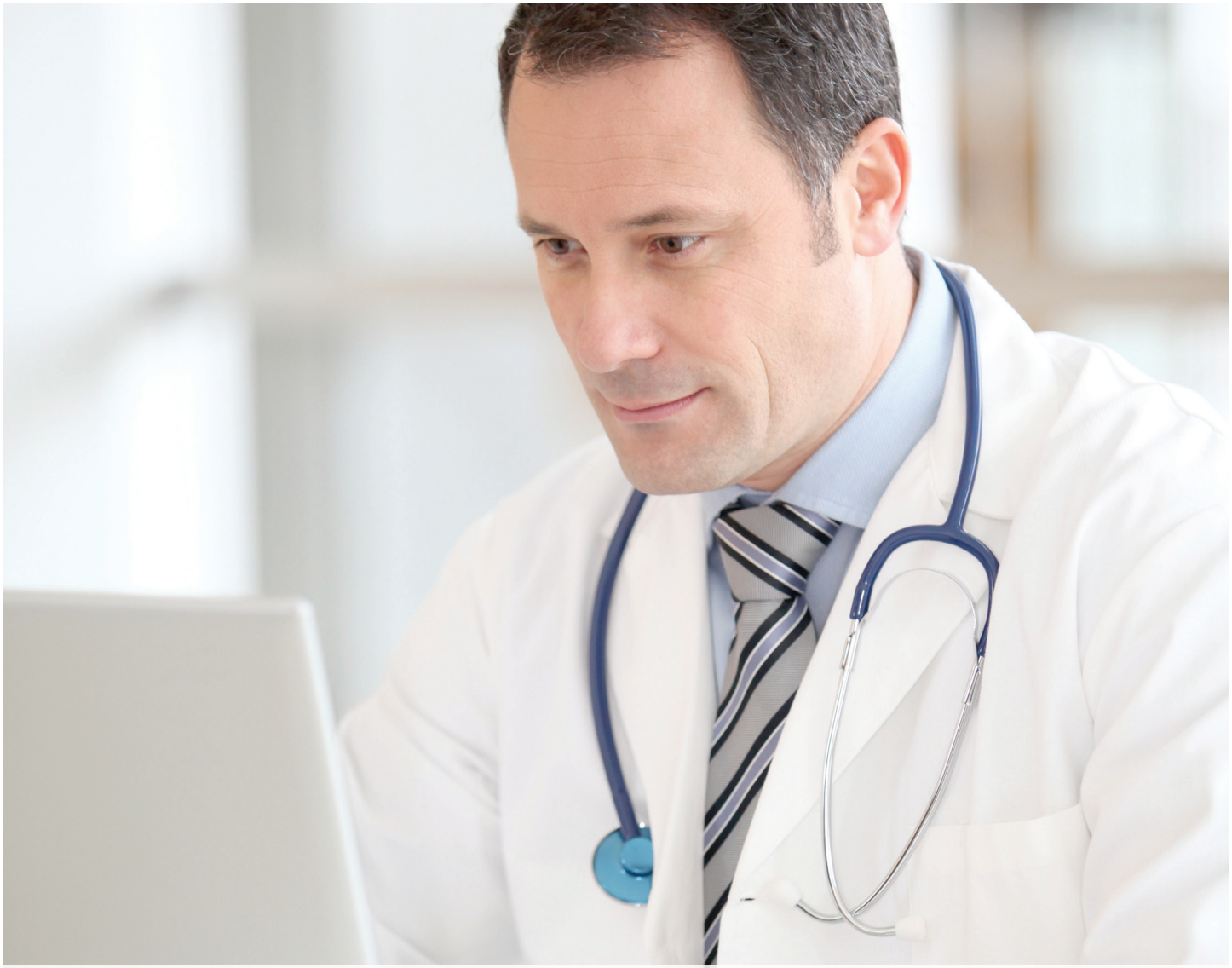

Managing the Unmanageable: Meeting the Challenge of Appropriate Safety Report Distribution

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A major concern in the clinical research industry is the over-reporting of expedited safety reports to investigative sites; letters notifying of new, urgent safety issues are distributed during clinical trials, even though the safety event does not meet criteria for being reported in such a manner. The volume of safety reports being sent to investigative sites is frustrating for investigators, sometimes causing them to disregard letters which may result in clinically-significant safety signals being missed in the noise of non-significant event reports, and the workload volume may even lead sites to consider ending their participation in the clinical trial. How can we ensure that investigative sites only receive the reports they truly need to review? This question must be answered in order to bring efficiency back to the review process and to ensure that investigators are spending their time where it matters most, with the study participants.

The Purpose of Safety Reporting

Within the realm of clinical trials, participant safety is, and always should be, at the forefront of everyone's focus. With incredible advances in medicine and technology, a large number of new investigational drugs continue to cycle through the clinical trial process, bringing with them hope to cure disease or to provide preferred alternatives to the existing options. To monitor participant safety in an ongoing trial, sponsors rely on their investigative sites to record and submit data on any adverse events study participants have experienced. The sponsor is responsible for reviewing and determining which adverse events meet the criteria to be considered as serious and unexpected, thereby representing new potential risks for trial participants. These must be disseminated to investigative sites in the form of a safety report. The purpose of these reports is to notify investigators, Institutional Review Boards/Research Ethics Committees, and regulatory agencies of any new, safety concerns that are suspected to be caused by the study drug and unexpectedly arise from its use so that necessary action can be taken to protect trial participants. However, in their effort to ensure that all events which meet the criteria are promptly distributed and that under-reporting does not occur, far too often sponsors instead over-report, by sending out notifications of events that actually do not represent new, serious, or clinically-significant risks.

Comparison of Safety Letter Distribution Methods

Electronic Solution	Overnight	Email	Fax
Automated acknowledgement tracking and reporting capabilities	Poor tracking of receipt by investigator	Cannot confirm receipt	Hard to confirm intended recipient received the fax
Dependable distribution algorithms	Package may make it to PIs facility, but not the individual themselves	Mistakes are made when spelling recipients email address or choosing from pick list	Potential for incorrect fax number to be entered or safety doc gets accidently picked up by unintended recipient
Real-time distribution worldwide	Delay in investigator receipt due to shipping and slow internal courier services at the medical facility	Emails get caught in spam filters delaying receipt	Delayed fax distribution in large facilities
Secure sign-on	Once delivered, safety document can be viewed by anyone if not secured	No authentication required to access safety document	Safety document can be access by anyone who has access to fax machine
Audit Trail reporting	No audit trail	No audit trail	No audit trail
Instantaneous Gap Pack at time of site activation	Delayed receipt of gap pack due to manual labor of packing and shipping	Manually compiling safety documents could lead to missed documents	Room for error when faxing large numbers of documents

Impact of Over-Reporting

The over-reporting of safety events has had a negative impact on both sites and sponsors. Investigators are overwhelmed and frustrated with the volume of reports they are required to review. Sites feel they are spending too much time figuring out how to handle the administrative burden of a voluminous number of safety reports so that they do not fall out of compliance, when they should really be concerned with assessing safety issues and communicating new risks to their trial participants. Continuing frustration amongst investigators also stems from the content of the reports; many of the safety reports are uninformative, are difficult to translate into meaningful clinical actions, and contain information that has already been identified in the investigator brochure.

This reaction from sites has had a negative impact on sponsors. Sponsors receive complaints from sites making it difficult to maintain positive working relationships. In some cases, sponsors have found that sites do not want to conduct additional clinical trials with them. It is a challenge for any sponsor to find high performing sites, and to lose a high performer due to over-reporting of safety information is not something sponsors want to see happen.

Why Do We Have Over-Reporting?

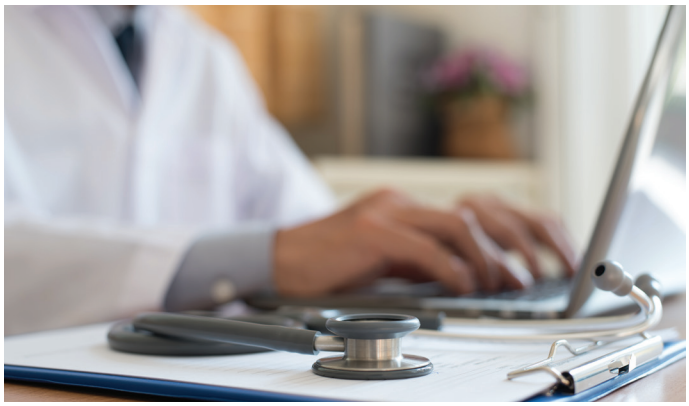
Initial FDA Guidance Interpretation

Historically, the over-distribution of safety reports often stemmed from sponsors' interpretation of safety reporting rules and guidelines. Sponsors misinterpreted the phrase "reasonable possibility" in the Food and Drug Administration's (FDA) guidance on safety reporting . The rule stated that sponsors were required to notify participating investigators of any adverse experience associated with the use of the drug that was both serious and unexpected if "there was a reasonable possibility that the experience may have been caused by the drug." Sponsors, sometimes relying on the causality assessment of the investigator reporting the event, often interpreted "reasonable possibility" very conservatively; if a causal relationship could not be definitely ruled out, there was a possibility of a causal relationship. Therefore, sponsors processed many events that had little evidence to support a causal relationship between the event and study drug as expedited safety events.

Lack of Harmonization amongst Countries

Another reason for the over-distribution of safety reports is that there is a lack of harmonization in the rules around safety reporting amongst countries and their governing bodies. As sponsors conduct multi-national clinical trials, it is important that each trial is conducted in accordance with participant countries' rules and regulations. For example, the conduct of a global trial that includes sites in the United States, Europe, and Japan would need to adhere to rules and regulations in accordance with the FDA, the European Medicines Agency (EMA), and the Japanese Pharmaceutical and Medical Devices Agency (PMDA). It is common that expectations concerning safety reporting vary across regulatory authorities; mostly in terms of the information that must be reported to investigators and in what time frame it must be reported.

For example, many countries require the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to investigators regardless of whether the adverse reaction originated within that country or outside of that country. However, there are several countries such as Iceland, Norway, and Switzerland that only require SUSARs to be reported if they occurred within the country. Some unique rules also exist; for example, Malaysia requires both unexpected and expected serious adverse reactions to be reported to investigators.



Resolving the Problem of Over-Reporting

Clarification of FDA Expectations

In 2010, the FDA addressed the issue of over-reporting and issued a Final Rule for safety reporting under an Investigational New Drug (IND) application; guidance for the operationalization of the new rule was then issued in 2012. This provided sponsors with clarified definitions and a much more clear indication of which events qualify for expedited reporting to investigative sites. Under the new guidance, sponsors "must report any suspected adverse reaction that is both serious and unexpected" and "the sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest causal relationship between the drug and the adverse event," with several examples provided to clarify what FDA considered to be a reasonable possibility of a relationship. The FDA's goal was to stop sponsors from distributing safety reports for events that did not have a causal relationship or were anticipated and already outlined in the investigator brochure, so that new safety signals could be more easily recognized.

Adhering to Country-Specific Regulations

The International Conference of Harmonization (ICH) has been involved in initiatives to harmonize reporting rules across countries and their associated regulatory bodies, however more work needs to be done before harmonization becomes a reality. Before this reality is met, understanding and adhering to the varying country rules is no easy task for sponsors.

As sponsors have moved towards automated technical solutions for the dissemination of safety reports, they are finding it difficult to accommodate the varying rules and regulations as many technologies that allow report distribution do not consider these complexities. Not wanting to risk regulatory non-compliance by failing to report an event to any given country agency, sponsors are still leaning towards the trend of over-distributing reports.

Moving Toward Real Solutions

An emerging trend is that sponsors are now pursuing advanced technical solutions to aid them in handling and adhering to the varying regulations. As many available technologies have not considered such complexities in rules, sponsors have voiced the need for an improved solution that allows for the tailoring of distribution rules by country. Key items must be considered when addressing the varying rules and regulations in a technical solution (see sidebar).

Key Considerations for Addressing Various Rules and Regulations in a Technical Solution

- Ability to distinguish if a country is only required to receive adverse reactions if the event took place in that country.
- Ability to distinguish whether a country should receive adverse reactions based on causality assessment. For example, there are a few countries including the United States, Israel, and United Arab Emirates, that only require the distribution of adverse reactions that have sponsor drug causality; if it was only the investigator that determined drug causality, distribution is not required.
- Ability to distinguish which countries require which specific document types. For example, some countries do not require 15 day SUSARs, but instead require a 6 month line listing.
- Flexibility to update country rules as regulatory rules and regulations continue to evolve.
- Ability to automatically utilize cover letters in a country's native language.
- Ability for sponsor and clinical research organization staff to access only the site and country information relevant to them.

Allowing rules to be set with such precision enables sponsors to ensure that they are compliant in all countries and across multiple governing bodies while at the same time preventing sites and regulatory agencies from receiving safety documents they do not want or need.

Conclusion

As sponsors strive to distribute only events that qualify for reporting to investigative sites, and as technological advances continue to improve the control sponsors have on adhering to varying regulatory guidelines, the industry will continue to see a decline in the number of unnecessary safety reports being disseminated. The industry can expect these improvements to have a positive impact on both sites and sponsors. Sites will be allowed to focus their attention on safety reports that truly affect the safety profile of the drug, while sponsors will find they have an improved relationship with their sites; both key items in ensuring that participant safety remains at the forefront of the clinical trial process.

About the Author

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