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Reducing Variability to Improve Safety in Clinical Trials

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The FDA is tasked with ensuring both the safety and efficacy of drugs, and recent actions have indicated the former is of paramount importance in the current regulatory environment. From the withdrawal of weight-loss drug Meridia (sibutramine) to an intense review leading to restricted access for diabetes drug Avandia (rosiglitazone), not to mention panels scrutinizing erythropoiesis-stimulating agents and a host of recent new drug rejections due to safety concerns, there can be little doubt that safety is top-of-mind with the Agency and hence with everyone involved in drug development. Following a recent evaluation, even the classic pain drug Darvon (propoxyphene) has been 'charged' with risk of cardiac toxicity and directed to be discontinued by the FDA.¹

Yet the simple truth is that all drugs have some side effects at some dosage level in some, if not all, patients. Thus, a primary responsibility of the clinical trial, per se, and those responsible for the strategic and thorough development of candidate drugs, is to elucidate which dosages under certain conditions in the target patient population negatively skew the risk-benefit ratio.

But even the actual conduct of clinical trials has not been immune from the FDA's focus on safety issues. This September, the Agency issued new rules strengthening their requirements for what safety information must be reported during clinical drug trials, specifying companies must report within 15 days findings that suggest a significant risk to study participants, serious suspected adverse reactions occurring at a rate higher than expected, and serious adverse events from bioavailability and bioequivalence studies.²

There are several steps clinical trial sponsors can take to ensure their studies effectively evaluate the safety of a candidate drug or device product, while simultaneously ensuring that no additional safety complications are introduced during the clinical trial process.

Maintain Uniform Operations

Reducing variability is key to monitoring safety in a clinical trial, and there are several ways a sponsor can achieve this. For example, whether the sponsor uses internal staff or contract monitors to oversee the trial, it is important to ensure these individuals are well-trained and to the extent possible remain on the job for the duration of the study. Maintaining consistent personnel reduces subjectivity and variability involved with data adjudication, collection, and analysis. Companies also need to make sure monitoring visits are being conducted as scheduled: regular monitoring by skilled, trained individuals is more likely to detect problems such as an investigator with a tendency to loosely interpret inclusion or exclusion criteria allowing patients into a trial who should not have been enrolled and might negatively impact safety data.

Report the Appropriate Data

Sponsors collect an increasing amount of data during clinical trials and institutional review boards (IRBs) often complain of being flooded with vague adverse event reports. The information overload can hurt rather than help an IRB's ability to ensure patient safety, which is why investigators and site monitors need to be trained in adverse event reporting. The FDA recognizes this issue as well: its new guidelines provide examples of when a single event should be reported or when there is need to wait for more than one occurrence in an attempt to better focus reporting on adverse events likely caused by an investigational product.

Communicate with IRBs/DMCs

There has recently been concern in the drug industry that conducting multi-site clinical trials involving protocol reviews by multiple IRBs is not only inefficient, but may raise ethical issues. For example, if an IRB has concerns about a trial protocol, the Board often simply refuses to allow the investigator to participate in the study, but no changes to the protocol are made and the concerns often are not communicated to other IRBs despite regulatory requirements regarding such communications.³ This problem can be addressed by maintaining good communication with each IRB and ensuring feedback is shared and incorporated into the protocol. Using a central IRB, whenever possible, can also enhance uniformity and decrease variability. Similarly, a data monitoring committee (DMC) provides independent safety oversight during a trial but is only as effective as the information it receives.

Use a Proven System for Collecting Data

Clinical site monitors must be vigilant about literally 'catching' toxicities and adverse events, and the sponsor must have a proven system in place to collect data. Sometimes, the right documentation and analysis of an adverse event can determine whether or not a compound is still viable. Additionally, variability in the data collection process might decrease the evaluable patient pool in the trial, decreasing the sponsor's chances to establish statistical significance or detect a rare safety signal.

Design for Success

Sponsors must ensure they have a sufficient sample size to track adverse events. The FDA is trending toward requiring larger safety databases and broader assessments of vulnerable populations, so sponsors must be current on the latest guidelines. Additionally, sponsors of global clinical trials must stay up to date on safety reporting standards emerging around the world, such as India's new guidelines regarding patient safety and good clinical practice compliance.

Find a Trusted Partner

Most sponsors and contract research organizations are well-aware of these best and better practices – the bottom line is how well they can execute. At INC Research, top-quality execution is ensured by our Trusted Process[®], a proven, metrics-driven clinical trial outsourcing methodology that allows us to reduce variability while maintaining flexibility. Time and cost savings are also benefits of this disciplined process.

The Trusted Process[®] means whether a trial enrolls subjects in Minneapolis or Moscow, in Malaysia or Mumbai, INC Research uses the same standardized and disciplined clinical trial operative approach. This approach produces a faster study start-up cycle; predictable, on-plan subject enrollment; and higher quality data enabling a 54% faster time to database lock.⁴

A key aspect of the Trusted Process[®] is the development of a Risk Assessment and Mitigation Plan for each clinical trial. We identify specific risks for every stage of the clinical trial process, from the risk of a site not having all essential documents completed prior to the enrollment of the first subject, to the risk of lost or damaged laboratory samples, to risks such as higher than expected attrition, missed subject visits, and delays with data reconciliation. We rate the probability and potential impact of each risk, and we create both a mitigation strategy and a contingency plan to manage each and every risk.

Such active risk management allows INC Research to be proactive rather than reactive about safety, and to react faster and more appropriately when reaction is called for.

For more information about INC Research's commitment to safety and our Trusted Process[®], contact Kevin Keim at klkeim@incresearch.com.

About the Author

Dr. Kevin Keim is credited with more than 42 years of research, discovery, clinical drug and device and strategic regulatory experience. Most recently, he served as president and CEO of Vela Pharmaceuticals Inc., and he was previously founder and managing director of K.L.Keim Consultancy Group LLC, and president of Quintiles Pacific Inc. He has served as a director of the American Society of Experimental NeuroTherapeutics (ASENT), NeuroMedix, Inc., Clinilabs, Inc., INC Research, and the Affiliated Research Institute. Kevin is currently Advisor to the Dean of Sciences of New York University and a director of the Pennsylvania Biotechnology Center of Bucks County, PA.

¹<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm234389.htm>

² <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm227386.htm>

³ The New England Journal of Medicine. Menikoff. The Paradoxical Problem with Multiple-IRB Review. October 13, 2010 (10.1056/NEJMp1005101)

⁴ For full service studies conducted by INC Research between 2008 and 2010