PP18: It's Time to Stop Collecting Investigator Assessment of Non-serious Adverse Event Causality

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PROs

There is no regulatory requirement to collect investigator assessment of causality

ICH E2A[1]	"Causality assessment is required for clinical investigation cases… judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product"
CIOMS VI[2]	"Collection of investigators' assessments for non-serious events adds little value and is not needed for routine regulatory reporting"
FDA Clinical Review Template[3]	"[A]nalyses of drug-related adverse events … usually based on assessments made by investigators at the time of an event, are highly dependent on information about the side effect profile of the drug available at the time. …[T]hese analyses are not expected to provide much useful information in assessing causality and should be disregarded."
FDA IND Safety Reporting Final Rule[4]	"For consistency, … assessment of whether the event is serious and unexpected should be based on the opinion of the sponsor (not the investigator)"
CDISC SDTM IG 3.4[5]	Causality of AE (AEREL) is Expected variable (variable should be included in the dataset, but can be blank for some or all records)

Best practices for AE Displays does not recommend[3]

PHUSE AE Analysis & Displays White Paper[6]	We do not believe summary tables for AEs considered related by the investigator are necessary for individual studies, nor necessary in submission documents to regulatory agencies other than the PMDA.

Reduces the amount of data collected

SCDM Good Data Management Practices[7]	Care should also be taken to ensure CRFs do not collect data that ultimately will not be used for analysis or will not support analyzed data. Extraneous data can adversely affect overall data quality by drawing the attention of site personnel away from key variables.

CONs

Some guidance documents have examples of using causality

2021 EU Layperson Summaries Guidance[8]	EU regulations require a layperson summary, but the Good Lay Summary Practice is a guidance handbook which suggests using investigator-assessment of causality because it "may be more understandable when reporting only investigator-identified adverse reactions so that the use of bulky tables with unrelated adverse events is avoided"
PMDA Notification on Practical Operations of Electronic Study Data Submissions[9]	• Notification refers to not needing to submit the TLFs for adverse reactions if the electronic data to support the table are submitted • In Japanese, this may mean 'treatment-related AE" and Japanese version prevails over English translation • No definition for how treatment-related is determined

Summary

In summary, most regulatory authorities want to minimize the over-reporting of adverse events so that everyone (regulatory authorities, ethics boards, and the public) can focus on critical safety information and eliminate confusion.

Most agencies agree that for serious adverse events, it is necessary to determine causality, but for non-serious adverse events the sponsor may be in **a better position to determine causality based on aggregate data, rather than an individual case.**

Therefore, we recommend that the collection of investigator assessment of causality be restricted to serious adverse events only.

REFERENCES: 1. ICH Guideline E2A. *Clinical Safety Data Management: Definitions And Standards For Expedited Reporting*, Step 4 as of 27 October 1994. Retrieved August 1, 2022, from https://database.ich.org/sites/default/files/E2A_Guideline.pdf. **2.** Report of CIOMS Working Group VI. *Management of Safety Information from Clinical Trials.* Council for International Organizations of Medical Sciences, Geneva, 2005. **3.** U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Manual of Policies and Procedures. Good Review Practice: Clinical Review Template, 2010. Retrieved August 1, 2022, from https://www.fda.gov/media/72472/download. **4.** U.S. Department of Health and Human Services, Food and Drug Administration, Final Rule. Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans, 75 FR 59935. **5.** Clinical Data Interchange Standards Consortium. Submission Data Tabulation Model Implementation Guide v3.4 (2021). **6.** PHUSE, Analysis and Displays Associated with Adverse Events: Focus on Adverse Events in Phase 2-4 Clinical Trials and Integrated Summary Documents, WP-003 (2017). **7.** Society for Clinical Data Management. (2013, October). Good Clinical Data Management Practices. Retrieved August 1, 2022, from https://scdm.org/wp-content/uploads/2019/05/Full-GCDMP-Oct-2013.pdf. **8.** European Commission. Summaries of Clinical Trial Results for Laypersons. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. Version 2. Retrieved August 1, 2022, from https://ec.europa.eu/health/sites/default/files/files/eudralex/vol10/2017_01_26_summaries_of_ct_results_for_laypersons.pdf. **9.** Pharmaceuticals and Medical Devices Agency, Revision of Notification on Practical Operations of Electronic Study Data Submissions (2019). Retrieved August 1, 2022, from www.pmda.go.jp/files/000229465.pdf.