Expert Meeting: IND Safety Assessment and Communication
February 28-29, 2012

Executive Summary

Project: IND Safety Assessment and Communication

Clinical Trials Transformation Initiative

August 2012
IND Safety Assessment and Communication
A Project of the Clinical Trials Transformation Initiative

Bethesda, MD

Executive Summary

Background

Since its inception, the Clinical Trials Transformation Initiative (CTTI) has had an interest in improving the quality and efficiency of safety reporting for serious adverse events (SAE) in studies performed under investigational new drug applications (INDs). CTTI’s first project on this topic focused on expedited safety reporting of serious, unexpected and possibly related SAEs to site investigators in multicenter trials. At the project’s conclusion, CTTI recommended that sponsors decrease the volume of uninterpretable and irrelevant safety reports to investigators, and instead supply investigators with meaningful reports that would improve investigators’ understanding of a drug’s benefit-risk profile. These recommendations were developed immediately prior to the FDA issuing a new final rule on safety reporting for drugs being studied under INDs.

FDA’s new IND safety reporting rule, published in the Federal Register on September 29, 2010, became effective on March 28, 2011. The intent of the new rule is to improve the quality of safety reports by minimizing the number of uninterpretable reports that sponsors submit to FDA and investigators. This is consistent with CTTI’s recommendations described above. However, CTTI members have expressed concern
that there may be some uncertainty about the best methods to implement the new rule. For this reason, CTTI formed a new project entitled “IND Safety Assessment and Communication,” with the goal of promoting responsible oversight of safety for pre-market drug products consistent with the intent of the FDA’s new IND safety rule. The project objectives are as follows:

1. To obtain a deeper understanding of sponsors’ current practices for assessing safety of a pre-market drug product across all trials and sources of safety information and for communicating potential safety signals
2. To facilitate an informed discussion of practices and challenges in assessing and communicating IND safety information
3. To issue recommendations for future approaches that will support the intent of the IND safety reporting rule effective March 2011

The project team first surveyed industry sponsors to obtain a deeper understanding of their current practices. CTTI then distributed anonymized survey results to a group of experts that included representatives from each sponsor organization that completed the survey, government (NIH, Department of Veterans’ Affairs, and FDA), academia, and patient advocacy. These experts participated in a meeting convened on February 28-29, 2012 in Bethesda, MD. A subgroup of attendees at this meeting were members of a biostatistical workgroup that the CTTI project team formed to advise on the methodological dilemmas related to implementing the new IND
Safety Reporting rule. A full list of workshop participants accompanies this report on the CTTI website (www.ctti-clinicaltrials.org).

**Objectives of Expert Meeting**

The main objectives of the 2-day workshop were to discuss the following:

1. Findings from the survey of sponsor practices
2. Companies’ strategies for implementing the new IND safety reporting rule
3. Challenges in implementing the new rule

Participants were specifically asked to identify gaps between current practice and a pre-market safety system optimized to detect and communicate valid safety signals as early as possible.

The survey contained 54 open-ended questions intended to elucidate the structures and methods that companies have developed to monitor product safety before marketing. Twelve of the 14 companies who were surveyed responded and answered all 54 questions. Based on review of the survey responses, there were 4 major areas identified that formed the basis for the presentations and discussion at the workshop: (1) organization of personnel and data; (2) methods and processes developed to conduct aggregate analyses of drug product safety; (3) confirmation and escalation of potential safety signals; and (4) analysis of blinded studies.

At the end of day 1, participants were asked to identify up to 3 gaps between current practice and a pre-market safety system optimized to detect and communicate
valid safety signals as early as possible. Participants were also asked to propose solutions to addressing these gaps.

The expert meeting ended on day 2 with presentations and discussions on the identified gaps and proposed solutions, a summary of the previously published Safety, Planning, Evaluation, and Reporting Team (SPERT) recommendations \(^1\)\(^2\) and plans for follow-on activities by the project’s biostatistics working group.

Meeting participants identified issues, such as blinding, lack of available methods for meaningful analysis, reporting thresholds, global harmonization, and role of data monitoring committees as gaps between the current practice and having an optimal pre-market safety system as described above. Preliminary ideas to address these gaps included the following:

1. To address issues of unblinding:
   a. Establish an industry-wide, firewalled, third-party consortium to assist small companies in assessing comparative safety across treatment groups in ongoing trials
   b. Establish recommendations for using “internal DMCs” and/or “internal Safety Review Committees”
   c. Create a hybrid internal–external approach

2. To improve data access: Create a clearinghouse or unified database with a comprehensive clinical dataset that also contains safety data in an accessible, standard format so the dataset can be mined and queried
3. To begin a dialog on developing best practices for analysis of pre-market safety
data: Publish methods papers on industry sponsors’ successful approaches to
complying with the new rule

4. To provide a model for pre-market safety monitoring: Consider using an
approach similar to the Periodic Safety Update Report (PSUR), which represents
the worldwide safety experience of a drug after approval

The biostatistical workgroup met as a small group at the end of this expert meeting
and are scheduled to meet, as necessary, to develop their final recommendations. After
this workgroup issues their recommendations to the project team in summer 2012, the
project team will integrate the biostatistical recommendations with those from the
expert meeting to develop overall project recommendations for discussion with
stakeholders.

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development: a report of the safety planning, evaluation, and reporting team.
Clinical Trials, October 2009; vol. 6, 5: pp. 430-440.

2. Xia HA, Crowe BJ, Schriver RC, et al. Planning and core analyses for periodic
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