The Clinical Trials Transformation Initiative IND Safety Advancement Project: Findings and Next Steps

Michael Jones, MBA
Senior Director, Clinical Operations
Eli Lilly & Company
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Clinical trials in crisis

The changing structure of industry-sponsored clinical research: pioneering data sharing and transparency.

Kuntz RE.
Addressing This Need

To identify and promote practices that will increase the quality and efficiency of clinical trials

Public-Private Partnership involving all stakeholders
60+ members

Formed in 2007
Collaboration Towards Solutions

Better Streamlined Fit for purpose

- Clinical investigators
- Patients / Patient advocacy groups
- Academia
- Industry: pharma bio device CRO
- Government and regulatory agencies
- IRBs
- Industry trade / Professional organizations
## Portfolio of CTTI Projects

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<th>Investigational Plan</th>
<th>Study Start-up</th>
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<td>• Uses of electronic data</td>
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<td>• Central IRB advancement</td>
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<td>• Patient groups &amp; clinical trials</td>
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<td>• Uses of electronic data application</td>
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CTTI IND Safety Advancement Project

Objectives

- Evaluate impact of FDA rule changes and original CTTI IND Safety project recommendations on volume of IND safety reports in oncology trials
- Understand what the sponsor challenges are to full implementation of the IND safety reporting rule in oncology trials
- Understand sponsor motivation to change practice of IND safety reporting in oncology trials in order to fully comply with the IND safety reporting rule
- Understand challenges to investigator receipt and management of IND safety reports at oncologic investigative sites and coordinating centers
- Explore FDA inspection findings related to IND safety reporting
- Facilitate adoption of best practices for communicating and managing IND safety reports consistent with FDA guidance, the IND safety rule and CTTI recommendations
How are We Collecting and Analyzing Information

- Sponsor and Investigator Surveys and Interviews
- Team meetings to discuss the output and synthesize information
- Discussion of common themes and gaps
- Open dialog to address identified opportunities to move the industry in compliance with the regulation
Deliverables

Recommendations to encourage best practices for IND safety reporting among stakeholders

Define strategies to facilitate adoption of best practices
CTTI IND Safety Advancement Project
Investigator Survey and Interview Findings
Methods

- Online survey: PI/Sub-I (n= 47) and study staff (n=154)
- In-depth interviews: 13 PIs, and/or study managers/staff

Objectives:
- Understand how sites process safety reports, and workload
- Assess perceived value of safety reports
- Understand how sites use safety reports that do not generate protocol/consent change
- Elicit suggestions for improvement
Safety Report Workload and Processing

- ~80% of sites received > 20 IND safety reports/month
- Over half of sites (61%) report > 10 hrs/month staff time required to process
- 20% of sites have refused to process reports, 73% ‘not sure’ if they have ever refused. Main reasons:
  - Do not meet IRB requirements (78% PIs, 68% staff)
  - Workload (43, 44%)
  - Do not comply with FDA rule (33, 54%)
- There is variability, and a potential disconnect, in PI engagement with IND safety report processing.
What is the estimated number of IND safety reports that you receive per month for the studies at your site?

- More than 20: 81.15%
- 11-20: 10.99%
- 1-10: 7.85%

Responses from 191 Respondents
What is the estimated number of staff hours per month that is required to manage IND safety reports?

**Investigators**

- Less than 5 hrs: 14%
- About 5-10 hours: 24%
- About 10-20 hours: 19%
- More than 20 hrs: 43%

**Other Study Staff**

- Less than 5 hrs: 22%
- About 5-10 hours: 17%
- About 10-20 hours: 23%
- More than 20 hrs: 38%

Responses from 42 Respondents

Responses from 144 Respondents
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?

- **No change in the quality of reports received**: 82.0% (82.20% of responses)
- **Only slight changes in quality of reports**: 10.5% (10.47% of responses)
- **Yes significant change**: 7.3% (7.33% of responses)

Responses from 191 Respondents
If you were starting from scratch, what would an ideal IND safety reporting system look like?

- Individual expedited reports should meet unexpected and serious criteria, not known adverse events or events related to disease process
- All other reports should be reported in aggregate, to show trends and possible conclusions
- Central database/portal used by all sponsors and sites
  - Easy access
  - Intuitive
  - Applications available on multiple platforms, keeping up with newer technology (eg not PC or Mac specific)
  - Have reports filterable by agent or investigator to stop duplicate reporting
  - Ability for PI electronic sign off
The intent of the IND Safety Reporting Rule --- to make trial patients safer -- is laudable, however, none believed that it has achieved that goal. They characterized IND Safety Reporting as a “failed system,” since the large volume of reports they still receive, accompanied by the fact that almost all are irrelevant, out of context and don’t meet the reporting criteria, make them useless to everyone.
All said that their need to comply with their FDA regulatory obligations imposes a significant burden on the sites as well as a drain on their time and resources. *None have ever used any information from these reports to improve their trials or make patients safer.* All but one said that the PIs sign off on the reports, but typically don’t read them because it is time consuming, and they find them irrelevant. They say this process takes time away from the important work they must do on their clinical trial studies.
Investigator Interviews: Summary

All of those interviewed praised the investigator alert emails that sponsors send to the PIs and the FDA. Some thought that this was the primary information they, as investigators need, because it alerts them to serious, unexpected events, caused by the investigative drug, which will trigger a change in the trial.

Even after the new IND safety reporting rule took effect, the investigative sites saw no drop-off in the number of individual safety reports they received.
The PIs and their teams want to see individual safety reports only for possible adverse events that are serious, unanticipated, probably related to the drug and would trigger a change in protocol.

All of the PIs and their investigative teams agree with the FDA that a meaningful system of IND safety reporting would keep the onus on the sponsor, but only send the reports that meet all four reporting criteria.
High Level of Frustration

“It’s like getting daily reports like – ‘Hey, Chevy has a problem with their tires’ because one person in Texas had his tire blown out and he had a Chevy. But where were they driving? Is this happening a lot? Is this a problem with the tire? Were they driving on a bed of nails? Chevy wouldn’t say, ‘We should have a recall of all these tires because of this one incident.’”
Overall Summary and Conclusions

- IND Safety Reports are perceived by investigators and sites as a substantial burden that fails to enhance safety of clinical research subjects.

- Efforts to streamline the IND Safety reporting process, such as the 2010 FDA rule and sponsor electronic reporting portals, have not decreased the number or improved the utility of these reports.

- Investigator alert emails were considered more valuable SUSARS.

- Respondents favored a centralized, platform-independent system for dissemination of aggregate safety data.
CTTI IND Safety Advancement Sponsor Survey and Interview Findings
Methods

- Survey: 14 Large, 1 Midsize and 5 Small
- Interviews: Seven Directors/Vice Presidents of pharmacovigilance operations from five large global pharmaceutical companies were interviewed

**Objective:**
- To better understand, from both report sender and recipient, the barriers to fully implementing compliance with the FDA’s new IND reporting rule
Interview and Survey Results:

- Most of those interviewed said that their companies have cut down by at least 40 to 75 percent on their individual IND safety reports.
- Two said that their companies achieved the 90 percent reduction goal.
With your organization's implementation of the FDA final rule on IND safety reporting requirements, did you see a reduction in the volume of initial safety reports distributed by your organization to US Investigators and FDA?

Yes

No

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Approximately what percent reduction did you see?

- **More than 75% reduction**: 2
- **About 50-75%**: 3
- **About 25-50%**: 0
- **About 10-25%**: 0
- **Less than 10%**: 0

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What are the internal organizational barriers to full implementation of the FDA final rule on IND safety reporting requirements?

- Liability Concerns
- FDA regulatory compliance concerns (if IND safety reporting is dramatically reduced)
- Regulatory compliance concerns arising from varying international requirements
- Difficulty defining the threshold at which a numerical imbalance of safety events reaches significance and
- Technical/IT challenges to pre-programming IND safety reporting rules due to varying international requirements
- Infrastructure limitations (financial and/or human resources)
- Vendor or third-party limitations
- Not Sure
- Other

Other – Large
Internal resistance to change on all organizational levels
Other - Small
None
Difference in reporting to investigators vs IRB
Difference between unexpected vs unanticipated
Summary of Common Themes

- Sponsors saying that very difficult to get to the actual 90% without more guidance/training from FDA
  - Most are citing ~40-75% reduction
- Harmonization across international regulatory agencies would be helpful
- Investigators still making many reports causally related and sponsors agree with their assessment (or don’t want to go against it)
- Conservativism: err on the side of over-reporting for fear of regulatory consequences if they misjudge causality
  - Concern inspectors may judge a report differently resulting in an inspection finding
  - No one wants to be cited for “hiding” events
Common Themes in Motivation to Change

Results ranged

From:
– Obeying the law and believing the rule is sensible and good for patients by reducing over-reporting and the number of meaningless reports going to investigators and thereby creating better relationships with the investigators

To:
– Avoiding being cited by FDA for over-reporting, Avoiding costly and embarrassing citations for submitting too many safety reports
Most Still Feel the FDA Plays a Role in Clarifying/Helping Sponsors

- Those interviewed said that the FDA has cleared up many points in its last guidance document. Nevertheless, they would like more clarity from the FDA on several aspects of the rule.
  - Consequences if a mistake is made
  - Thresholds for aggregate analysis

- The respondents who had clarifying conversations with the FDA suggested that a series of workshops or webinars with FDA officials would help clear up confusion with the IND rule.
Project Next Steps

► Multi-stakeholder meeting to discuss
  – Best practices for communicating both routine safety issues and aggregated IND Safety Reports
  – Considerations related to information systems for entering and reporting safety information
  – Clarification of FDA inspection policies related to IND safety reporting

► Additional opportunities for education and dialogue (webinars, etc.)
Thank You

Michael Jones
Senior Director, Clinical Operations
Eli Lilly & Company

Presenting on behalf of CTTI IND Safety Project Leaders

• Patrick Archdeacon, FDA
• Robert Goodwin, Pfizer
• Jonathan Jarow, FDA
• Michael Jones, Eli Lilly & Co.
• Raymond Perez, University of Kansas
• Nancy Roach, Fight Colorectal Cancer
• Annemarie Forrest, Project Manager, Duke