EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000
An agency of the European Union

<Date of submission>

Submission of comments 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 these comments and the identity of the sender will be published unless a specific justified objection is received.
When completed, this form should be sent to the European Medicines Agency electronically, in Excel format (not PDF), to the following address:
ICH@ema.europa.eu

All the cells with an asterisk (*) should be filled in prior to completing the columns "Comment and rationale" and/or "Proposed changes / recommendation".
For more details on how to use this template please refer to the tab "Manual for commenter".

Name of organisation or individual*	Line from* (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)
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.
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).
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.

Name of organisation or individual*	Line from* (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)
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.
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.
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."
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.
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)
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.

Name of organisation or individual*	Line from* (line Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)
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).
IQWiG	541	542	5.3	There is an incorrect cross-reference in line 542.	Correct the cross-reference in line 542.
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."
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.
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) [...]."
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."
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.
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 Nr or 0 for general comment)	Line to* (line Nr or 0 for general comment)	Section number	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)
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. (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.