JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 14, No. 7, July 2018 "Happy Trials to You"

Causality Determination in Pharmacovigilance

By Sameer Thapar

Pharmaceutical companies monitor the safety of their drugs during clinical studies and after their products are on the market. This process, called "pharmacovigilance," is also called "safety monitoring" during a clinical study. During a study, investigators submit "clinical safety reports" of serious adverse events (SAEs). Once a drug is on the market, patients, caregivers, physicians, pharmacists, other healthcare providers, and anyone else can submit "spontaneous reports" of adverse events that concern them. (This article will not discuss the similar process for medical devices. This article focuses on practices in the U.S., so it will not delve into the FDA final rule guidance, which still relies on causality determination, even though causality determination is no longer included in U.S. spontaneous reports.)[1]

These reports alert the company and the governing health authority (e.g., the FDA) of potential health problems caused by drugs, so appropriate action can be taken to protect the public. The fundamental question in all of these reports is whether the drug caused or contributed to the health problem (i.e., a side effect was observed) or the health problem was just coincidental to use of the drug.

Causality

By definition, a major purpose of clinical research is to learn whether a drug causes adverse events. SAEs seldom present with the complete package of unambiguous information needed to determine causality with 100% confidence. In addition, the person assessing causality might have conscious or unconscious biases. While the treating physician's judgment might be influenced, for example, by his or her responsibility for causing the SAE, he or she is presumed to be the patient's advocate and the person most familiar with the specific circumstances.

In the U.S., spontaneous reports require identification of the drug that is presumed to have caused the problem, even though the person who submitted the report might not have the knowledge or expertise to make such a determination. Nevertheless, the reports go straight into a database for statistical analysis. Spontaneous reports typically include very little of the data that would be required to assess causation with certainty. In the Europe Union, experts review spontaneous reports to determine causality, perhaps after talking to the submitter.

In both U.S. and EU clinical studies, the principal investigator submits clinical safety reports to the study sponsor (or CRO). The FDA assumes that the investigator is best qualified to assess causation because of his or her proximity to the patient, even though the principal investigator might not understand the physiology or pharmacodynamics of the drug, might not have read the investigator's brochure, and has access only to his or her site's study subjects and IND safety reports from long-past SAEs.

Study sponsors employ "medical monitors" to review clinical safety reports, especially with respect to causation. Safety reports are often incomplete, ambiguous or illogical, so it is common for medical monitors to request clarification or more information. Causation is very important to study sponsors. On one hand, they want to protect the health of study participants and terminate development of any drug that will be too dangerous to put on the market. On the other hand, they do not want their studies torpedoed by safety reports that incorrectly blame the drug for SAEs.

In most cases, medical monitors, like investigators, are working with blinded data, so they do not know whether the injured study participant was even taking the drug. However, study sponsors are generally better off when causation is not found, since findings of causation can result in a failed study, or financial or reputational damage. Nevertheless, the stakes are very high either way, so most study sponsors much prefer accurate causality findings.

If a medical monitor disagrees with, or is uncertain about, the investigator's determination of causation, the medical monitor can attempt to persuade (perhaps very forcefully) the investigator to change his or her determination of causation, but the investigator has the final authority.

Categories of Causality

The World Health Organization (WHO) has defined six categories of causality likelihood:[2]

1. **Certain.** A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2. **Probable/Likely.** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
3. **Possible.** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
4. **Unlikely.** A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
5. **Conditional/Unclassified.** A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment, or the additional data is under examination.
6. **Unassessable/Unclassifiable.** A report suggesting an adverse reaction that cannot be judged because information is insufficient or contradictory, and that cannot be supplemented or verified.

The most common causality assessments in safety reports are Possible or Probable/Likely. In practice, choosing between these two categories (and those adjacent) is often a matter of judgment, since concepts like "plausible" and "reasonable" must be applied.

Methods for Determining Causality

There are three methods for determining causality:[3]

- **Expert Judgment.** As discussed above, this method relies on an expert to determine causation. In clinical studies, the principal investigator is the expert, with review by a medical monitor. With spontaneous reports (except the U.S., where causation is assumed), the regulatory authority employs the expert.

- **Algorithmic.** With this method, the sponsor prepares a set of rules (like a computer algorithm) in advance to assess causation. In a clinical study, the sponsor reviews the rules with the investigators, typically at an investigator meeting. If the investigators, as a group, accept the rules, the study sponsor then expects them to follow the rules. If an investigator, at that time or later, disagrees with the rules, the expert judgment method will be used for him her going forward, and his or her prior safety reports will be revised accordingly. A weakness of this method is that it assumes the rules cover all relevant factors.
- **Probabilistic.** With this method, the causation analysis starts with the assumption that the case at hand is similar to previous cases. The reviewer can accept this assumption or justify a different finding based on the specifics of the case at hand.

The algorithmic and probabilistic methods are susceptible to automation. The algorithmic method is most popular in very large studies, in which large volumes of safety reports must be processed and the necessary data can be collected in structured form.

Since 1968, WHO has collected over 14 million spontaneous "individual case harm reports" (ICHRs), and the number continues to grow exponentially. Detailed clinical evaluation of so many spontaneous reports is impractical. However, analysis of the reports might generate a signal that prevents further patients from harm or at least assists with earlier recognition of drug-related harm and better management of such harm.[4] Machine learning is being tested to find subtle patterns in the data. However, machine learning systems are usually opaque, so justification can be a challenge. This opacity has been the source of controversy in the regulatory acceptance of such systems, and efforts are underway to make the black box of machine learning systems transparent. By doing so, the systems will gain greater acceptance by both clinical researchers and regulators.

Conclusion

While clinical researchers focus on the primary hypothesis, and marketing departments focus on sales and profits, the pharmacovigilance system arguably generates the most important findings. Safety is paramount. New methods and technologies are being developed to streamline the pharmacovigilance process and detect the tiny safety signals that foreshadow potentially larger problems down the road.

References

1. Wittes, J. (2015). The FDA's Final Rule on Expedited Safety Reporting: Statistical Considerations. *Statistics in Biopharmaceutical Research*, *7*(3), 174–190.
2. Centre, U. M. (2011, March 21). The use of the WHO-UMC system. Retrieved from WHO-UMC: who-umc.org
3. Khan, L. e. (2016). Dilemmas of the causality assessment tools in the diagnosis of adverse drug reactions. *Saudi Pharmaceutical Journal*, 485-493.
4. Edwards, R. (2017). Causality Assessment in Pharmacovigilance: Still a Challenge. *Drug Safety*, 365-372.

Author

Sameer Thapar, PharmD, is Global Pharmacovigilance Director at Oracle Health Sciences Consulting. Contact him at linkedin.com/in/Thapar or sameer.thapar@oracle.com.

