2022.21383
EFPIA	1144	1153	13	We have noted that several concepts on data quality may have been derived from documents that may not have been referenced in the guideline (e.g., "Determining Real-World Data's Fitness for Use and the Role of Reliability" from the Duke-Margolis Center for Health Policy 2019). Furthermore, we have noted that there are no references to the recently-released HMA EMA Data Quality Framework for EU medicines regulation, which may cause some confusion on which data quality metrics should be applied in the evaluation of fitness-for-purpose. While we acknowledge that the harmonization of data quality terminology, definitions, and guidelines is likely beyond the scope of the current work, further clarification on the provenance of key data quality concepts (e.g., data accrual) will provide readers with guidance on what exactly is meant.	We would suggest the addition of the definition of data quality-related terms to the glossary. We would also encourage a statement on how the HMA EMA Data Quality Framework for EU medicines regulation, including the upcoming RWD annex, should be used interoparably with ICH M14. The example below is for purposes of illustration: Data accrual: Data accrual refers to how data are collected, assesssed through the operational manual or other documentation that pre-specifies the data elements to be collected, data element definitions (i.e., data dictionary to provide a common definitional framework), methods for data aggregation and documentation (e.g., common case report form, abstraction from verifiable sources), and the relevant time windows for data element collection (i.e., common temporal framework). Note that some RWD sources such as EHRs or claims data may not fulfill all of these characteristics. From "Determining Real-World Data's Fitness for Use and the Role of Reliability" from the Duke-Margolis Center for Health Policy 2019)
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	1144	1153	14	The listed non-regulatory guidelines are incomplete. Sometimes only the name of the statement is given (e.g., RECORD statement). The full references should be provided.	Provide the complete data for the references. For example, the full reference for the RECORD statement is the following: "Benchimol EI, Smeeth L, Guttmann A et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med 2015; 12(10): e1001885."

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
International Society for Clinical Biostatistics, ISCB; Statistics in Regulatory Affairs Subcommittee	1144	1153	14	The list of non-regulatory guidelines contains only 4 references. We propose to add further important non-regulatory guidelines such as STROBE and TARGET.	Please consider to add the following references: (1) von Elm E, Altman DG, Egger M et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. Ann Intern Med 2007; 147(8): 573-577. (2) Vandenbroucke JP, von Elm E, Altman DG et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. Ann Intern Med 2007; 147(8): W163-W194. (3) Fortier I, Raina P, Van den Heuvel ER et al. Maelstrom Research guidelines for rigorous retrospective data harmonization. Int J Epidemiol 2017; 46(1): 103-105. (4) Hansford HJ, Cashin AG, Jones MD et al. Development of the TrAnsparent ReportinG of observational studies Emulating a Target trial (TARGET) guideline. BMJ Open 2023; 13(9): e074626.
IQWiG	1144	1153	14	The listed non-regulatory guidelines are incomplete. Sometimes only the name of the statement is given (e.g., RECORD statement). The full references should be provided.	Provide the complete data for the references. For example, the full reference for the RECORD statement is the following: "Benchimol EI, Smeeth L, Guttmann A et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med 2015; 12(10): e1001885."
IQWiG	1144	1153	14	The list of non-regulatory guidelines contains only 4 references. We propose to add further important non-regulatory guidelines such as STROBE and TARGET.	Please consider to add the following references: (1) Digitale JC, Martin JN, Glymour MM Tutorial on directed acyclic graphs. J Clin Epidemiol 2022; 142:264-267. (2) Fortier I, Raina P, Van den Heuvel ER et al. Maelstrom Research guidelines for rigorous retrospective data harmonization. Int J Epidemiol 2017; 46(1): 103-105. (3) Hansford HJ, Cashin AG, Jones MD et al. Development of the TrAnsparent ReportinG of observational studies Emulating a Target trial (TARGET) guideline. BMJ Open 2023; 13(9): e074626. (4) Hernán MA, Sauer BC, Hernandez-Diaz S, Platt R, Shrier I Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol 2016; 79:70-75.

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
IQWiG	1144	1153	14	The list of non-regulatory guidelines contains only 4 references. We propose to add further important non-regulatory guidelines such as STROBE and TARGET.	(5) Vandenbroucke JP, von Elm E, Altman DG et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. Ann Intern Med 2007; 147(8): W163-W194. (6) von Elm E, Altman DG, Egger M et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. Ann Intern Med 2007; 147(8): 573-577. (7) Webster-Clark M, Stürmer T, Wang T et al. Using propensity scores to estimate effects of treatment initiation decisions: State of the science. Stat Med 2021; 40(7): 1718-1735. (8) Yao XI, Wang X, Speicher PJ et al. Reporting and guidelines in propensity score analysis: A systematic review of cancer and cancer surgical studies. J Natl Cancer Inst 2017; 109(8): djw323.
IQWiG	1239	142	4.1	Both the target trial approach as well as the estimand framework are mentioned as examples for "a principled framework for study design". However, both concepts reflect the state-of-the-art approaches. The estimand framework, presented in the ICH E9 addendum referenced in the glossary, describes the statistical principles for conducting randomized clinical trials. On the other hand, the target trial emulation, proposed by Hernán and Robins, is a well acknowledged approach to translate causal question to non-randmized situations.	The importance of both state-of-the-art approaches (estimand and target trial) should be highlighted by summarizing and discussing these in an additional introducing paragraph in Section 4.
Euromedicat Steering Group	Figure 1			Figure 1 starts the process with a specific signal. But what about signal detection using real world data (RWD)? And how should researchers decide which signal to investigate?	
AESGP			5.2	In general, the guidance should pre-empt the availability of technologies in current adoption stage and provide a position/viewpoint as to their likely acceptability in Regulatory pathways. These technologies are those not using real patients but models effectively able to create a synthetic population or patient clones from pre-existing data. These may also be used as potential control options.	
EFPIA		826	5.6	What is the relationship between validation studies and feasibility assessments? Given that a validation should be completed in a separate protocol, does this place limits on the study design that the study pharmacoepidemiology protocol can propose? For example, if there is limited information regarding validity of an outcome in administrative claims, is this document suggesting a primary data collection study should be conducted until validation studies are completed? Perhaps this recommendation changes depending on the context. For example, if a proposed pharmacoepi study evaluates a malignancy outcome, perhaps a full study protocol could reasonably be delayed until results of a validation study are obtained given the long latency of cancer. The recommendation may be different in the context of an infectious disease epidemic and an acute outcome.	Please clarify the relationship between protocol development including a "fit for purpose assessment" and validation studies particularly within the context of regulated timelines and protocol expectations . Practical considerations and suggestions would be quite helpful.
EFPIA			7	Section 5.4.3 discusses considering effect modifiers, if any, however, the analysis section does not mention the importance of using these variables in the analysis.	add "effect modifiers" to the analysis section
Euromedicat Steering Group				Figure 1 and the text with it also suggests one should not choose the question that suits the data, but undertake a scan of all potential data sources, given a specific signal, and then choose appropriate data sources. That is unrealistic. Researchers may choose the signals (among many) that suit their data source(s) to investigate. Moreover, later (line 193) it is acknowledged that researchers may choose data sources (from their scan of all sources) that they know best for a quicker study.	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Euromedicat Steering Group				L717 I would suggest that the use of Directed Acyclic Graphs (DAGs) should be proposed to enable confounding and effect modification to be systematically evaluated. I see they are mentioned on L804, but would mention earlier on.	
Euromedicat Steering Group			9	Section 9 didn't mention the ENCePP code of conduct.	
Euromedicat Steering Group			1.1	11.1 Pregnancy Studies	
Euromedicat Steering Group				There is no mention of breastfeeding. A section on 'Breastfeeding Studies' be added, to reflect developments in the literature, for example in the ConcepTION study (Jordan et al. 2022, 2023).	
Euromedicat Steering Group				L1038 – maternity records/medical birth registries should be included here, as these would have information on all pregnant women (as opposed to pregnancy registers).	
Euromedicat Steering Group			Glossary	Page numbers and links for the references are needed. https://members.imi-conception.eu/Login?returnurl=%2fMember-Area%2fWork-Package-1%3ffolderId%3d5702%26view%3dgridview%26pageSize%3d10 Medicine is defined, but in the document the term used is 'medication'. This should be added to the glossary. References to above: - Bakker MK, Loane M, Garne E et al. Accuracy of congenital anomaly coding in live birth children recorded in European health care databases, a EUROlinkCAT study. Eur J Epidemiol (2023). https://doi.org/10.1007/s10654-023-00971-z - Dolk H, Damase-Michel C, Morris JK, Loane M. COVID-19 in pregnancy-what study designs can we use to assess the risk of congenital anomalies in relation to COVID-19 disease, treatment and vaccination? Paediatr Perinat Epidemiol. 2022 Jul;36(4):493-507. doi: 10.1111/ppe.12840. Epub 2022 Mar 2. PMID: 35234297; PMCID: PMC9115419. - Elwert F, Winship C: Endogenous selection bias: The problem of conditioning on a collider variable. Annu Rev Sociol 2014, 40:31-53 - Fisher, R., Dunn, P., Asaria, M., & Thorlby, R. (2020). Level or not? Comparing general practice in areas of high and low socioenconomic deprivation in England The Health Foundation. https://www.health.org.uk/publications/reports/level-or-not https://reader.health.org.uk/level-or-not - Garne, E., Urhoj, S. K.,Bakker, M., Gissler, M., Given, J., Heino, A., Limb,E., Loane, M., de Walle, H., & Morris, J. (2022).The quality and the accuracy of codes for terminations of pregnancy for fetal anomalies recorded in hospital databases in three countries in northern Europe. Birth Defects Research, http://dx.doi.org/10.1002/bdr2.2133 - Griffith GJ, Morris TT, Tudball MJ, Herbert A, Mancano G, Pike L et al: Collider bias undermines our understanding of covid-19 disease risk and severity. Nat Commun 2020, 11(1):5749 - Jordan S, Bromley R, Damase-Michel C, Given J, Komninou S, Loane M, Marfell N, Dolk H. Breastfeeding, pregnancy, medicines, neurodevelopment, and population databases: the information desert. Int Breastfeed J. 2022 Aug 2;17(1):55. doi: 10.1186/s13006-022-00494-5. PMID: 35915474. https://internationalbreastfeedingjournal.biomedcentral.com/articles/10.1186/s13006-022-00494-5 - Jordan S, Komninou S, Lopez Leon S (2023) Where are the data linking infant outcomes, breastfeeding and medicine exposure? A systematic scoping review. PLOS ONE 18(4): e0284128. https://doi.org/10.1371/journal.pone.0284128	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Euromedicat Steering Group			Glossary	References continued: - Khezrian, M., McNeil, C. J., Murray, A. D., & Myint, P. K. (2020). An overview of prevalence, determinants and health outcomes of polypharmacy. Therapeutic Advances in Drug Safety, 11, 204209862093374-2042098620933741. - Mur J, Cox SR, Marioni RE, Muniz-Terrera G, Russ TC. Increase in anticholinergic burden from 1990 to 2015: Age-period-cohort analysis in UK biobank. Br J Clin Pharmacol. 2022 Mar;88(3):983-993. doi: 10.1111/bcp.15045. Epub 2021 Sep 19. PMID: 34409635. - Payne RA, Abel GA, Guthrie B, Mercer SW. The effect of physical multimorbidity, mental health conditions and socioeconomic deprivation on unplanned admissions to hospital: a retrospective cohort study. CMAJ. 2013;185(5):E221-8. - Sackett DL (1979) Bias in analytic research. J Chronic Dis 32(1-2): 51-63.	
ISPE		826	5.6	Further clarification between validation studies and feasibility assessments is needed. Given that a validation should be completed in a separate protocol, does this place limits on pharmacoepidemiology study design? For example, if there is limited information regarding validity of an outcome in administrative claims, when and how would it be decided if a primary data collection study should be conducted until validation studies are completed? Would this recommendation vary depending on the context. For example, when studying a malignancy outcome, perhaps a full study protocol could be delayed until results of a validation study are obtained given the long latency of cancer vs an infectious disease epidemic and an acute safety outcome of interest?	Please clarify the relationship between protocol development including a "fit for purpose assessment" and validation studies, including practical considerations and suggestions relevant to context.