IND Safety Reporting: final results and best practices from the Clinical Trials Transformation Initiative IND Safety Advancement Project

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CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

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The 2010 FDA IND Safety Reporting Regulation requires sponsorsto report serious and unexpected adverse events only if there is evidence to suggest a causal relationship between the drug and the adverse event. However, a 2016 FDA analysis showed stable to increased numbers of reports from 2011-2015 versus 2006-2010; most (86%) were 'uninformative.' We sought to understand 1) sponsor challenges to full implementation of the Regulation, 2) sponsor motivation to change IND safety reporting practice, 3) investigative site IND safety report management, and 4) best practices for communicating safety reports. Methods: Surveys of sponsors (n=28) and investigator sites (n=201) were conducted, followed by interviews. Best practices were shared at a July 2015 Expert Meeting. Results: 'Sponsor' survey respondents were large and small companies, with diverse, active portfolios (median > 30 current trials, across all phases). Barriers to implementation included concerns over international regulatory harmonization, legal liability, over-riding investigator determinations, and thresholds for aggregate reporting. Investigator site respondents were experienced (median > 10 years), active clinical researchers, mainly in academic and community settings. While processing IND safety reports imposed a substantial workload, investigators found sponsor reporting systems cumbersome and the reports lacking in actionable information. Two companies reduced numbers of IND safety reports by 50-90% while improving the communication of safety information to investigators. Both utilized independent physician-led internal safety review, extensive training on causality thresholds, iterative review of past safety reports, and open communication with investigators. Support by senior management was essential. Stakeholders favored increased reporting of aggregate data. Conclusions: Sponsor best practices can improve IND safety reporting. Dissemination of these findings, sponsor/site education, and regulatory clarity offer the potential to further enhance the safety of oncology trials.

BACKGROUND

The US FDA published a "final rule," clarifying the reporting requirements for serious and unexpected suspected adverse reactions occurring in clinical trials conducted under an IND application (21 Code of Federal Regulations [CFR] part 312) in 2010 and a related final guidance in 2012. The rule was intended to improve the quality of safety reporting by reducing the number of uninformative reports generated by trial sponsors, allowing for easier and quicker detection of true safety signals.

The Clinical Trials Transformation Initiative (CTTI) undertook two projects to address the challenges associated with safety reporting. The first project developed recommendations that offered an approach for sponsors to monitor the safety of an IND throughout the development program. The second project ("IND Safety Advancement") focused specifically on safety reporting in oncology trials to determine barriers to and identify solutions for compliance with the final rule. The IND Safety Advancement Project aimed to identify 1) sponsor challenges to full implementation and motivation to change practice in order to fully comply with the final rule, and 2) challenges to investigator receipt and management of safety reports.

METHODS

Gathering data:

- Two online surveys targeting sponsors (28) and investigative staff (201) to assess challenges and motivations related to IND safety reporting
  - No data is available describing the number of potential respondents
  - Participation was voluntary, anonymous and uncompensated
  - Collected from November – December 2014
  - Aggregated by Duke Center for Learning Healthcare
- 20 in-depth interviews to gather qualitative information about reporting process
  - 13 PIs and/or other research staff
  - 7 pharmacovigilance leaders from 5 large global pharmaceutical companies
  - 1 hour interviews conducted by professional intervieweer using pre-specified interview guide
- The surveys and interviews were designated as exempt research by the Duke University Institutional Review Board (IRB).

REFERENCES

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RESULTS

Investigative staff respondents

- Processing safety reports was a substantial workload
  - No noticeable reduction in volume or change in quality over past year
- Safety reports that did not trigger protocol or consent changes were viewed as not useful

Sponsor respondents

- Major challenges to full implementation:
  - lack of global harmonization in reporting rules
  - Conservative approaches in assessing causality
  - fear of regulatory repercussions, which results in a "conservative" approach to safety reporting.
  - Even so, most sponsors believe the rule is reasonable and can reduce the number of uninformative safety reports
- How to improve implementation:
  - Additional direct interaction with the FDA to clarify nuances of the final rule
  - Increase FDA efforts to provide clarity

Table 1. Sponsor Staff Survey Respondents

CATEGORY	LARGE N=18 (68%)	MIDSIZE N=3 (11%)	SMALL N=7 (21%)
PORTFOLIO			
Diverse	1	0	3
Oncology-only	17	3	4
NUMBER OF ACTIVE ONCOLOGY TRIALS			
<10	1	1	3
11-30	2	1	3
31-50	4	0	0
>50	10	0	0
PHASE OF TRIAL			
Phase 1	15.5	2	5
Phase 2	15.5	2	5
Phase 3	15.5	2	5
Phase 4/Post-marketing	15.5	2	2
Other	7	0	0

Figure 1. What are the internal org. barriers to full implementation of the FDA final rule on IND safety reporting requirements?

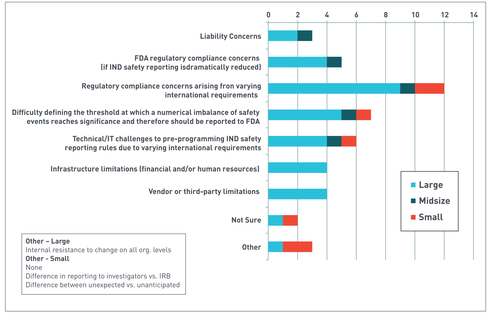


Figure 2. What is the average number of expedited IND safety reports for clinical trials (initial plus follow up, all therapeutic areas) reported to the FDA per year by your organization?

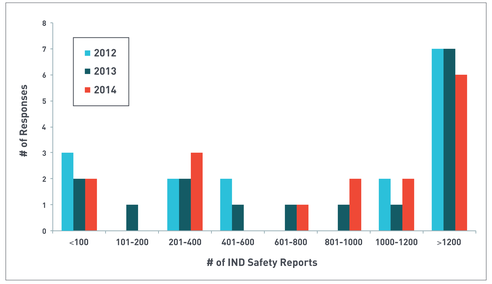


Table 2. Summary of Sponsors' Perceptions

REGULATORY
Investigators still making many reports causally related and sponsors may not agree with their assessment
A desire to not go against the Investigators causality assessment as they feel they are at point of care and understand the patient better than the sponsor
Fear that underreporting may lead to regulatory repercussions, such as inspections or audits
Lack of global harmonization on reporting rules
LEGAL
Impact on the marketplace of a perception of under-reporting events
Perception of concern if during a legal challenge cases were marked as related by investigators but not many by sponsor (i.e., may be interpreted as the sponsor "hiding" events)
TECHNOLOGICAL
More popular safety systems can route reports based on reporting rules to recognize the different regulatory requirements in different countries
Sponsor companies may be "masking" the real issue of "overreporting" to investigators by trying to make the process easier with electronic portals
ORGANIZATIONAL
Fully complying with the final rule requires cultural and infrastructural changes that are difficult and time-consuming to implement
Important personnel may not fully understand nuances of the final rule

Figure 3. What is the estimated number of staff hours per month that is required to manage IND safety reports?

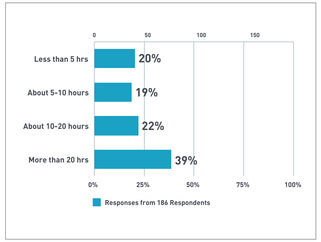


Figure 4. Have you noticed a decrease in the quantity of IND safety reports that you have received over the last year?

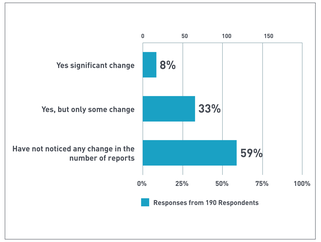


Figure 5. Over the past year, have you noticed that IND safety reports have become more useful, less useful or have you not noticed a change from before?

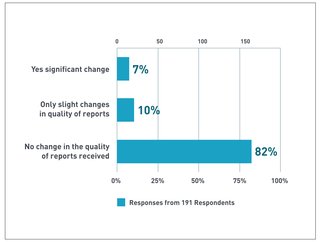
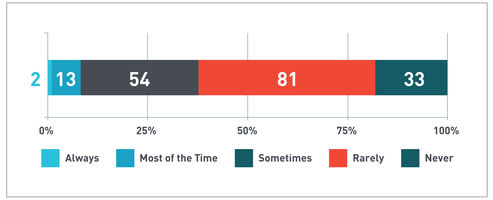


Table 3. Investigative Staff Survey Respondents

CATEGORY	INVESTIGATORS N=47	OTHER STUDY STAFF N=154
EXPERIENCE IN ROLE		
<1 year	0%	4%
~1-3 years	9%	28%
~4-6 years	9%	18%
~7-10 years	19%	18%
>10 years	64%	32%
EXPERIENCE IN CLINICAL TRIALS IN GENERAL		
<1 year	0%	3%
~1-3 years	2%	9%
~4-6 years	4%	13%
~7-10 years	6%	25%
>10 years	87%	51%
PRIMARY CATEGORIZATION OF INVESTIGATIVE SITE		
Academia	32%	37%
Community-based private practice	57%	39%
Cancer consortium	4%	13%
Hospital	4%	8%
Other	2%	3%
NUMBER OF ACTIVE ONCOLOGY TRIALS		
<5	9%	2%
~5-10	28%	7%
~11-20	13%	14%
~21-30	15%	10%
>30	36%	67%
PHASE OF TRIAL		
Pilot/Phase 0	0%	5%
Phase 1	62%	58%
Phase 2	85%	89%
Phase 3	89%	89%
Phase 4/Post-marketing	34%	27%
Registry	6%	0%
Other	4%	3%
TYPES OF TRIAL SPONSORS		
Industry	56%	52%
Government	3%	4%
Investigator-initiated	10%	11%
National Clinical Trials Network	30%	31%
Other	1%	3%

Figure 6. Some IND safety reports DO NOT generate a protocol change or consent change. Are these types of reports still useful in managing the care of research participants at your site?



Common Practices at Companies That Fully Implemented the 2010 Regulation

- Increased numbers of Medical Safety Review physicians, organized into review teams
- Intensive training on level of evidence for causality assessment
  - Clear documentation of rationale
  - 'Insufficient information' = 'unrelated'
- Medical judgment and quantitative aggregate evidence are applied to decide whether expedited an individual IND Safety Report is justified
- Follow-up reports only sent when there is new, actionable information

Impact:

- Company A: > 90% reduction in initial and follow-up IND safety reports submitted to FDA and US Investigators within 6 weeks of implementation
- Company B: 50-80% reduction in reports to FDA and investigators, respectively

CONCLUSIONS

- Many oncology investigators still receive a high volume of reports, most of which are uninformative, due to incomplete implementation of the FDA regulations on safety reporting.
- This high volume of uninformative safety reports consume substantial time and resources and are not believed to be valuable for ensuring patient safety.
- The onus of implementing the final rule is on oncology trial sponsors. However, concerns about global harmonization, thresholds for determining causality, and fear of regulatory repercussions have deterred some sponsors from implementing processes consistent with FDA's final rule.
- The clinical trial enterprise can benefit from additional educational materials on the final rule and proactive, bidirectional communication between sponsors and the FDA, and sharing of best practices among sponsors.