PSUR in EU MDR:
Signal Detection Process & Challenges

Signal detection and risk management are new to medical devices. As PSUR reports for high-risk devices will be needing Signal Detection, manufacturers need to gear their processes Though the processes and methods are well established in BioPharma, some of the areas that worked for those products may not work or applicable to Devices.

This process is a key area for companies in safety surveillance and benefit-risk monitoring of Medical Devices.

- Though some companies may have adapted some signal detection methods and systematic assessments (i.e. quantitative methods) to identify safety signals, the challenge of accurate, timely and evidence-based signal detection remains, which results in the missing or delay in identification of potential signals and implementation of required risk mitigation plans to safeguard patients.

- Quantitative methods from source data sometimes result in a high number of false-positive signals due to lack of clinical relevance which would require significant human effort for assessment.

This white paper discusses the need for qualitative methods to identify accurate signals.

INTRODUCTION:

- Routine safety surveillance of approved Medical Devices is needed to ensure the benefit-risk profile of products that are on the market remains favorable for the patient population and that the benefits outweigh the risks of the devices.

- One of the most important aspects of device safety monitoring is the identification and analysis of new, medically important findings called ‘signals’ that might influence the use and life cycle of a Medical Device.

» Routine safety surveillance of approved Medical Devices is needed to ensure the benefit-risk profile of products that are on the market remains favorable for the patient population and that the benefits outweigh the risks of the devices.

» One of the most important aspects of device safety monitoring is the identification and analysis of new, medically important findings called 'signals' that might influence the use and life cycle of a Medical Device.

» As per the World Health Organization (WHO), a Safety Signal is defined as reported information on a possible causal relationship between an adverse event and a device, the relationship being unknown or incompletely documented previously.

» A more recent definition was given by the Council for International Organizations of Medical Sciences (CIOMS)-'information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify the verificatory action.

SIGNAL MANAGEMENT PROCESS:

» Signal management process can be defined as the set of activities performed to determine whether, based on an examination of individual safety reports, aggregated data from active post marketing surveillance systems or studies, literature information or other data sources, there are new risks associated with a medical device or whether known risks have changed.

» Single and aggregate reports and "root cause analyses" are useful for identifying unexpected major harms.

» For example, the ASR artificial hip failure was recognized by MHRA in collaboration with clinicians based on case series reports with unique failure features (Medical Device Alert). However, only systematic processes will ensure continuous evaluation of implants to determine comparative performance and differences between them. Many important considerations, such as comparisons of rates of events between distinct sets of devices, are best addressed on the basis of summary measures rather than by informal aggregation of individual anecdotes. By shifting the focus from individual reports towards systematic summary analyses, we can exploit the power of registries to detect strong signals.

- The signal management process can include all steps from
- Signal detection
- Signal validation
- Signal analysis and prioritization
- Signal assessment
- Recommendation for action
- Exchange of information

METHODS OF SIGNAL DETECTION:

Qualitative	Quantitative
Causality Orientated	Statistically orientated
Clinical Outcome / Diagnosis	Code data
Reviewers Skills	Computational Algorithms
Depends on established knowledge	Independent from established knowledge
Small number of reports	Large databases

QUALITATIVE METHOD:

Qualitative methods include analysis of:

- Individual case safety reports
- Published scientific information from clinical and other studies on the usage of device and occurrence of reaction.
- Qualitative signal detection is based on the routine review of spontaneous data and scientific literature from clinical studies etc. However, this approach is best for a small number of reported cases and literature review, since a routine review of safety reports for signal detection purpose via the qualitative approach will be highly cumbersome and time-consuming process for many manufacturers considering the enormous device portfolio and a diverse/sporadic number of reported cases.
- As an alternative, quantitative methods can identify the risks associated with the use of devices from large spontaneous data using algorithm principles.

Discussion:

- Some of the challenges include: Lack of device usage data, unknown and incomplete event reporting rate to the FDA, uncertain device marketing sales data, event reporting time lags, device-or not device-related adverse events, ascertainment of events, questionable and unclear correlation between adverse events and device usage data (if available), unclear effect of regulatory actions on device safety reporting rates, possible correlation between device marketing date and event report rates, absence of a gold standard for true regulatory intervention, the reliability of the MDR reporting system, and others.

CONCLUSION:

The proper signal detection and their assessment is the most important aspect in vigilance. Various methods are used for the detection of signals. Signal management for medical devices spans a variety of sources. Manufacturers may not rely upon one single method, but needs a strategy of complementary activities. The quality of the reports can be increased through proper training and re-training of the teams engaged in the vigilance activity. No single causality assessment method is universally acceptable. Therefore a single universally acceptable efficient method is the demand of the time.

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