

## **Analytical Methods for Post-Marketing Safety Surveillance**

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### **ABSTRACT**

Safety surveillance can be part of a comprehensive post-marketing program to satisfy a regulatory requirement or to collect additional data for use in drug development. The objectives of a safety surveillance program are to assess and quantify known or suspected drug safety issues, identify and characterize potential new risks following product marketing, and to monitor product-use patterns. The common types of post-marketing surveillance are passive and active surveillance, stimulated reporting, comparative observational studies, targeted clinical investigations, and other descriptive studies.

### **INTRODUCTION TO SAFETY SURVEILLANCE**

Postmarketing Safety Surveillance is part of a comprehensive program. The objectives of a safety surveillance program are to assess and quantify known or suspected drug safety issues, identify and characterize potential new risks and risk factors following product marketing, and to monitor medication use patterns. The data collected can improve the understanding of "real world" use of a product, and identifying off-label use and potential medication errors and detect new safety information.

### **TYPES OF SAFETY SURVEILLANCE**

Common types of post-marketing surveillance are passive and active surveillance, stimulated reporting, comparative observational studies, targeted clinical investigations, and other descriptive studies.

Active surveillance is defined within the European Commission Volume 9A to be the ongoing, proactive monitoring of product use and potential adverse events (AEs) "to ascertain more completely the number of adverse events in a given population via a continuous organised process." One objective of active surveillance is to detect safety issues early in the post-marketing environment that were not identified during development, such as rare events or latent onset. Active surveillance can also quantify the effects of misuse or overdose. Another objective is to characterize drug use patterns, including profiles of prescribers and patients, indications, and dosing and discontinuation. Active surveillance can include the regular, periodic and stimulated collection of case reports from healthcare providers or facilities, such as sentinel sites. The use of sentinel sites may involve the review of medical records or patient and/or physician interviews for complete and accurate data on reported adverse events. This method may allow for a focus on patient subgroups that would not be available in a passive reporting system, and is most efficient when employed in the surveillance of products frequently used in an institutional setting. However, the use of sentinel sites is limited by small sample size, selection bias, and expense. Additional methods for active surveillance include prescription monitoring, patient registries, and database and/or electronic medical record research.

Passive surveillance primarily includes the analysis of spontaneous adverse event reports. Sources for reports include regulatory systems such as MedWatch in the US. Passive surveillance often involves assembling a series of cases to examine specific types of events, such as overdose and product re-challenge. This method of safety surveillance is limited by incomplete reporting information (which can impede determination of causality), potential underreporting of events, and unknown parameters for calculation of incidence (denominator and numerator). A component of passive surveillance is data mining looking for disproportionality patterns.

Stimulated reporting is achieved through direct encouragement of event reporting through communication with potential reporters, such as via a Dear Healthcare Provider Letter. Stimulated reporting can be limited by the same factors as passive surveillance: underreporting, incomplete information, and unknown mathematical parameters.

Comparative observational studies can be analytic, such as case-control studies, or descriptive, including cross-sectional surveys and cohort studies. Observational studies do not recruit participants into a controlled environment, as in a random-controlled trial, but instead observe the outcome of interest (e.g., a specific adverse or other drug event) in a population that already takes the drug compared to a population that does not. Case control studies that compare individuals with the outcome of interest to a matched sample of the population without the outcome of interest and ascertain exposures. These studies are commonly used to identify side effects rather than evaluate treatment effectiveness, and may be used to calculate relative risk, but usually cannot be used to calculate absolute risk. Cross-sectional surveys examine a "snapshot" in time to quantify prevalence of an outcome of interest, such as a disease, within a defined population. These studies can be used to calculate both absolute and relative risk. Cohort studies compare data from an exposed-population to an unexposed-population in order to analyze predictive

risk factors for an outcome of interest. In cohort studies, participant exposure is self-determined and not controlled or assigned by the study. Cohort studies may be conducted retrospectively or prospectively.

Targeted clinical investigations include large-streamlined trials (LSTs) and randomized controlled trials (RCTs). These studies compare outcomes of interest in an exposed population to an un-exposed population. . Double-blind RCTs are considered the "gold standard" of research; however, they can be the most costly and time-consuming to conduct and may not be representative of actual using populations.

Other descriptive studies include natural history and drug utilization studies. Natural history studies are resources for background morbidity and mortality rates, as well as background incidence of serious adverse events (SAEs). These studies can also inform the expected diversity of the exposed patient population and likely concomitant products. Drug utilization studies can be used to assess disease prevalence, but also provide information on how drug use (prescribing patterns, administration, dosing) relate to outcomes of interest

## **DATA COLLECTION AND ANALYTICAL METHODS**

There are many tools and resources available for post-marketing safety surveillance: spontaneous adverse event report databases, large administrative databases (e.g., Medicaid, managed care organizations, insurers), registries, and electronic medical records. In the UK, for example, Prescription Event Monitoring (PEM,) developed in the 1980's, uses a questionnaire to collect outcomes information from a panel of all physicians who prescribe a new drug. Notably, PEM does not require the clinician to determine whether there is a causal relationship to the product. This reporting also allows for follow-up on events of interest, such as pregnancy or death.

Larger automated databases, can be used in retrospective cohort studies to identify users of a new product and an appropriate matched control cohort treated with standard-of-care or conventional drugs. Patients can be matched on demographics such as age, gender, and other factors including medical history. These databases may provide large sample sizes and are amenable to computerized processing. These reflect real-world practice, and identified outcomes can be verified through medical record review. Unfortunately, these databases are only available as a resource if the product is used to a degree to allow for meaningful exposure data, consequently they may not be available immediately after initial marketing of a product. Use of large automated databases can also be challenging due to false positives from multiple comparisons (type I errors). Within the US, some commonly used databases include: United HealthCare, PharMetrics data, Tennessee Medicaid, and HMO Research Network.

For a registry or a prospective cohort study, the treating clinician can collect data from patients treated with the new product (product registry) or treated for the same disease (disease registry). These data can include baseline data, such as medical history, disease severity/duration, and treatment history. Enrolled patients are typically followed for a defined period of time, and data on product exposure and AEs is evaluated to compare the active cohort with the historic controls.

Analytic observational studies, such as case-control studies, cohort studies, and "nested" case-control studies can also make use of mail, phone, or face-to-face interview surveys to collect data. A case-control network organizes multiple hospitals and/or treatment facilities to prospectively identify cases of newly-diagnosed outcomes of interest. The facilities also identify appropriate controls (based on age, gender, medical history, etc.) to allow drug exposure histories prior to onset of the event to be compared between the cases of interest and controls. The odds ratio can be calculated to assess an association between the outcome of interest and the product use.

Another important new role for safety surveillance is to evaluate risk mitigation and interventions. This entails assessing whether risk information has been received and understood and complied with by patients and physicians.

## **CONCLUSION**

Drug approval has inherent limitations due to restrictive populations studied under the somewhat artificial circumstances of preapproval trials. For this reason postmarketing safety surveillance is essentials. Such surveillance involves passive case reporting and assessment, active surveillance and a variety of study options.

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