Quantitative Signal Detection for Small and Specialized Safety Database

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Abstract

Objective: Quantitative signal detection is challenging with smaller databases (containing one or a few products) as it may lead to multiple false positive signals. Our objective was to establish a quantitative method to use on smaller datasets to reduce the number of false positive signals.

Method: Targeted literature search to identify various guidelines and literature publications that discuss quantitative signal detection methods. After reviewing various quantitative signal detection methods, their suitability was assessed for safety databases which are too small and specialized in nature.

Result: Quantitative analysis of spontaneous adverse drug reaction reports is routinely used in drug safety research. Several articles have been published on statistical signal detection which describes the core concepts behind the most common methods, the proportional reporting ratio (PRR), reporting odds ratio (ROR), information component (IC) and empirical Bayes geometric mean (EBGM). Based on our review and compatibility check, none of existing methods are well suited to small and specialized safety database. To overcome this limitation, we have developed Product Fractional Reporting Ratio (PFRR) which is intra product quantitative signal detection method for safety database which are too small and/or contains only data for one product or few products. PFRR is the ratio of two fractions. It compares the reporting ratio of a given event term in the interval period with the reporting ratio of this event term cumulatively (excluding the interval period). PFRR can be calculated at various Medical Dictionary for Regulatory Activities (MedDRA) levels such as System Organ Class (SOC), High-Level Terms (HLT) and Preferred Terms (PT). A PFRR > 1 for any specific PT indicates that the reporting trend for that PT during the review period is higher than prior to the review period.

$$FR\,(_{for\ PT})\ interval\ period = \frac{n\ events\ PT\ interval}{N\ cases\ interval}$$

$$FR\,(for\ PT)_{cumulative\ \ period} = \frac{n\ events\ PT\ _{cumulative\ \ period}}{N\ cases\ _{cumulative\ period}}$$

$$PFRR_{PT} = \frac{FR\,(for\ PT)_{interval\ period}}{FR\,(for\ PT)\ _{cumulative\ period}}$$

PFRR above predefined threshold does not represent a signal by itself. In addition to the PFRR thresholds, additional qualitative measures can be applied, such as focused reviews of DME reported during the review period, fatal events, and safety topics with a focus on newly received events during the review period. Based on our experience, we have observed PFRR method works well for identifying signals in small and specialized databases where other data mining methods may not be suitable due to one or few products.

Conclusion: Careful consideration should be applied when to perform quantitative signal detection as it may not be suitable for products with very low case volume (e.g. <10 cases in surveillance period).

Quantitative signal detection should adhere to a methodology that considers the nature of the data, the characteristics, and the type of medicinal product involved. Various factors affect how pharmaceutical companies and CROs monitor the safety profile of the marketed product. At present, there is no guidance on which quantitative signal detection methodology is best suited for small and specialized safety database. We conclude that it would be advantageous to use the intra-product ratio such as PFRR along with other qualitative measures to identify signals where there is no data for comparison or to implement sophisticated data mining methods. Pharmaceutical companies, CROs, and patients will ultimately benefit from this approach.

Track / Interest Area: Clinical Safety and Pharmacovigilance.

Keywords

Quantitative signal detection, small and specialized database, Product Fractional Reporting Ratio.