

Welcome to the CTTI IND Safety Advancement Project Expert Meeting

July 21-22, 2015



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Introduction to The Clinical Trials Transformation Initiative

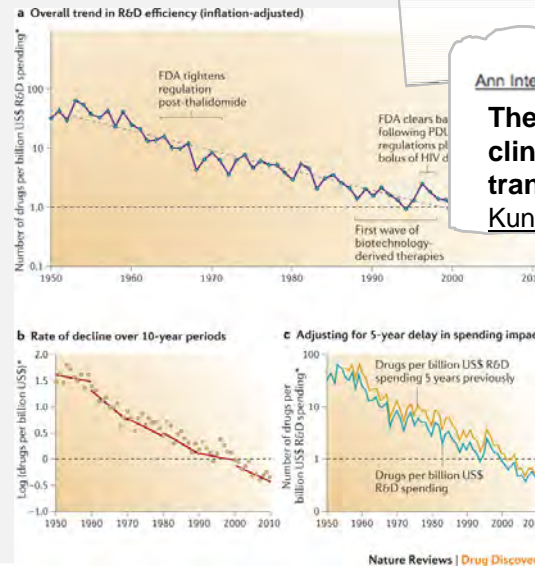
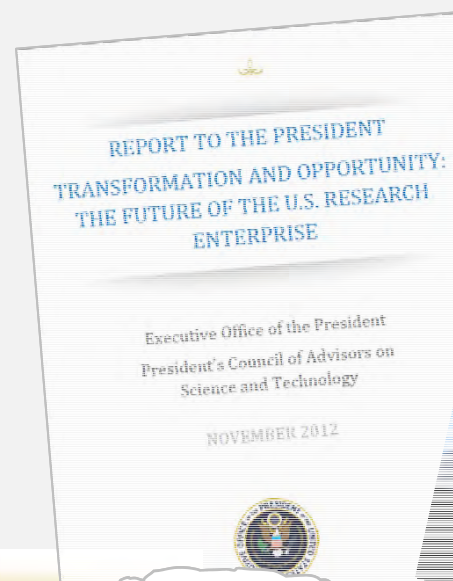
Annemarie Forrest, Senior Clinical Project Leader, CTTI

July 21, 2015



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Clinical trials in crisis



Ann Intern Med. 2013 Jun 18;158(12):914-5. doi: 10.7326/0003-4819-158-12-201306180-00011.

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

Kuntz

BROOKINGS

RESEARCH ▾

EVENTS

EXPERTS

ABOUT ▾

MAR
5

PAST EVENT

Biomedical Innovation: Identifying Challenges and Prioritizing Needs

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

CTTI Organization

Executive Committee (EC)

Provides oversight and strategic direction

Steering Committee (SC)
(member organizations representatives)

Gives input into strategy and project selection
Conducts projects and develops strategies for implementation of project results

CTTI Staff

Support projects and organization in pursuit of mission

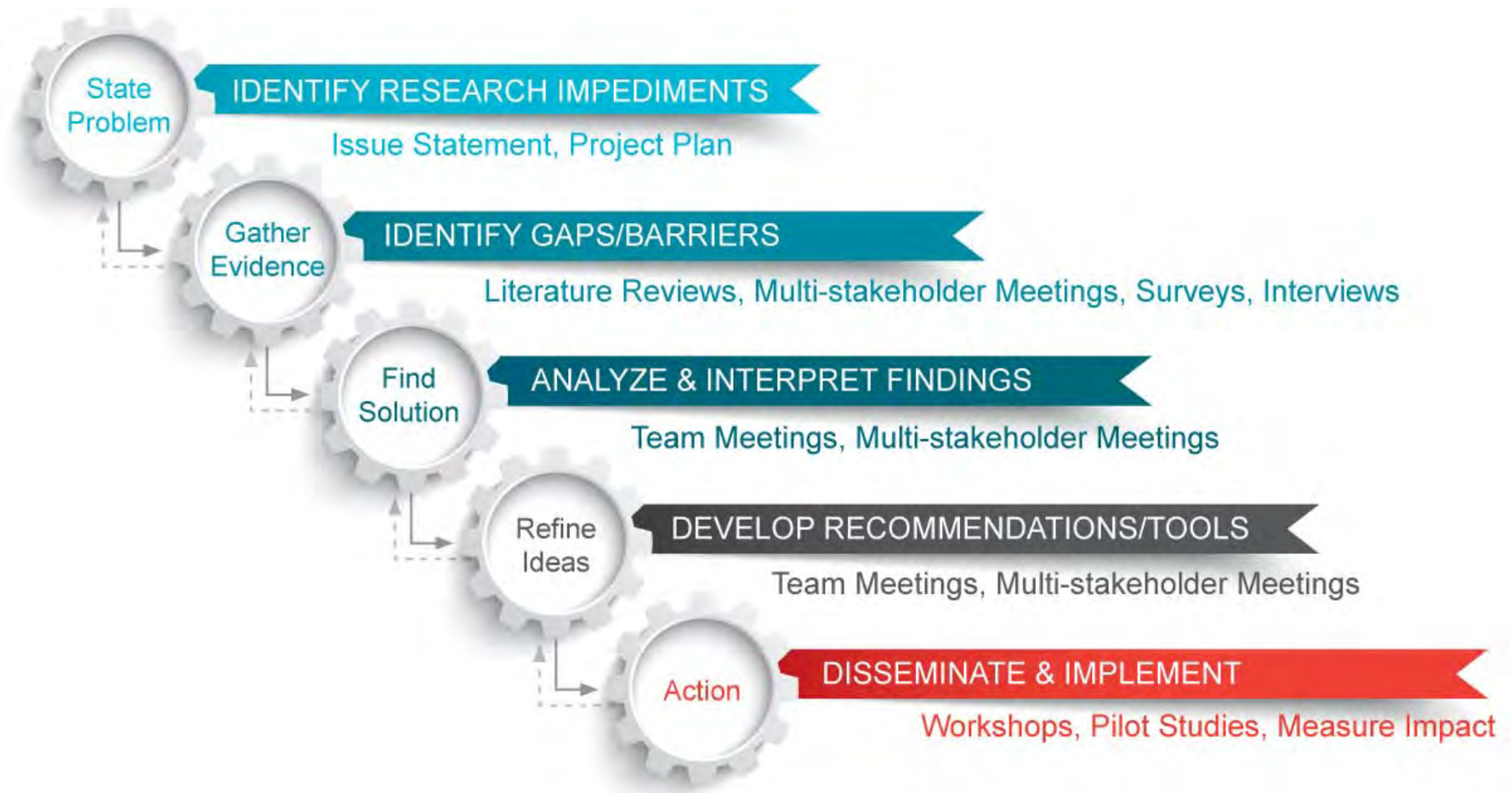
Collaboration Towards Solutions



How does CTTI work?

- ▶ Engage & value all stakeholders equally
- ▶ Understand incentives to maintain non-value added activities and have solutions that are mindful of those incentives
- ▶ Plant the seeds for change throughout all phases of a project
- ▶ Develop actionable, evidence-based, consensus driven recommendations
- ▶ Create and share knowledge, tools & resources to facilitate change that improves clinical trials

CTTI Methodology



Portfolio of CTTI Projects

	Investigational Plan	Study Start-up	Study Conduct	Analysis & Dissemination	Specialty Areas
Closed Projects	<ul style="list-style-type: none"> • Large simple trials • Uses of electronic data 	<ul style="list-style-type: none"> • Central IRB • Site metrics • Central IRB advancement • GCP training 	<ul style="list-style-type: none"> • Adverse event reporting • IND safety • Monitoring 		<ul style="list-style-type: none"> • Long-term opioid data
Ongoing Projects	<ul style="list-style-type: none"> • Mobile clinical trials (program) • Patient groups & clinical trials • Pregnancy testing • QbD • Trials based on registries • Uses of electronic data application 	<ul style="list-style-type: none"> • Informed consent • Investigator turnover • Recruitment 	<ul style="list-style-type: none"> • IND safety advancement • Safety case studies 	<ul style="list-style-type: none"> • State of clinical trials • DMCs 	<ul style="list-style-type: none"> • Pediatric antibiotic trials • Streamlining HABP/VABP trials • Unmet need in antibiotic development • ABDD pilot

Session I – Project History and Overview

Objective

- Understand past and current efforts to improve the efficiency of expedited IND safety reporting

Agenda

- Expedited IND Safety Reporting: History and Current Guidance
- Expedited IND Safety Reports Submitted to FDA's Office of Hematology and Oncology Products
- Patient Perspective on Safety Reporting
- Project Overview and Meeting Objectives

The Patient Perspective on Expedited IND Safety Reporting

Nancy Roach, Fight Colorectal Cancer

July 21, 2015



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Expedited IND Safety Reporting: History and Current Guidance

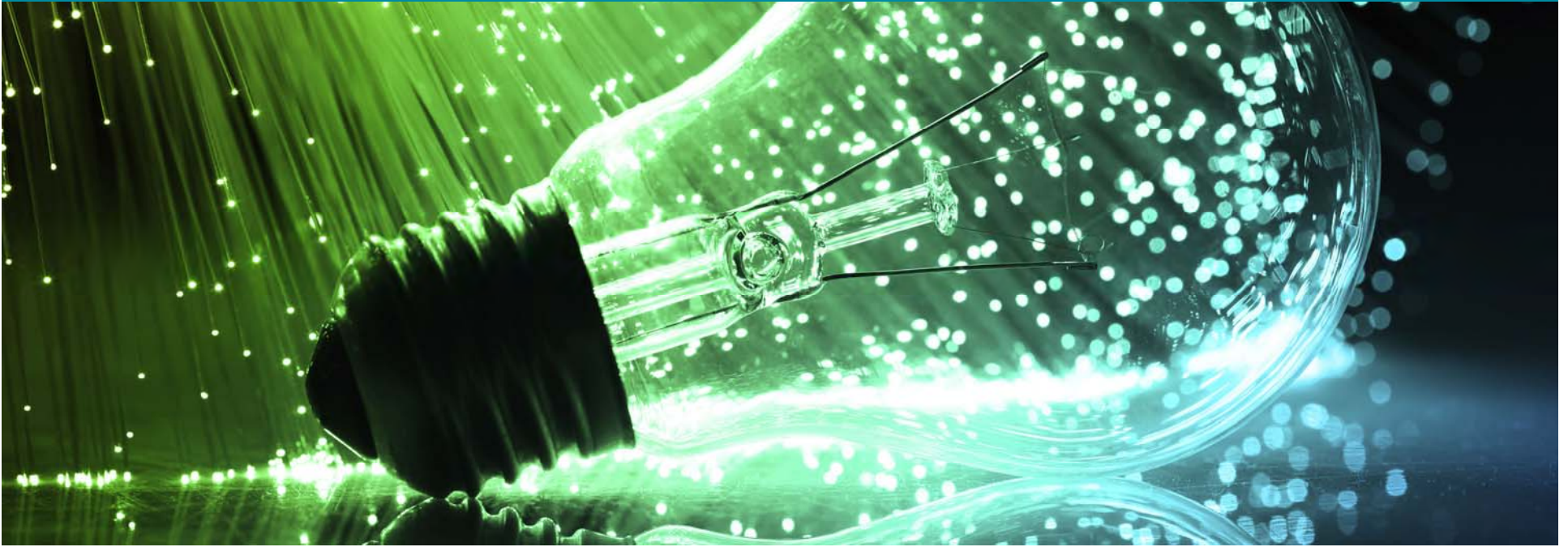
José M. Vega, M.D.

Chief Safety Officer, Merck

July 21, 2015



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Disclaimer

The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.

The presenter is a full-time employee of Merck Research Laboratories.

FDA Final Rule on Pre-marketing IND Safety Reporting

- ▶ US FDA published a new rule and draft guidance regarding IND pre-marketing safety reporting *

* Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans (21 CFR Parts 312 and 320; Federal Register, Vol. 75, No. 188)

- ▶ Published on 9/28/10, with an effective date of 3/28/11

- 3/25/11: FDA notice of enforcement discretion with expectation of full compliance by 9/28/11

FDA's IND Safety Reporting Rule

▶ Goal

- Improve the utility of premarket expedited safety reports, thereby enhancing human subject protection
 - Eliminate confusing terminology
 - Clarify sponsor and investigator responsibilities
 - Eliminate uninformative individual case reports

▶ The rule describes the FDA's expectation of a higher threshold for the sponsor's reporting of suspected adverse reactions to the FDA based on the sponsor's assessment of causality (not the investigator's)

FDA's IND Safety Reporting Rule

▶ Problems prior to the new rule:

- FDA and investigators receiving large numbers of uninformative IND safety reports
- Sponsors often report serious adverse events as individual cases that:
 - Are likely to have been **manifestations of the underlying disease** (e.g., mortality or major morbidity)
 - **Commonly occur in the study population** independent of drug exposure (e.g., strokes or acute myocardial infarctions in an elderly population)
 - **Are study endpoints** (i.e., the study was evaluating whether the drug reduced the rate of these events)
- Making a judgment about causality is generally not possible for these single cases

FDA's IND Safety Reporting Rule

- ▶ Report any **suspected adverse reaction** that is both serious and unexpected – must meet all three definitions
 - *Suspected adverse reaction* means any adverse event for which there is a **reasonable possibility** that the drug caused the event
 - *Unexpected* means not listed in the investigator brochure...
 - *Serious* means results in death, is life-threatening, hospitalization...

Enhanced Compliance with FDA IND Safety Reporting Rule

- ▶ Differential Expedited Reporting due to FDA IND Safety Reporting Rule*
 - For the purposes of IND safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event
 - FDA reporting is driven by Sponsor’s independent assessment of causality ONLY
 - For ROW, most conservative assessment continues to drive reporting; higher threshold for FDA reporting
- ▶ Expect > 90% reduction in initial and follow-up individual case safety reports (ICSR’s) expedited to FDA and to US investigators

*FDA 21CFR 312.32

2009-10 CTTI Project: Expedited safety reporting to IND investigators

- ▶ Focused on expedited reporting from sponsors to site investigators
- ▶ Investigators had complained of a large volume of expedited reports that were not interpretable as individual cases
- ▶ Methods:
 - Survey of sponsor practices
 - Data collection from a small number of sites re: time and personnel required to process expedited reports
 - Patient focus groups

Recommendations from 2009-10 Project

- Decrease the volume of uninterpretable and irrelevant safety reports to investigators
- Supply investigators with meaningful reports that would improve investigators' understanding of a drug's safety (benefit-risk) profile.
- Engage patient groups to discuss optimal systems for safety reporting to investigators and patients during the conduct of a trial; re-evaluate consent language

CTTI Project: IND Safety Assessment and Communication

Project Goal:

Promote responsible oversight of safety for pre-market products consistent with the intent of the FDA's new IND safety rule

This was the 2nd CTTI IND Safety Reporting Project (2011-2013)

Objectives: IND Safety Assessment and Communication

- Understand sponsors' current practices
 - Assessing safety of a pre-market product across all trials and sources of safety information
 - Communicating potential safety signals
- Facilitate discussion of practices and challenges in assessing and communicating IND safety information
- Issue recommendations for future approaches that will support the intent of the final IND safety reporting rule

Methods

- Survey sponsors about current safety practices
- Summarize anonymized results of survey
- Convene an expert meeting
- Establish a workgroup of biostatisticians from industry, FDA, and academia
 - To attend expert meeting and meet separately to work on methodological issues
- Synthesize output and make recommendations

Summary of CTTI Recommendations

I. Upfront safety planning for a development program

- Identify *anticipated** serious adverse events as early as possible
 - Standardize terms
- Specify in the protocol that *anticipated* serious events will not be reported as individual IND safety reports

***Events that commonly occur in the study population independent of drug exposure or manifestations of the underlying disease**

Summary of CTTI Recommendations

(continued)

I. Upfront safety planning (continued)

Plan to periodically analyze frequency of *anticipated* serious adverse events by treatment group

- Report study endpoints according to protocol, not as individual IND safety reports
- Ensure timely access to all study data, e.g. electronic collection
- Ensure integrity of ongoing trials if planning to incorporate unmasked data in analyses

Summary of Recommendations (continued)

II. Implementation of safety assessment in clinical trials

- ▶ Arrange for periodic evaluation of the totality of safety information in the development program
 - Do not wait for NDA or BLA
 - Frequency depends on drug, disease, stage of development, & nature of serious adverse event (SAE)
 - Because comparisons of event rates in the overall study population vs. historical controls are less sensitive than comparisons across treatment arms, unmasking of SAEs may be required
 - Unmasked analyses should be conducted by firewalled committees (internal or external to the sponsor)

Summary of Recommendations (continued)

II. Implementation of safety assessment in clinical trials (cont' d)

▶ When appropriate, sponsors should perform a meta-analysis of completed studies; in some cases that might include unmasked data from ongoing studies

- To the extent feasible, analyses should preserve the randomization of individual studies and account for differences in study designs, nature of control groups, and duration of exposure
- Since looking for reportable SAEs, do not correct for multiplicity or depend on p-values

Summary of Recommendations (continued)

II. Implementation of safety assessment in clinical trials (cont' d)

▶ Sponsors should be prepared to incorporate into aggregate analyses the totality of data on an investigational product, including laboratory results and other relevant measures

▶ FDA should issue additional guidance on how internal or external safety committees might notify appropriate individuals at sponsor company of a safety signal in a way that protects both patient safety and the integrity of the trial, should it be continued

Summary of Recommendations (continued)

III. Threshold for expedited reporting of *anticipated* events

- Sponsors should report serious adverse events that are anticipated to occur in the study population in aggregate safety reports when the totality of data suggests a causal relationship

Summary of Recommendations (continued)

IV. Adverse events not pre-specified in the protocol (presumably uncommon and/or not known to be strongly associated with drug exposure and not study endpoints)

▶ If a single case meets the definition of a suspected adverse reaction, report it

▶ Often more than one event is necessary to suggest a reasonable possibility that the drug caused the event. If there is uncertainty or weak evidence of causality, the sponsor could consider reporting these as individual events via expedited mechanisms to FDA

Thank you.



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www.ctti-clinicaltrials.org



Project Overview and Meeting Objectives

Michael Jones, Eli Lilly

July 21, 2015



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Issue

- ▶ There is an opportunity for further work to achieve the goals of all the projects' efforts to date
- ▶ It is time to get it right
 - Remove non-value-added activity and burden
 - Ensure appropriate and timely information to investigators and regulators

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

Project Methodology

Report
Volume
Analysis

Review
FDA
Inspections
(483s)

Surveys
and
Interviews

Expert
Meeting

Determine
Additional
Opportunitie
s for Impact

Session II – Presentation of Project Findings

Objective

- Present and discuss findings and conclusions from the project evidence gathering activities

Agenda

- Investigative Site Survey and Interview Findings
- Sponsor Survey and Interview Findings

CTTI IND Safety Advancement Project Investigator Survey and Interview Data

Raymond Perez, MD; on behalf of the 'Investigator' Subgroup

July 21, 2015



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Methods

➤ Online survey

➤ In-depth interviews

➤ 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

Respondents

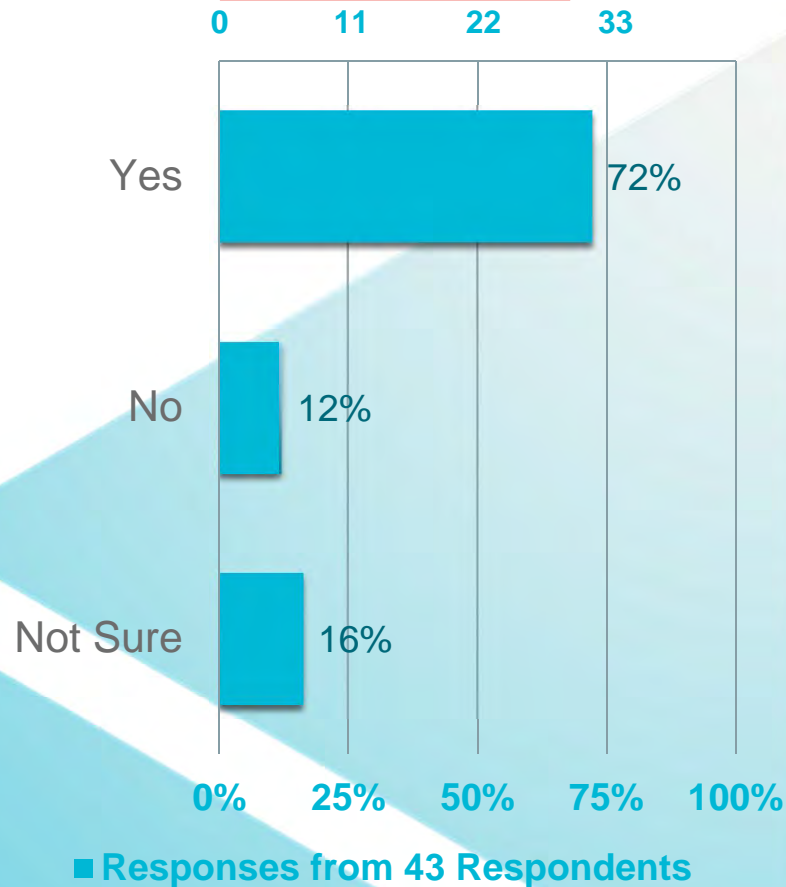
- ▶ Online survey: PI/Sub-I (n= 47) and study staff (n=154)
- ▶ In-depth interviews: 13 PIs, and/or study managers/staff
- ▶ Academic and community-based
- ▶ >10 years clinical trials experience
- ▶ >30 studies concurrently
- ▶ All trial phases
- ▶ Industry and government sponsored trials

Safety Report Workload and Processing

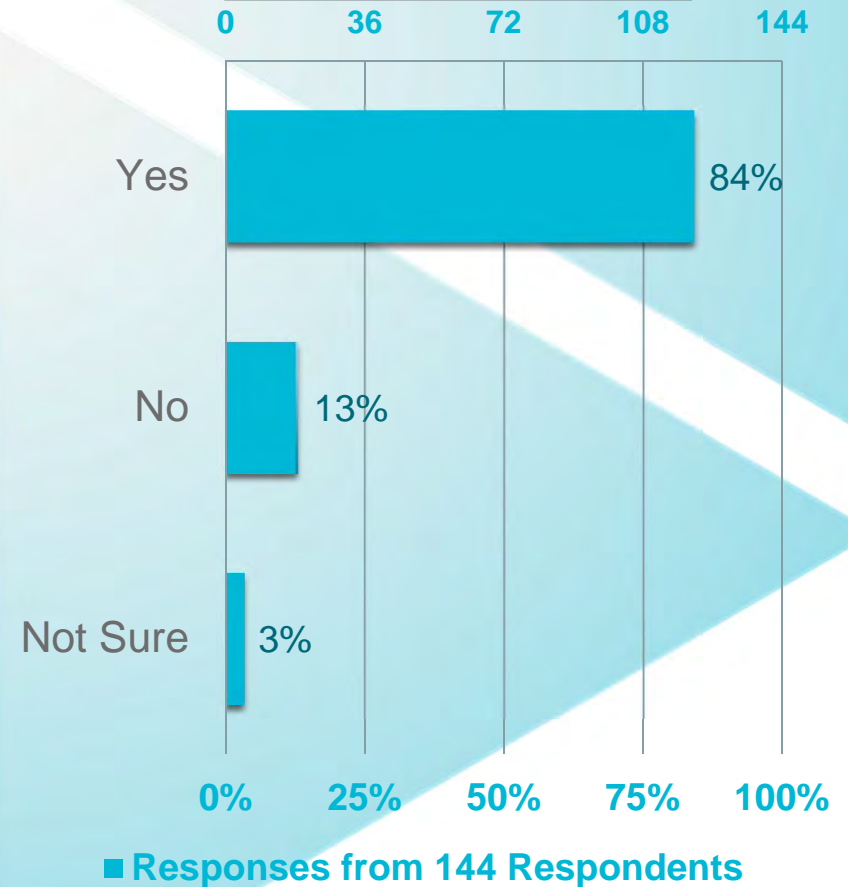
- ▶ ~80% of sites received > 20 IND safety reports/month
- ▶ Over half of sites (61%) report > 10 hrs/month staff time required to process
- ▶ 20% of sites have **refused to process** reports, 73% 'not sure' if they have ever refused.
- ▶ Reasons:
 - Do not meet IRB requirements (78% PIs, 68% staff)
 - 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.

Is there a Standard Operating Procedure in place at your site for the management of IND safety reports?

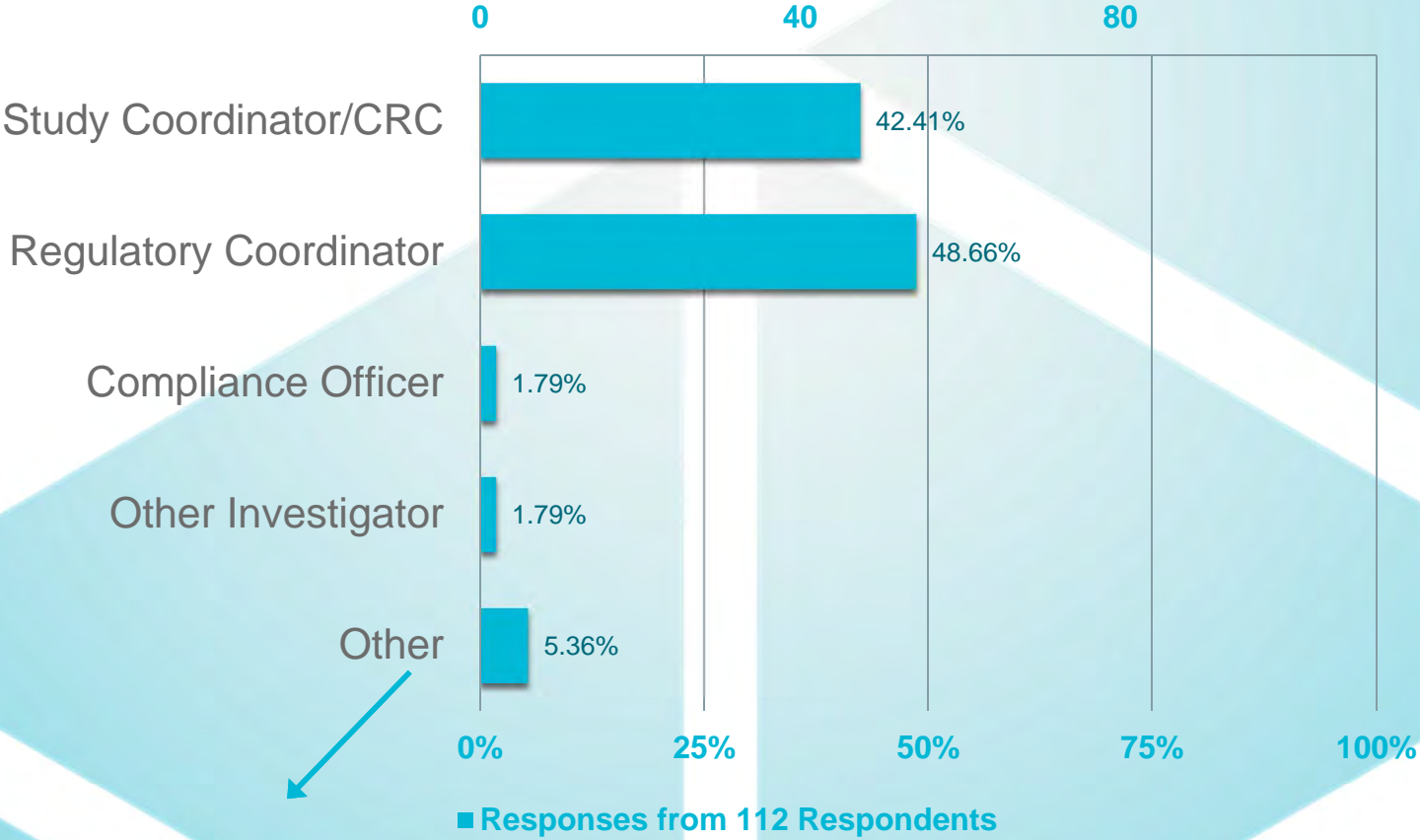
Investigators



Other Study Staff



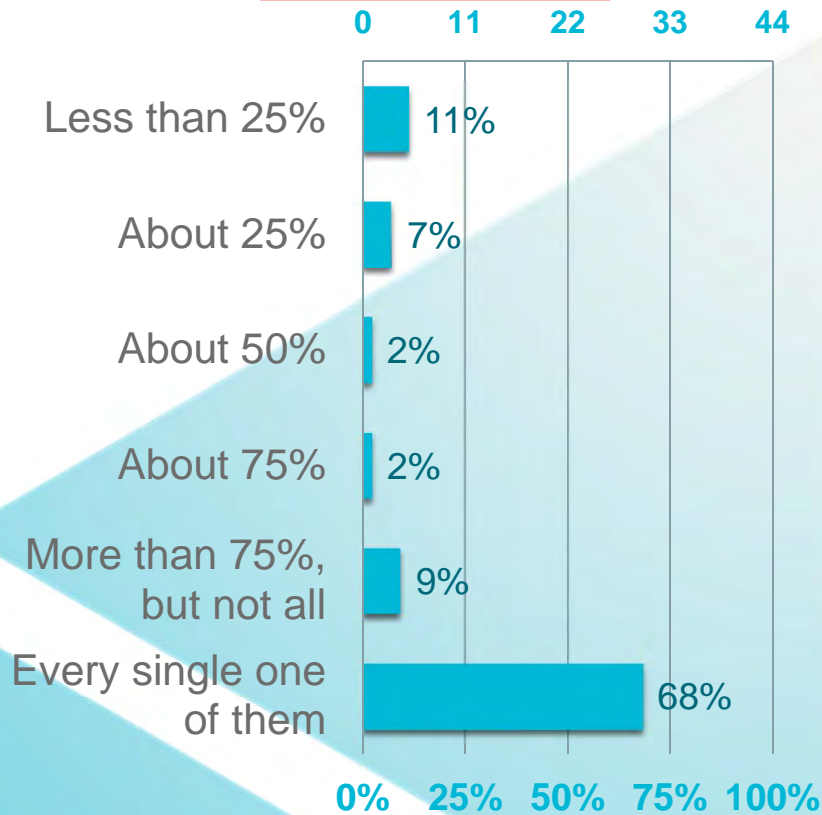
Who is the initial reviewer of the reports before the Principal Investigator?



PI
Varies according to Investigator
Research Manager/Program Specialist

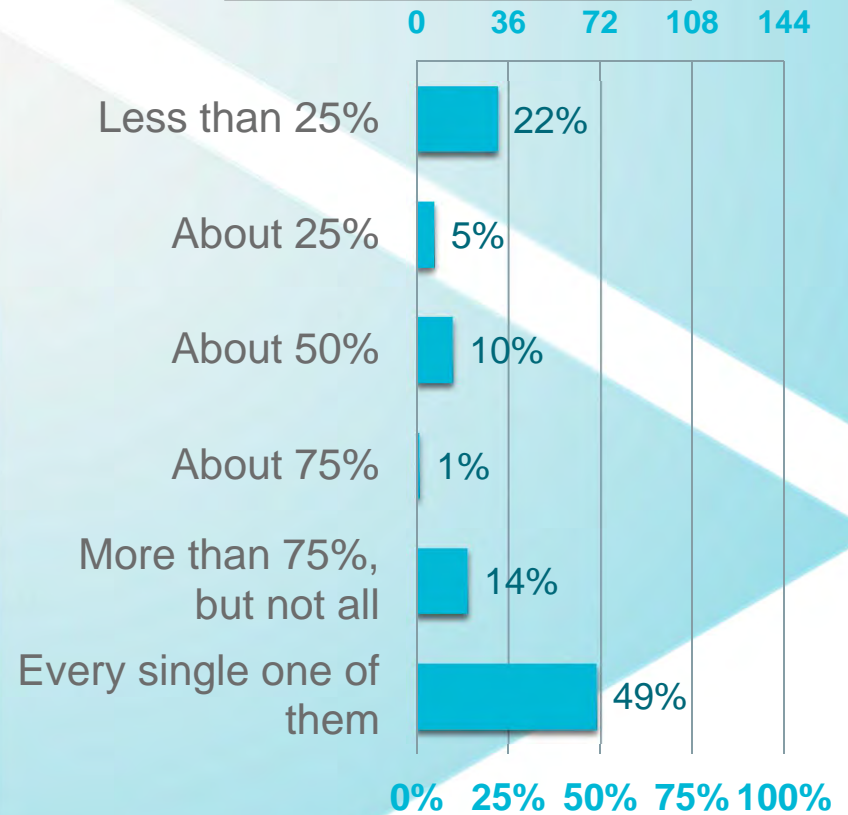
Of the IND safety reports received at your site, what % gets reviewed by the Principal Investigator for the trial?

Investigators



■ Responses from 44 Respondents

Other Study Staff



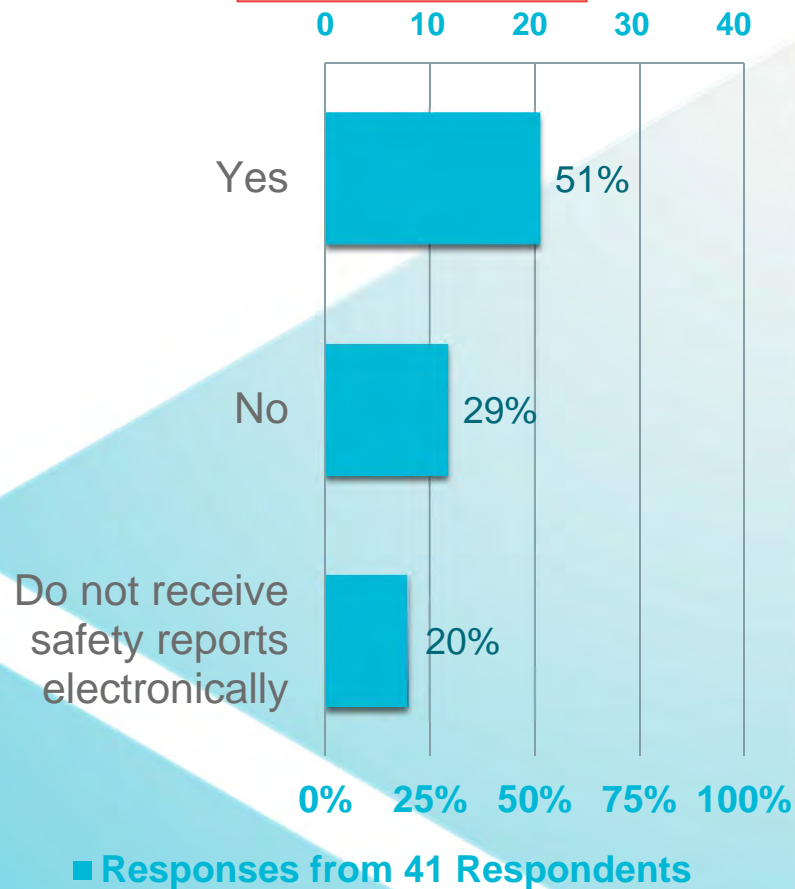
■ Responses from 144 Respondents

2010/2011 Safety Reporting Rule

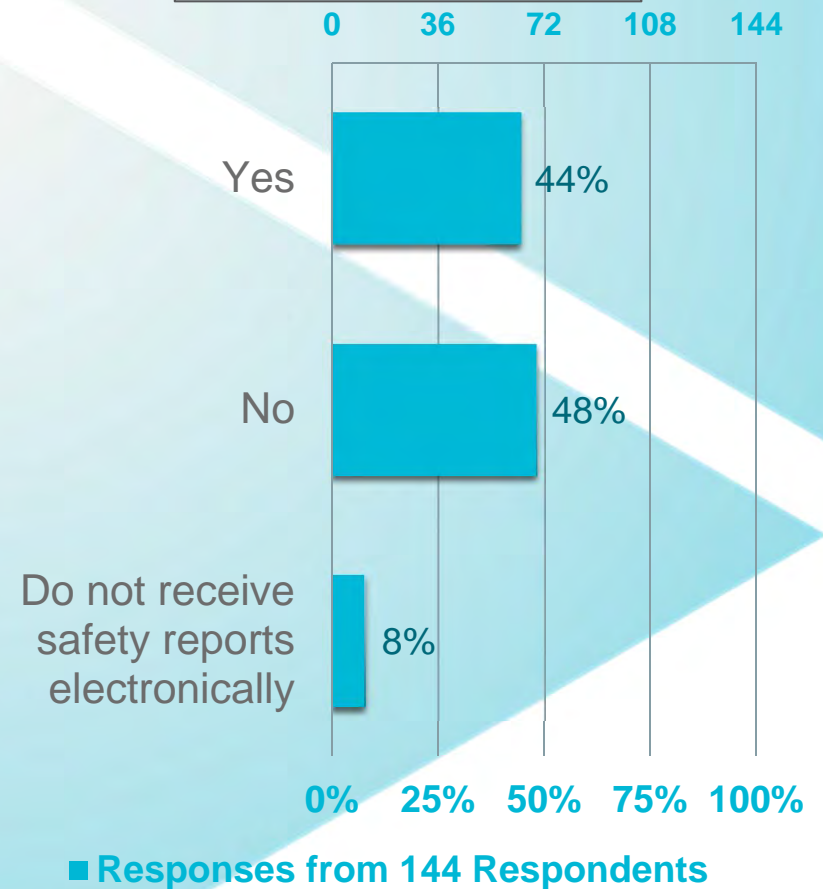
- ▶ Majority of investigators (54%) and staff (63%) were aware of new rule
 - Many investigators (46%) and staff (37%) were not.
 - Most investigators (72%) and staff (81%) who were aware were also familiar with changes made by the new rule.
- ▶ Majority of investigators (71%) and staff (54%) noted **NO CHANGE** in **VOLUME** of reports over the past year.
- ▶ 82% noted **NO CHANGE** in **QUALITY** of reports over the past year.

If IND safety reports are distributed via a sponsor safety reporting portal, do you have difficulty accessing the IND safety reporting portal?

Investigators



Other Study Staff

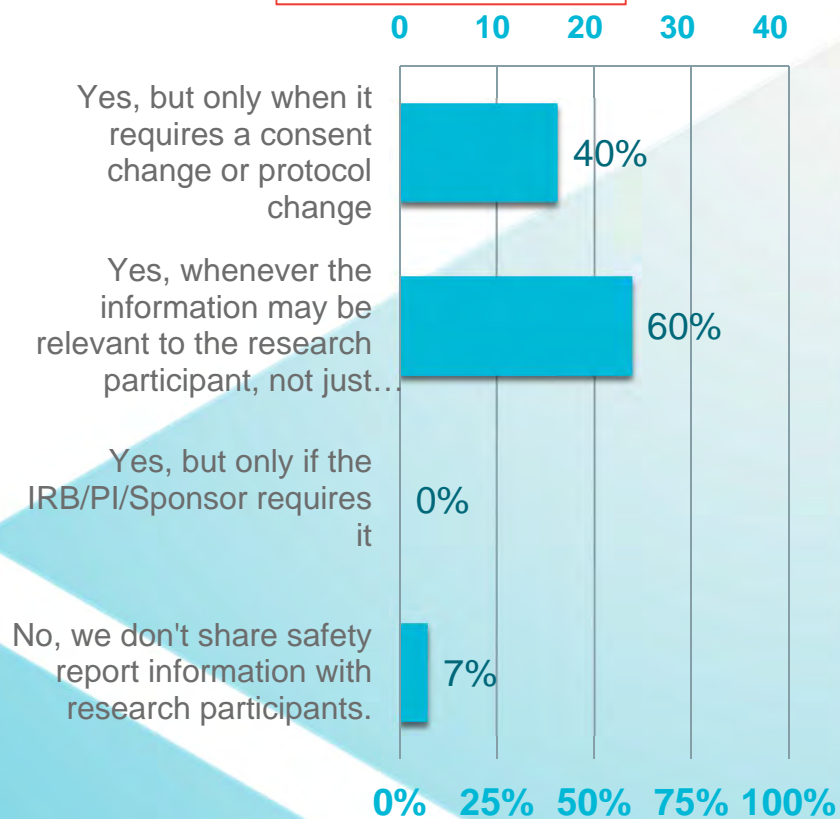


Please describe the difficulty you have accessing the IND safety reporting portal:

- **Keeping track of passwords** due to number of trials/portals and security
- Operating system, software compatibility, application versioning and robustness
 - Mac vs PC
 - Applications go down
 - Difficult to navigate, not intuitive
 - Sites are slow
- Time consuming report downloads
- Site access, staff turnover
- Generic email notifications, network can block emails

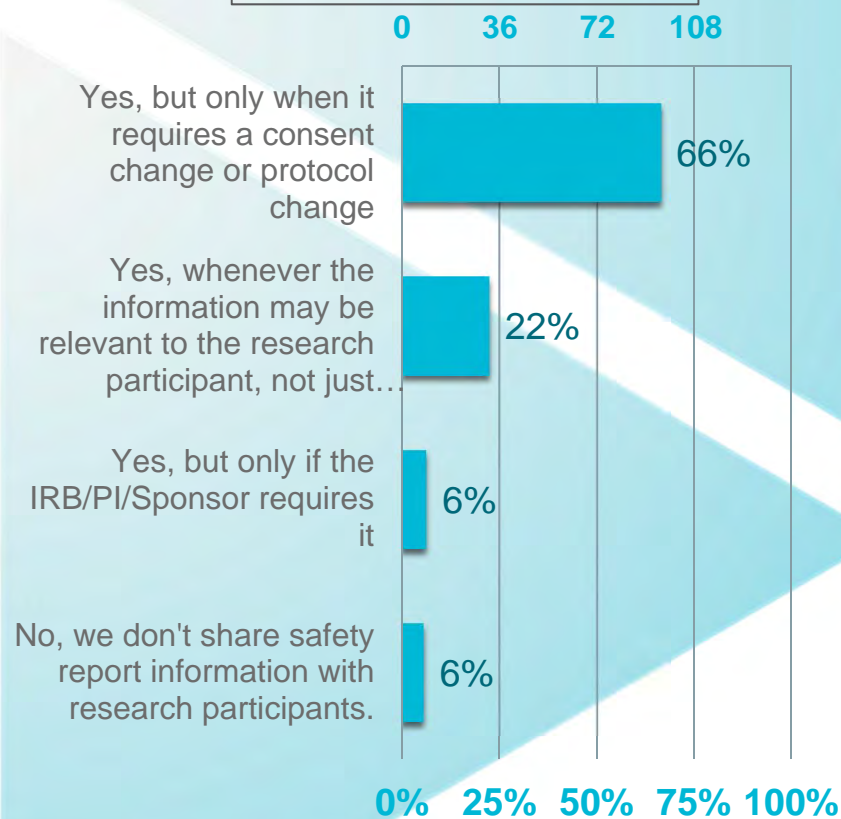
Do you share safety report information with research participants?

Investigators



■ Responses from 42 Respondents

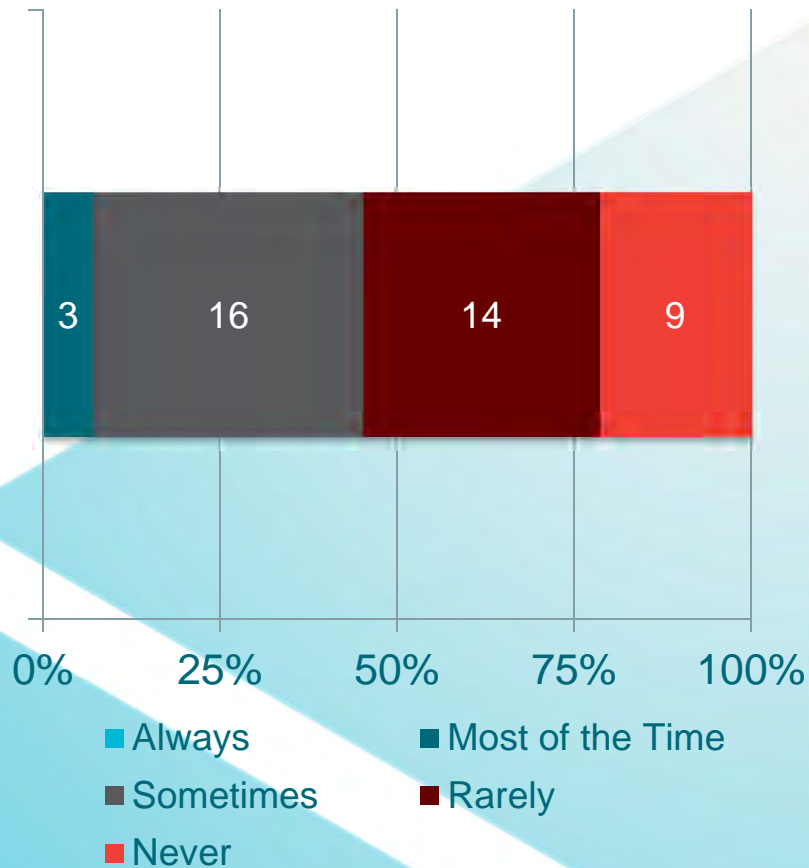
Other Study Staff



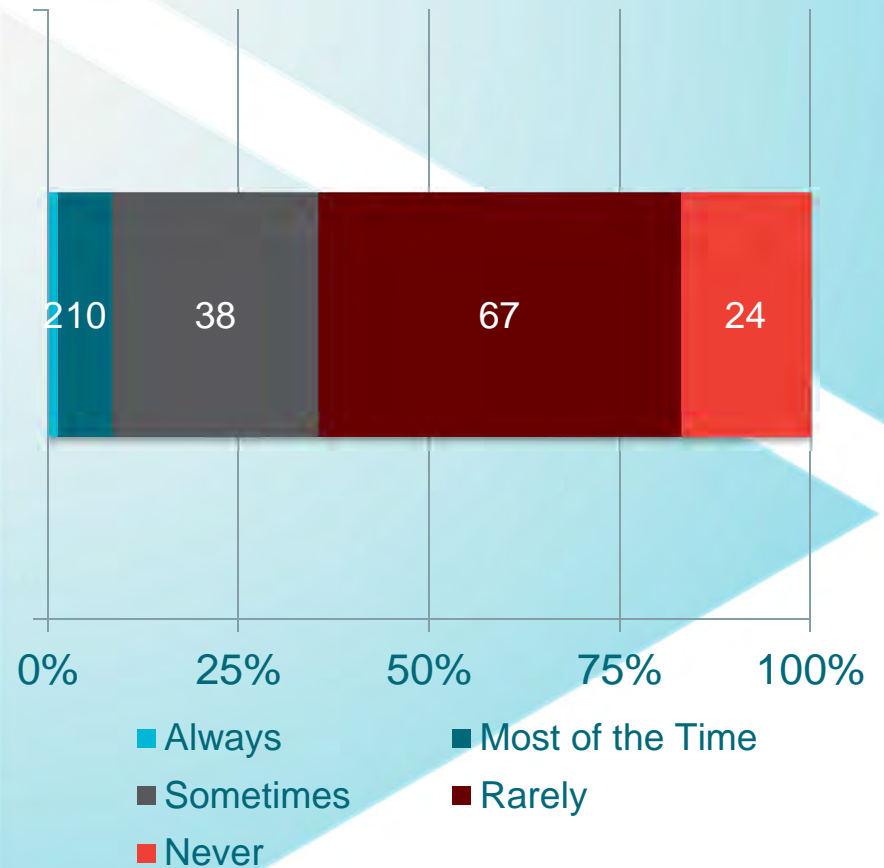
■ Responses from 143 Respondents

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?

Investigators

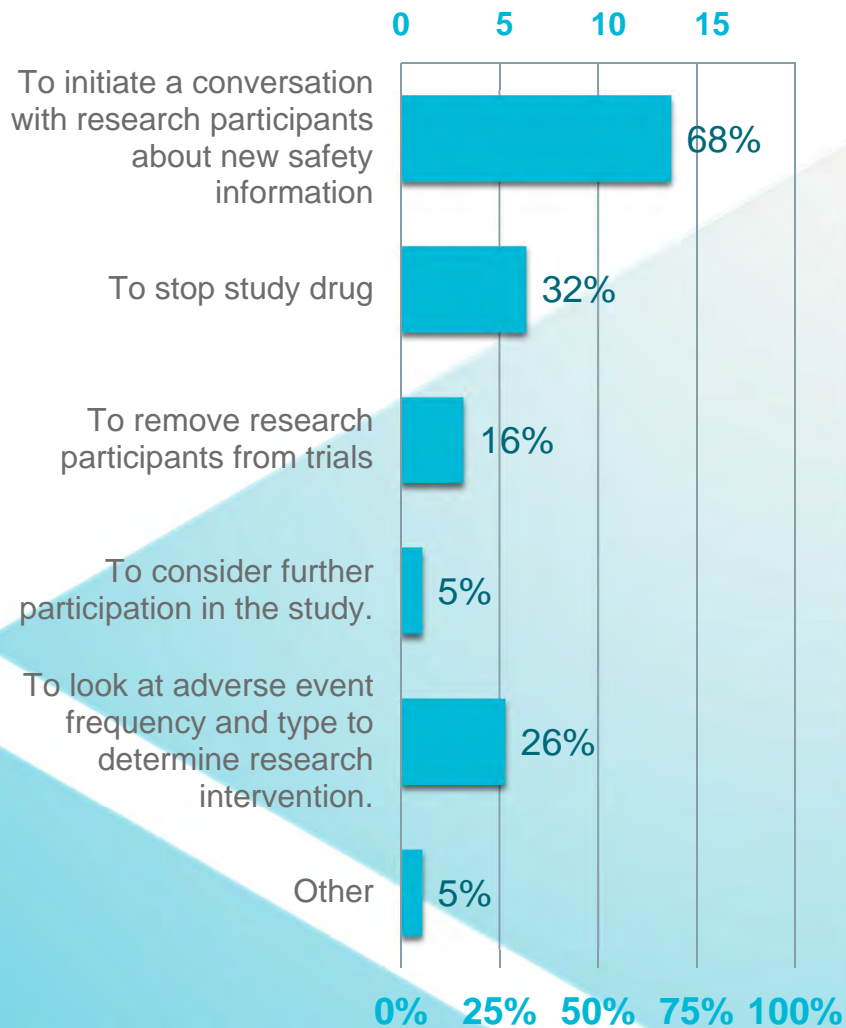


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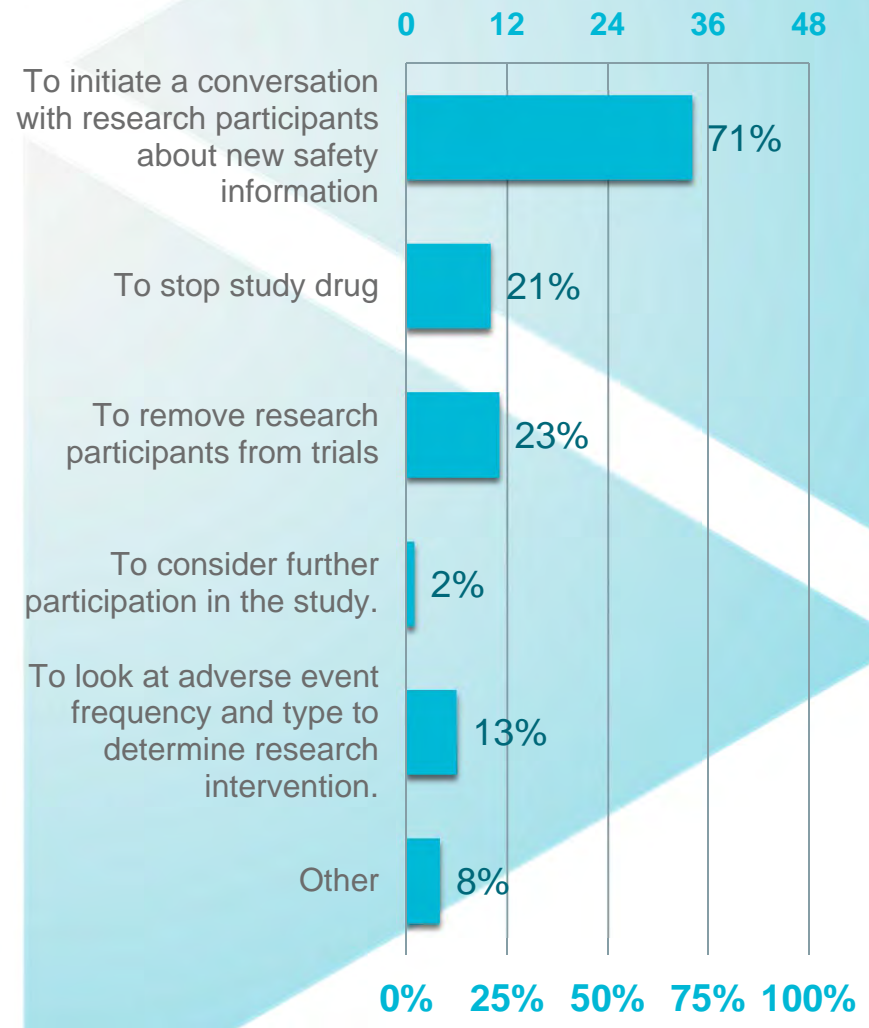
How are these types of reports still useful?

Investigators



Responses from 19 Respondents

Other Study Staff



Responses from 48 Respondents

What things about the current IND safety reporting system should be changed?

- Too many reports
- Too time consuming
- Individual reports have little value
- External reports provide little info
- Sponsor or DMC should not receive unexpected and possibly related reports
- Duplicate reports
- Redaction can hide important and useful information
- Sponsors should make summary reports and assessments
- Only report actionable items i.e., changes to protocol or consent
- Too many websites to access

CONTEXT!

What would an ideal system look like?

- Summaries for better trending data with conclusions
- Reports should meet unexpected and serious criteria, not known adverse events or events related to disease process
- Sponsor/DMC should assess and appropriate reports should be sent
- External reports should be assessed by sponsor and only sent if they meet site criteria
- Central database/portal used by all sponsors and sites
 - Easy access
 - Intuitive
 - Applications available on multiple platforms, keeping up with newer technology
 - Have reports filterable by agent or investigator to stop duplicate reporting
 - Ability for PI electronic sign off

Investigator Interviews: Summary

- ▶ 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.
- ▶ The respondents said the individual **IND safety reporting requires a huge time commitment** on the part of the investigative sites **without yielding any useful information.**

Investigator Interviews: Summary

- ▶ Respondents said handling the IND safety reports is **labor-and time-intensive** for the staff as well as the PI. Most said it becomes an **exercise in “just checking the boxes.”**
- ▶ All but one said that the **PIs sign off** on the reports, **but typically don’t read them.**
- ▶ ***None has ever used any information from these reports to improve their trials or make patients safer.***

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.
- ▶ **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.**

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.

Thank you.



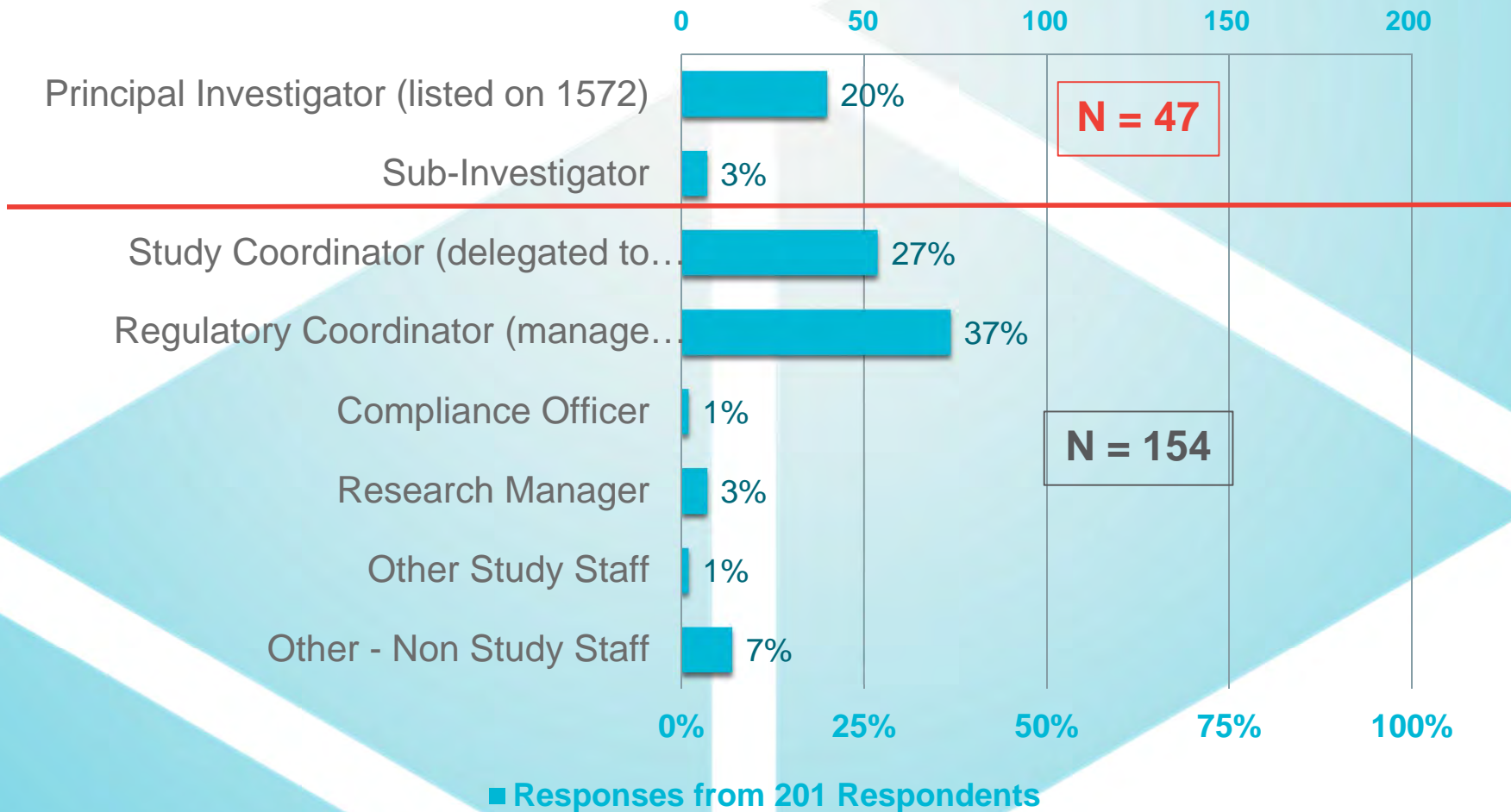
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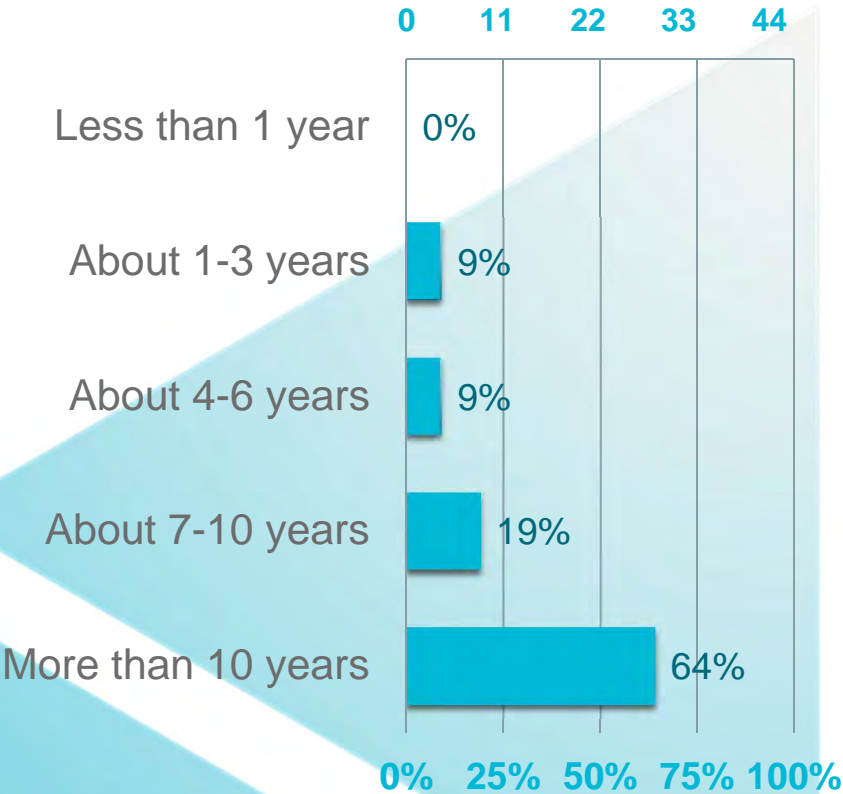


What capacity do you serve when you interact with IND safety reports?



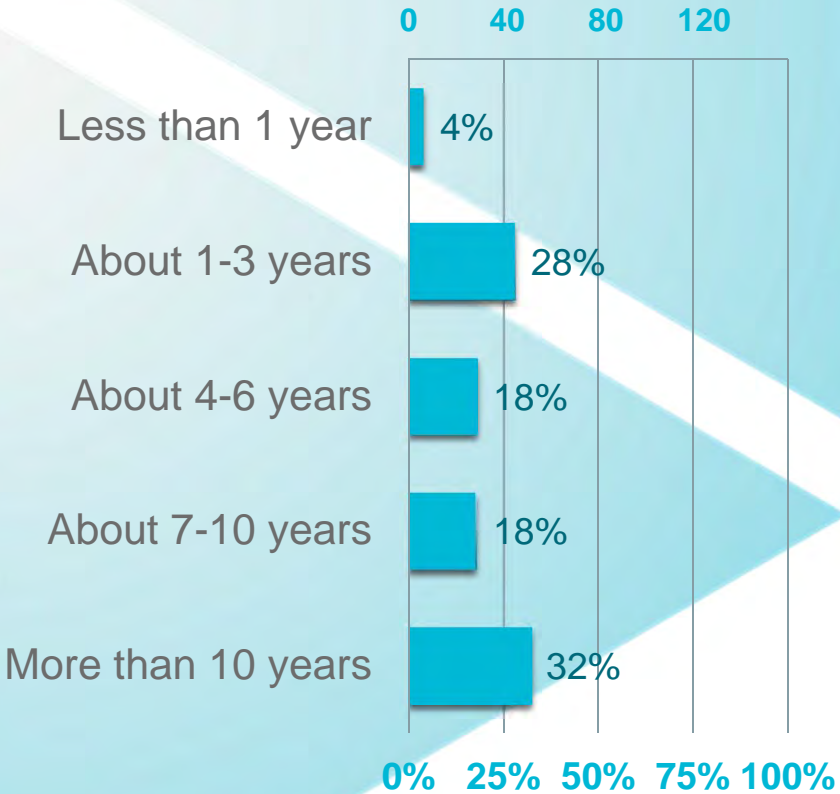
How many years of experience have you had in this particular role?

Investigators



■ Responses from 47 Respondents

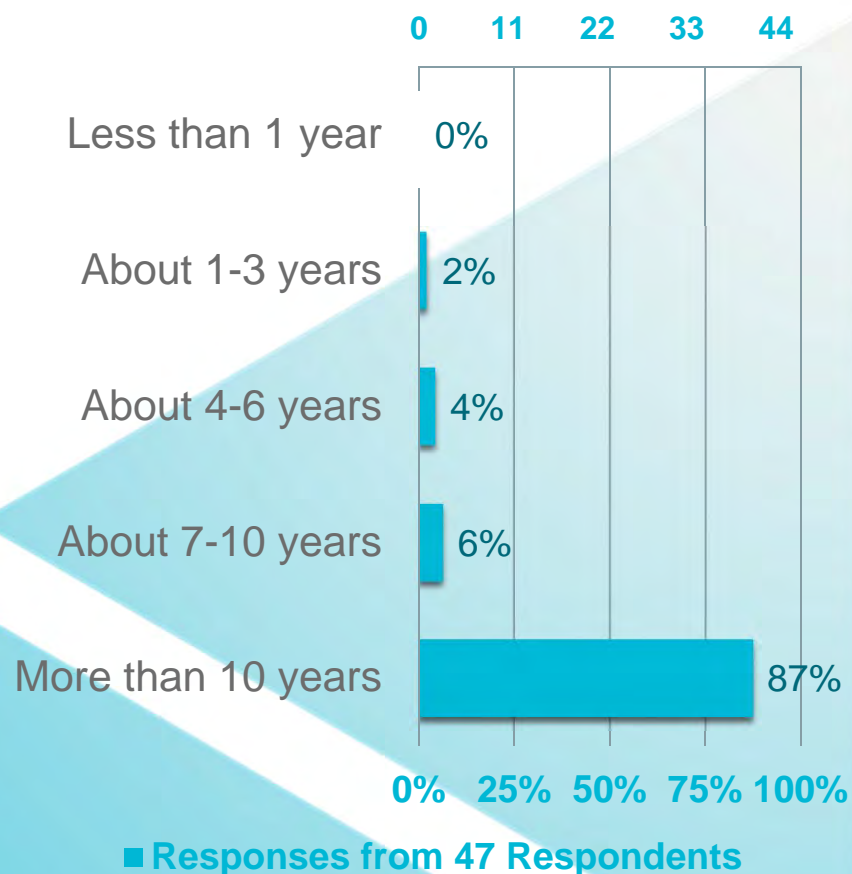
Other Study Staff



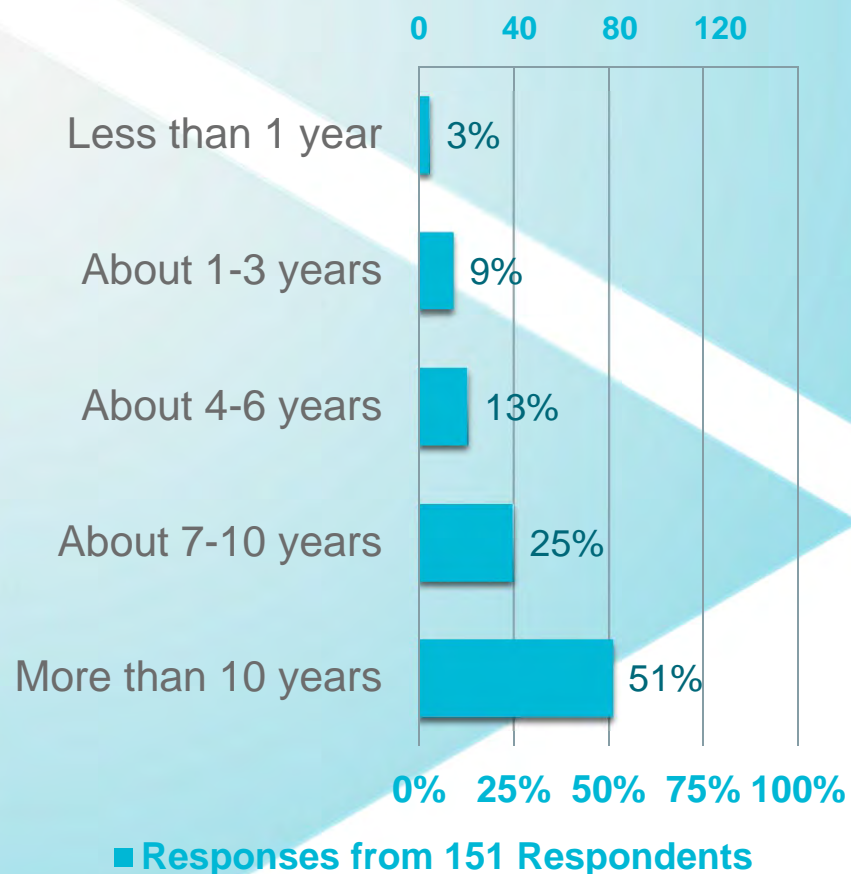
■ Responses from 154 Respondents

How many years of experience have you had in clinical trials IN GENERAL?

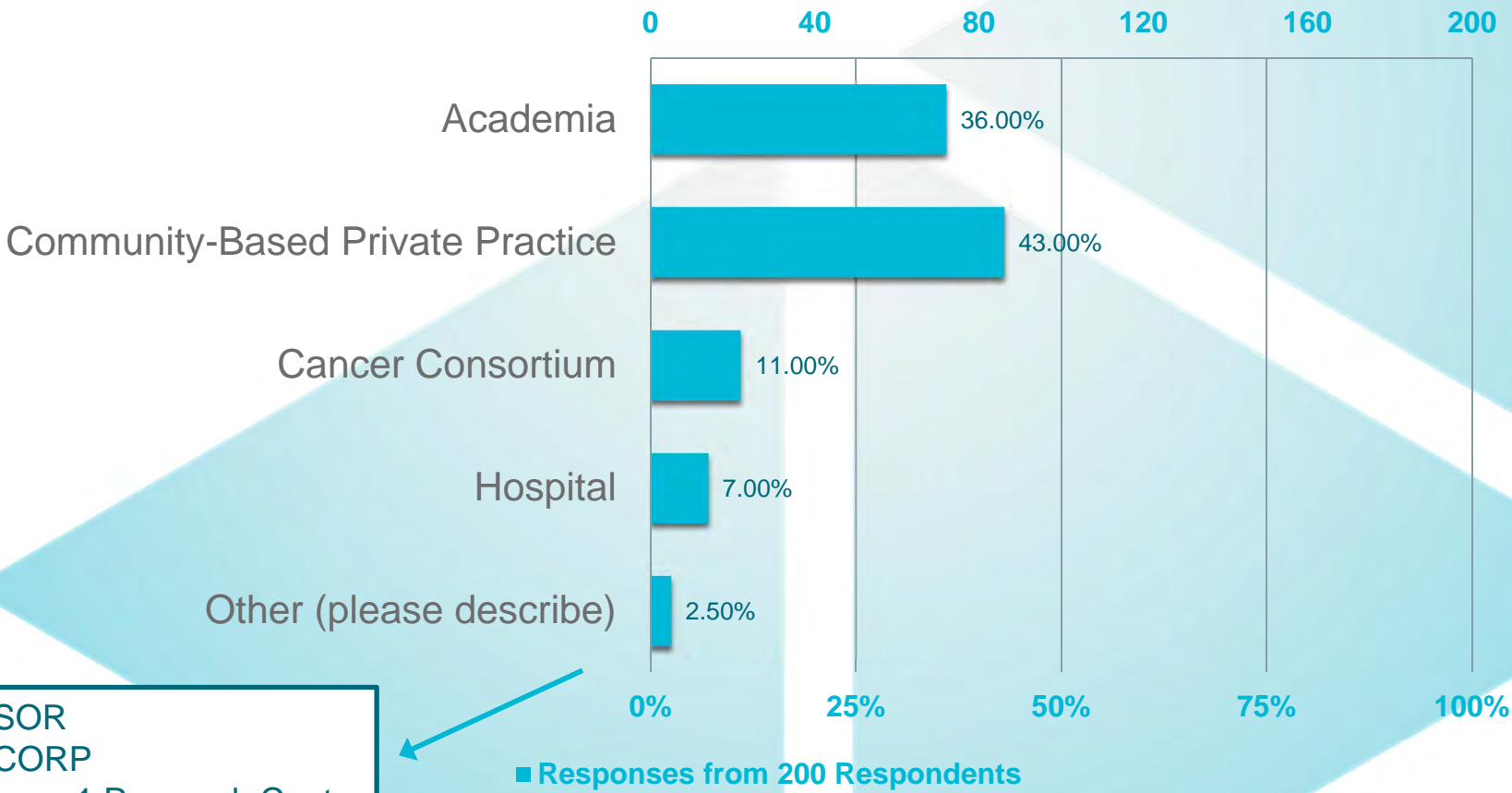
Investigators



Other Study Staff



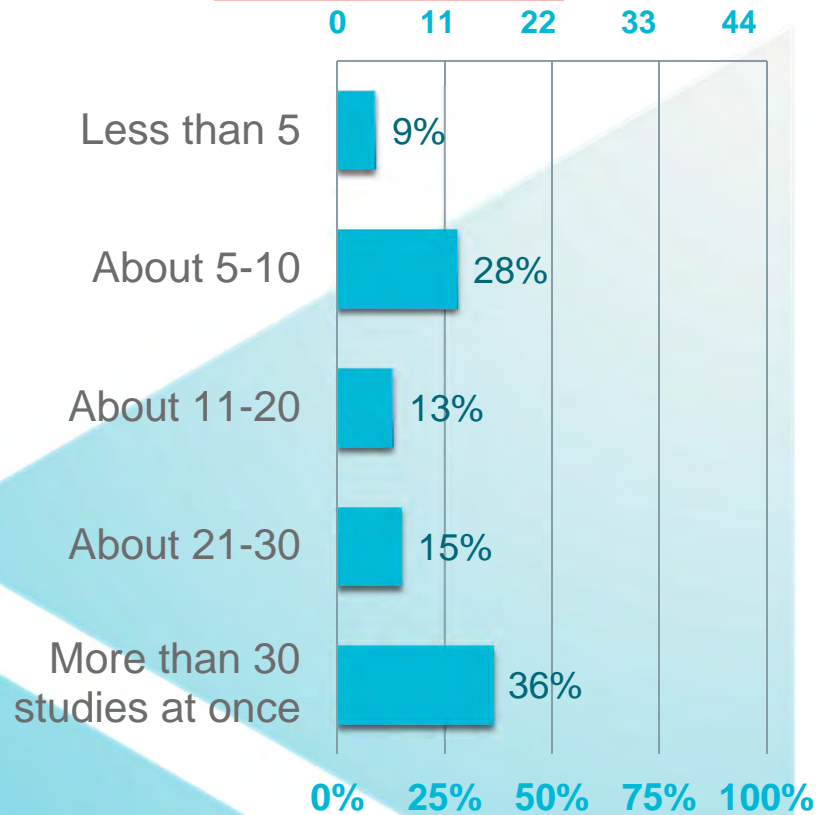
What is the primary categorization of your investigative site?



USOR
NCORP
Phase 1 Research Center
Many Varied Sites

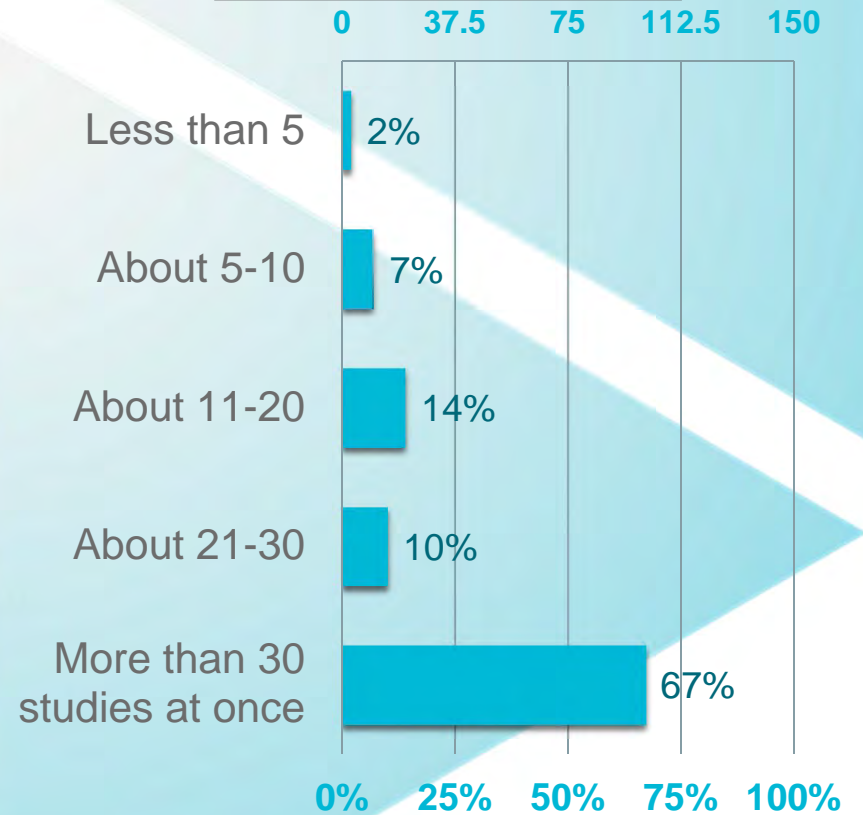
How many oncology clinical trials are currently active at your site (specifically studies for which you receive IND safety reports)?

Investigators



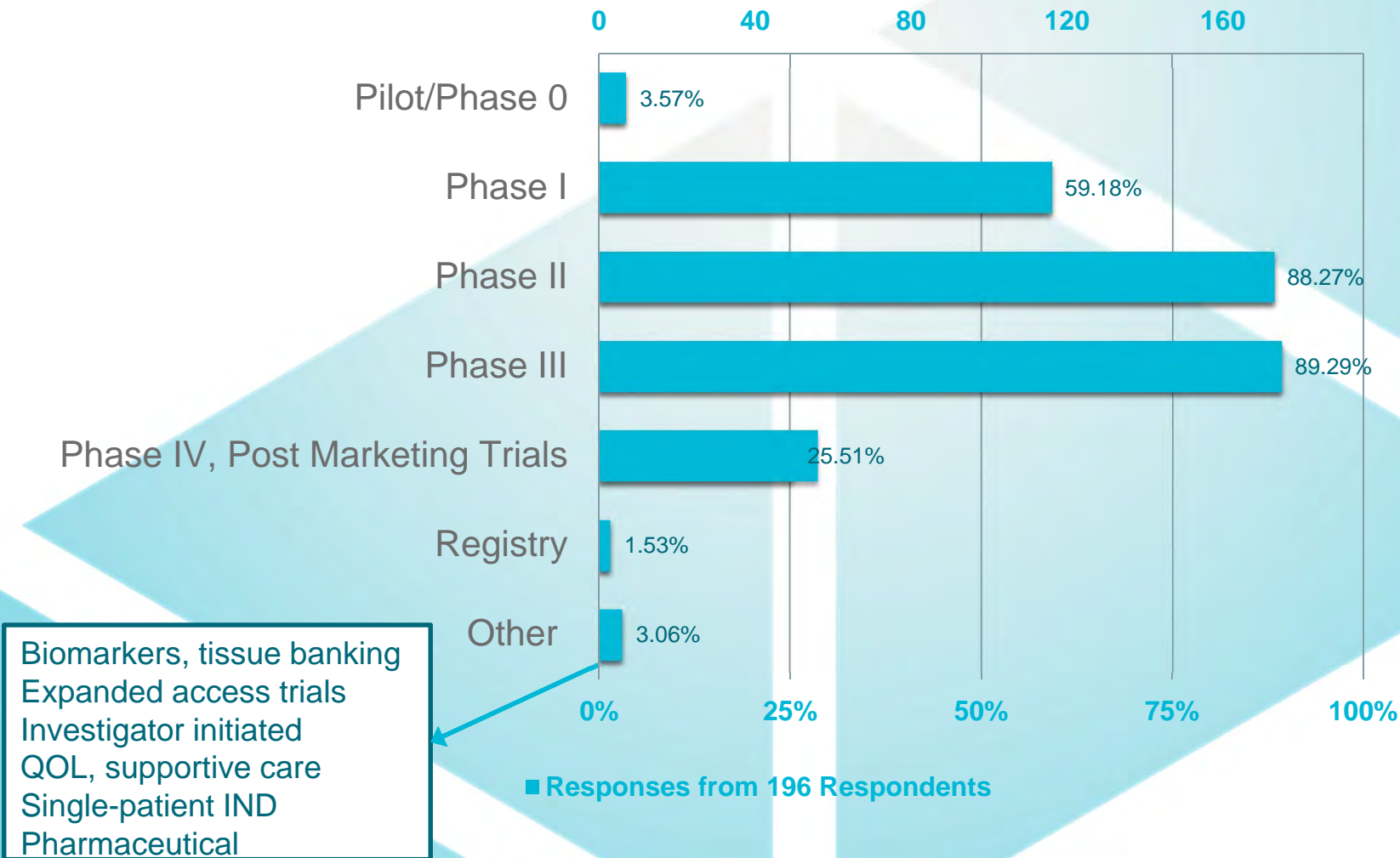
■ Responses from 47 Respondents

Other Study Staff

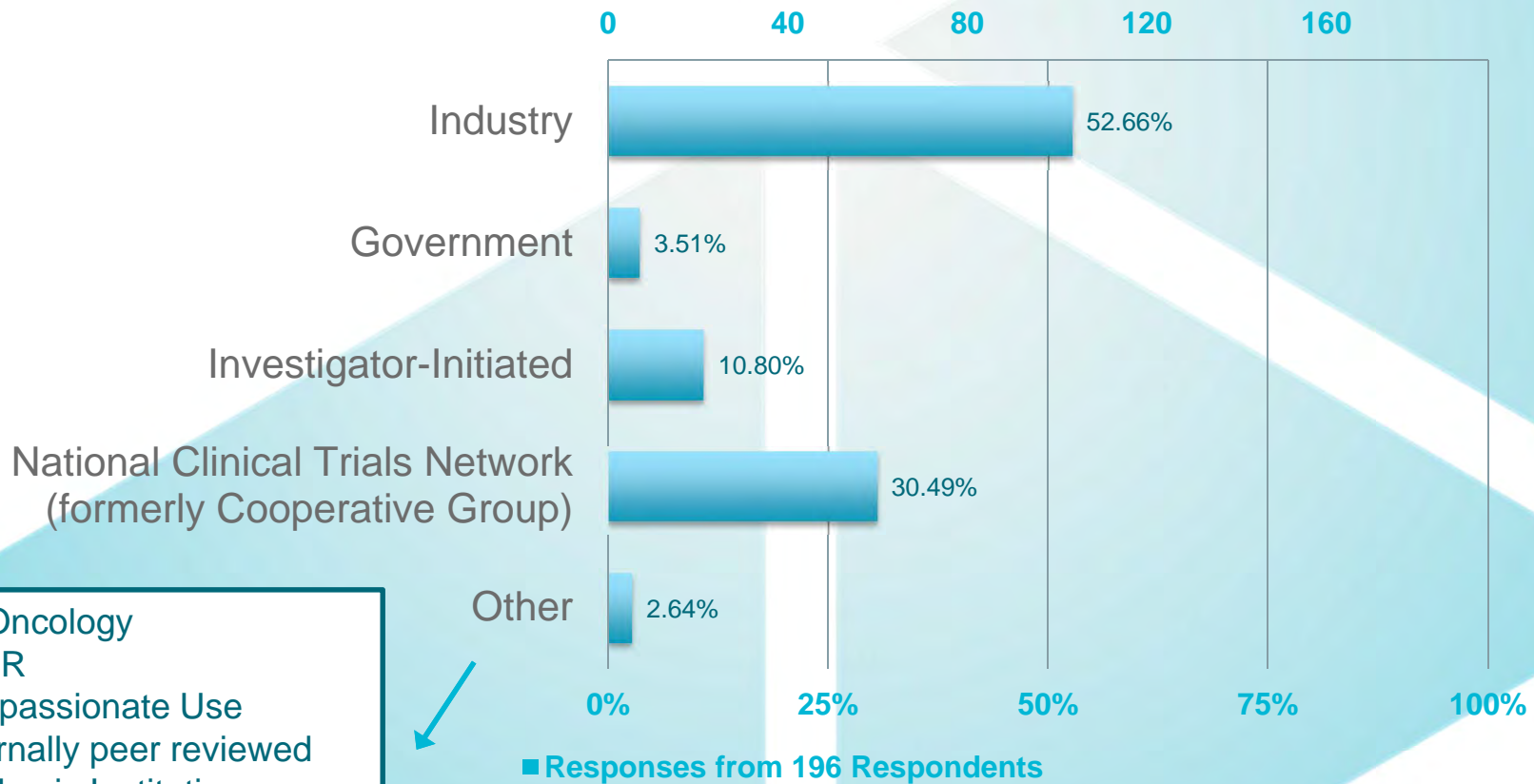


■ Responses from 150 Respondents

What phase of trials are typically conducted by your site?

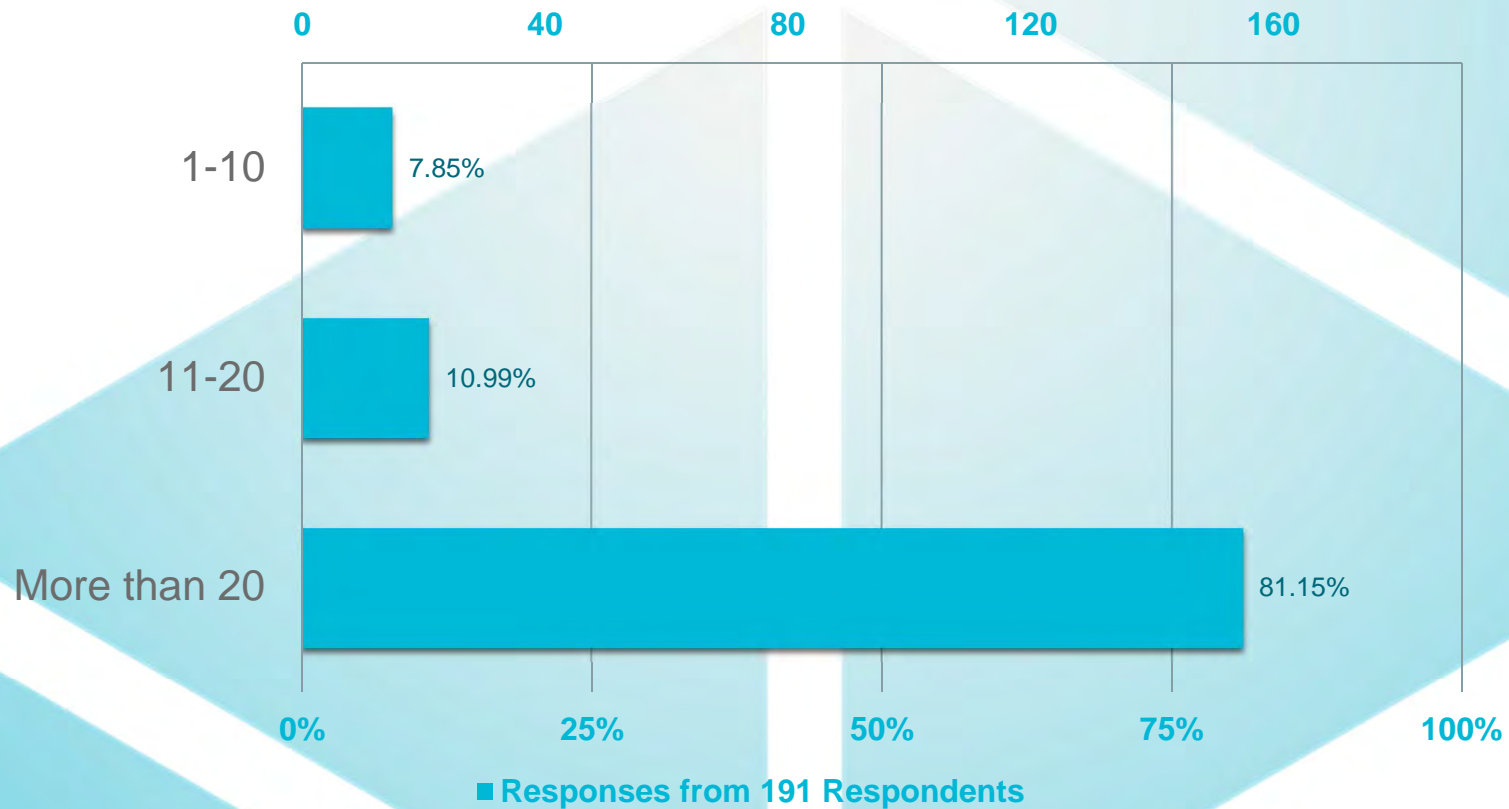


Estimate the mix of types of sponsors of the trials at your site by percentages



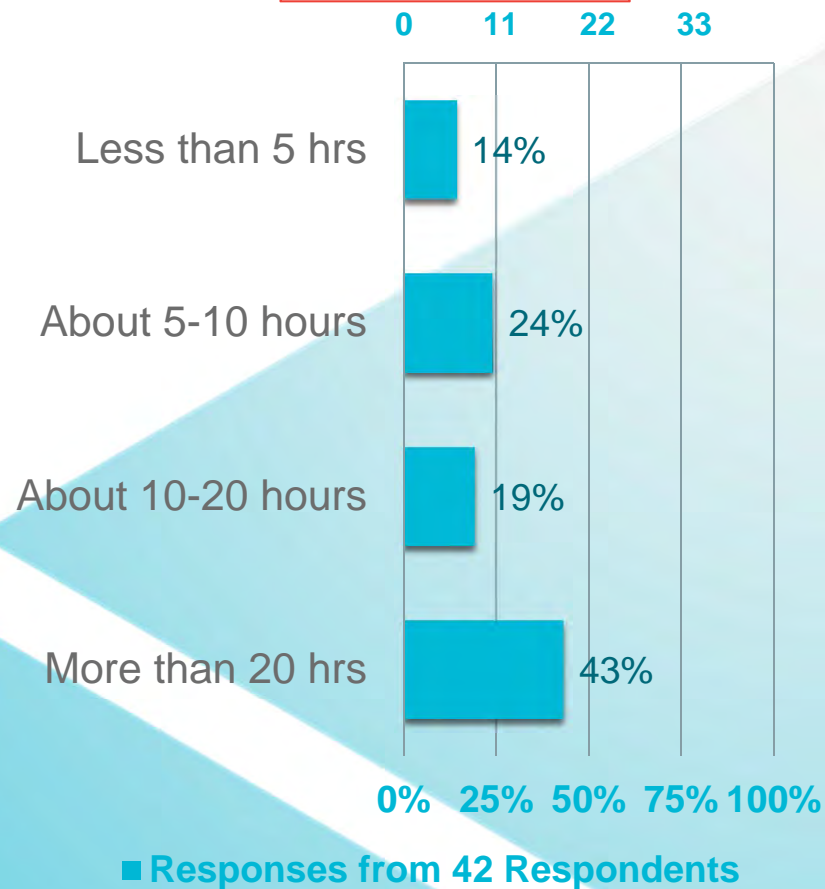
- US Oncology
- USOR
- Compassionate Use
- Externally peer reviewed
- Academic Institution
- Collaboration
- Consortium
- None

What is the estimated number of IND safety reports that you receive per month for the studies at your site?

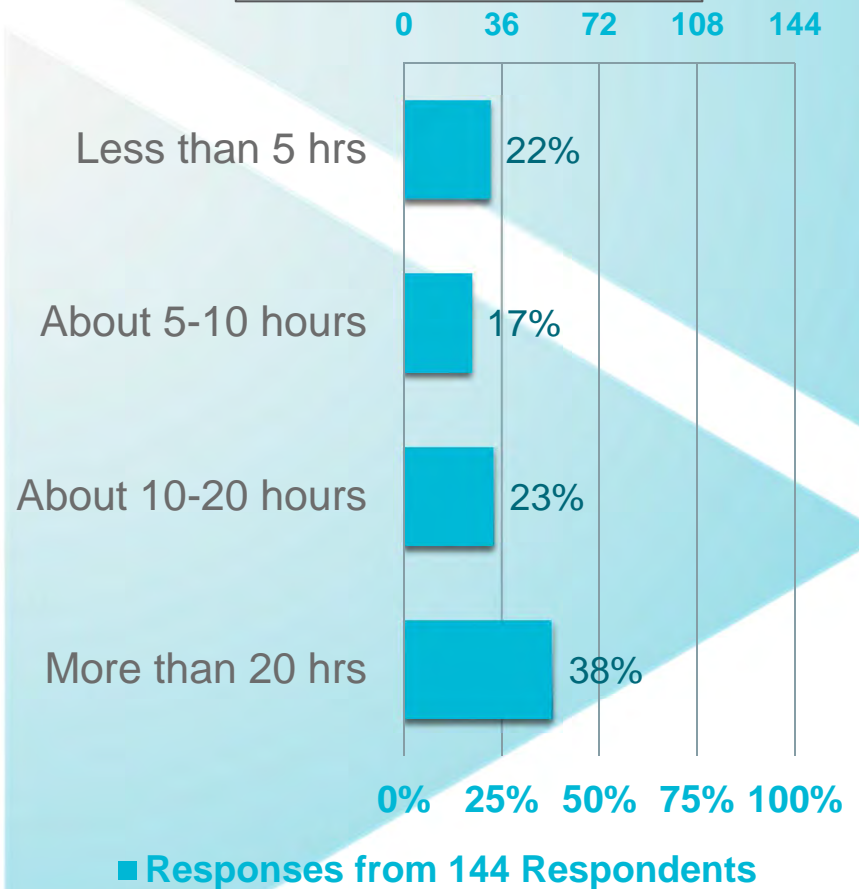


What is the estimated number of staff hours per month that is required to manage IND safety reports?

Investigators

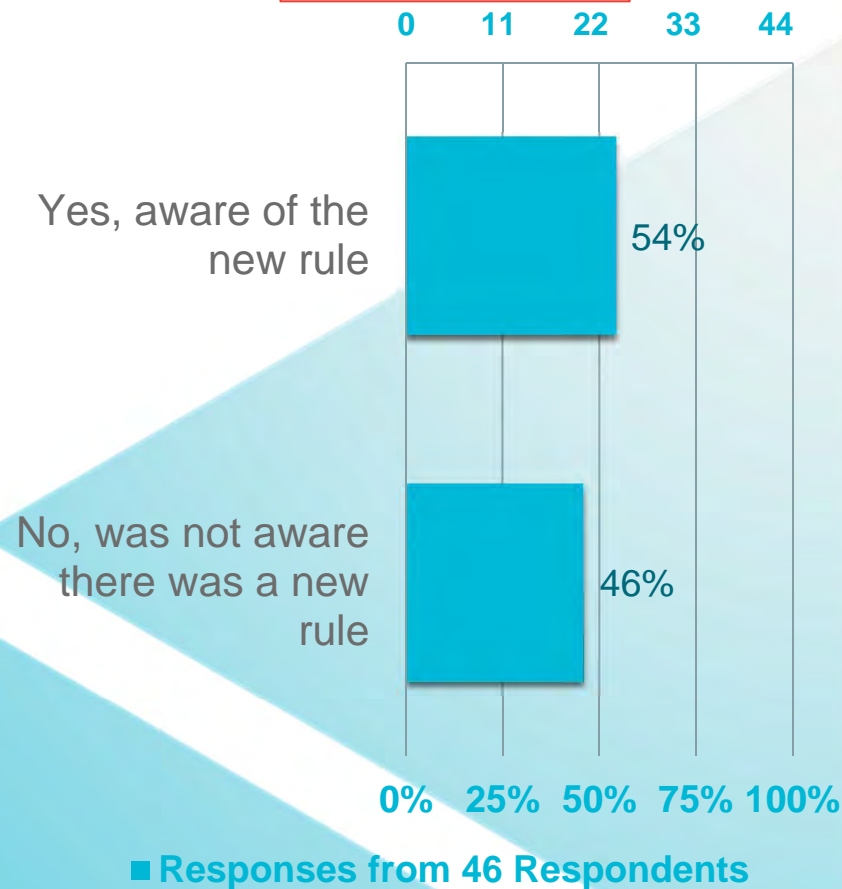


Other Study Staff

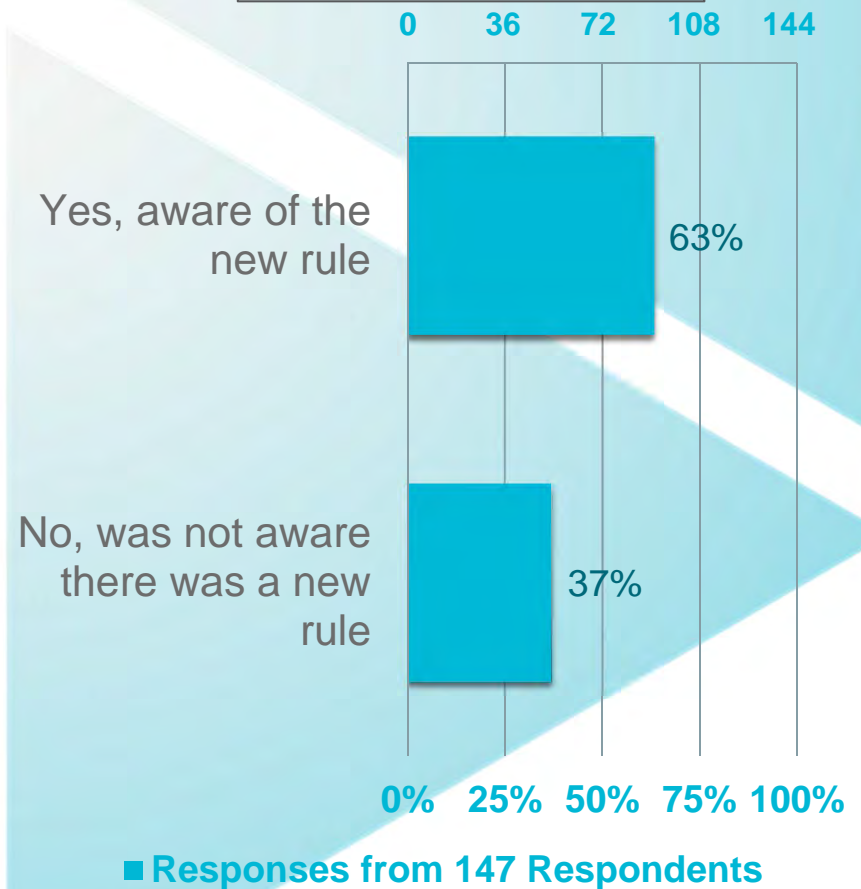


Are you aware that a new FDA rule related to IND safety reporting went into effect in 2011?

Investigators

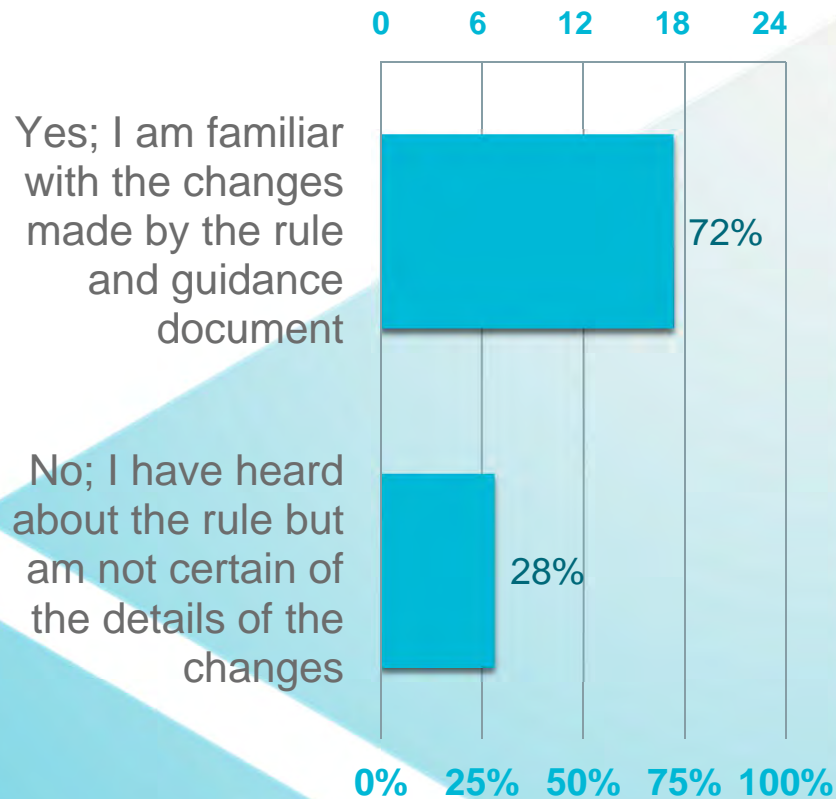


Other Study Staff



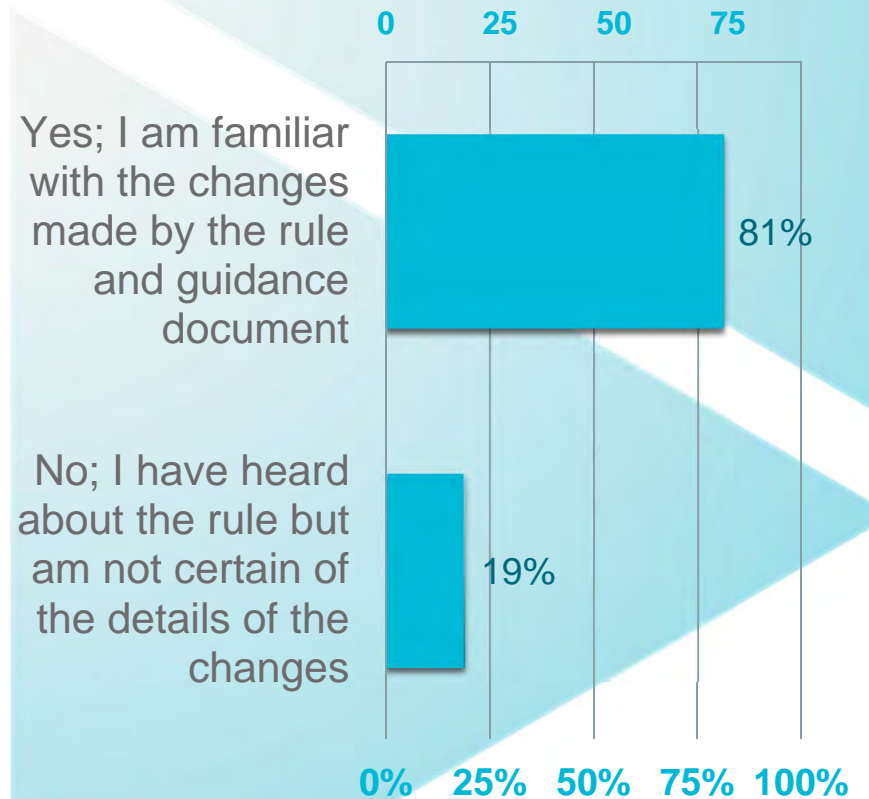
Are you familiar with the CHANGES that were made by the rule and the accompanying guidance document?

Investigators



■ Responses from 25 Respondents

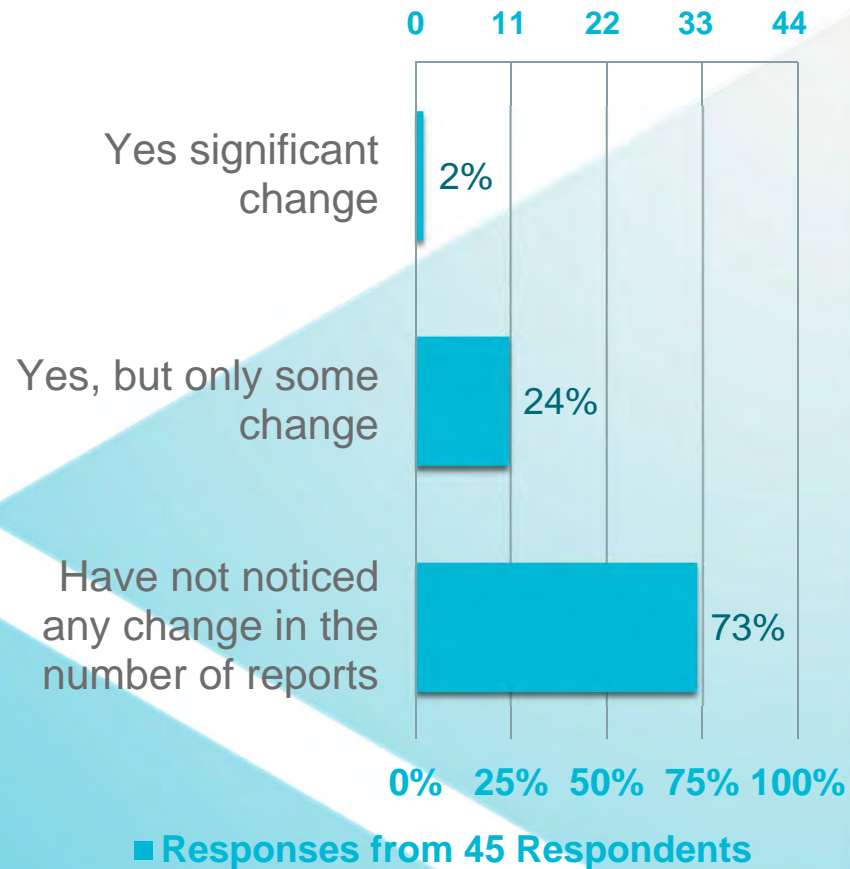
Other Study Staff



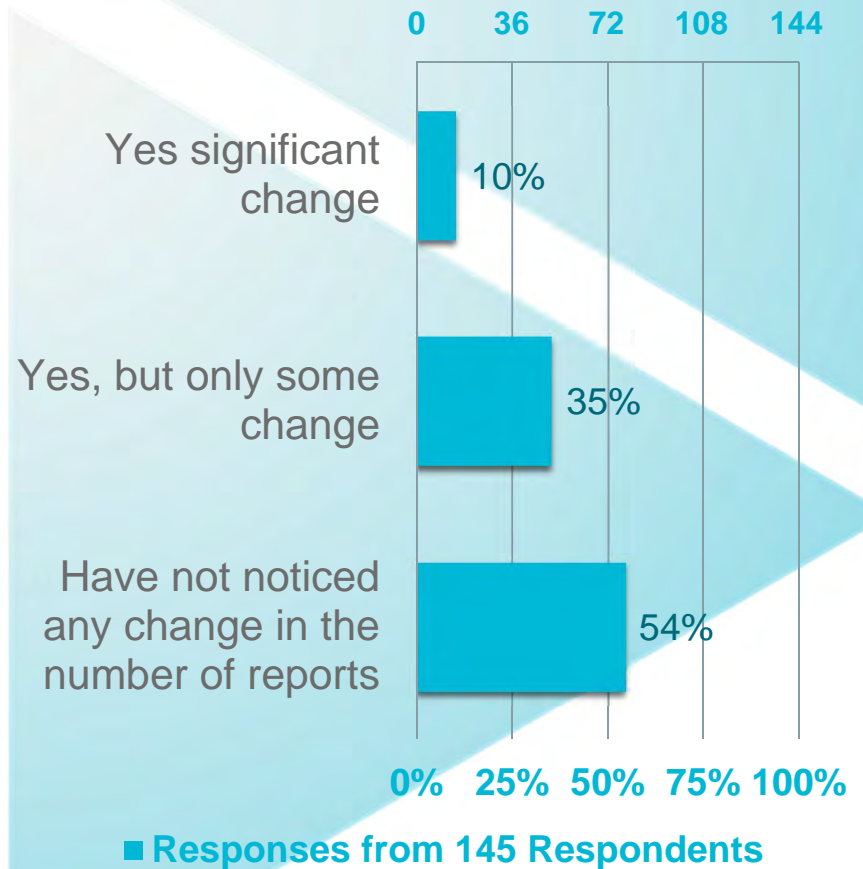
■ Responses from 91 Respondents

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

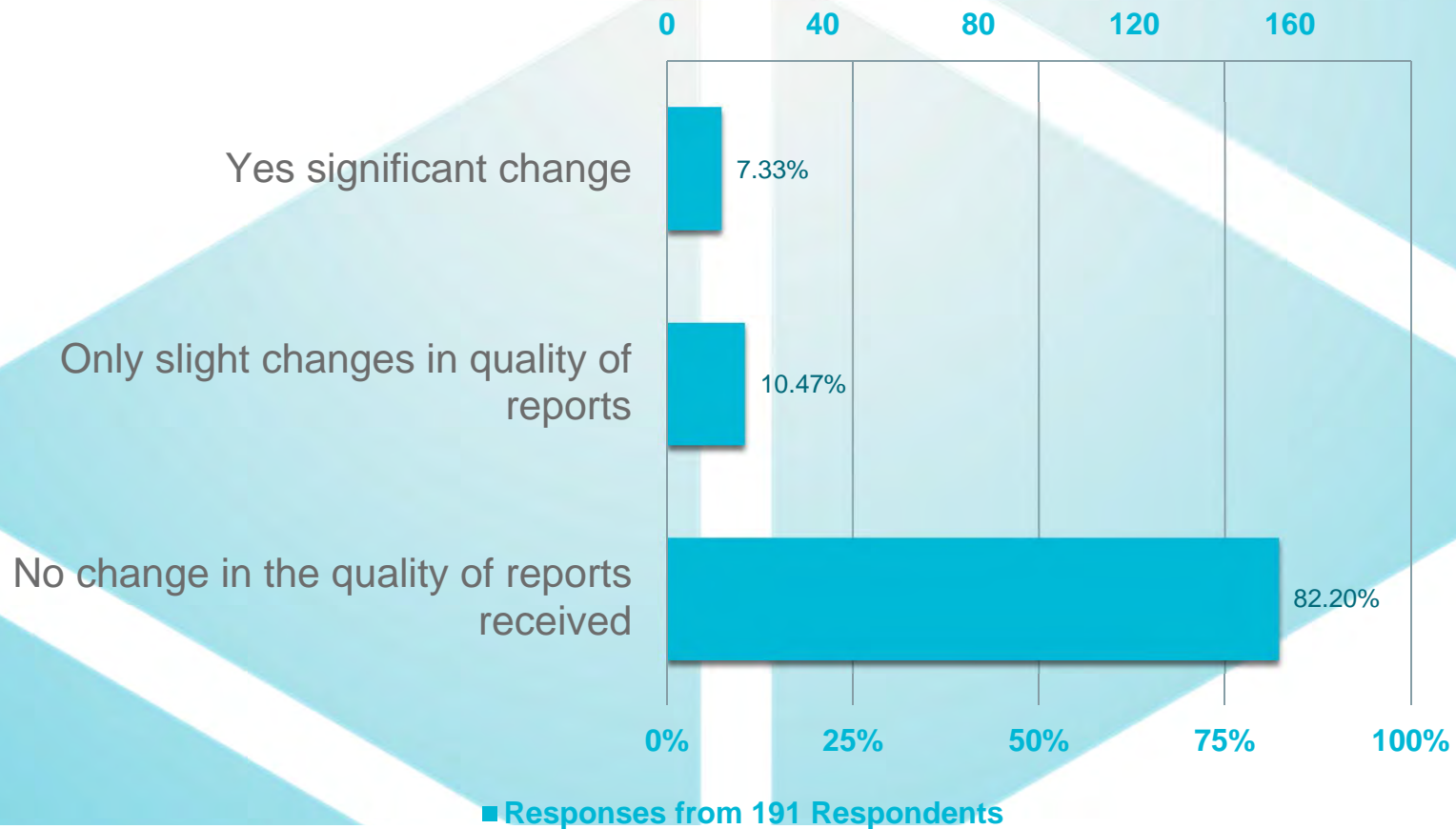
Investigators



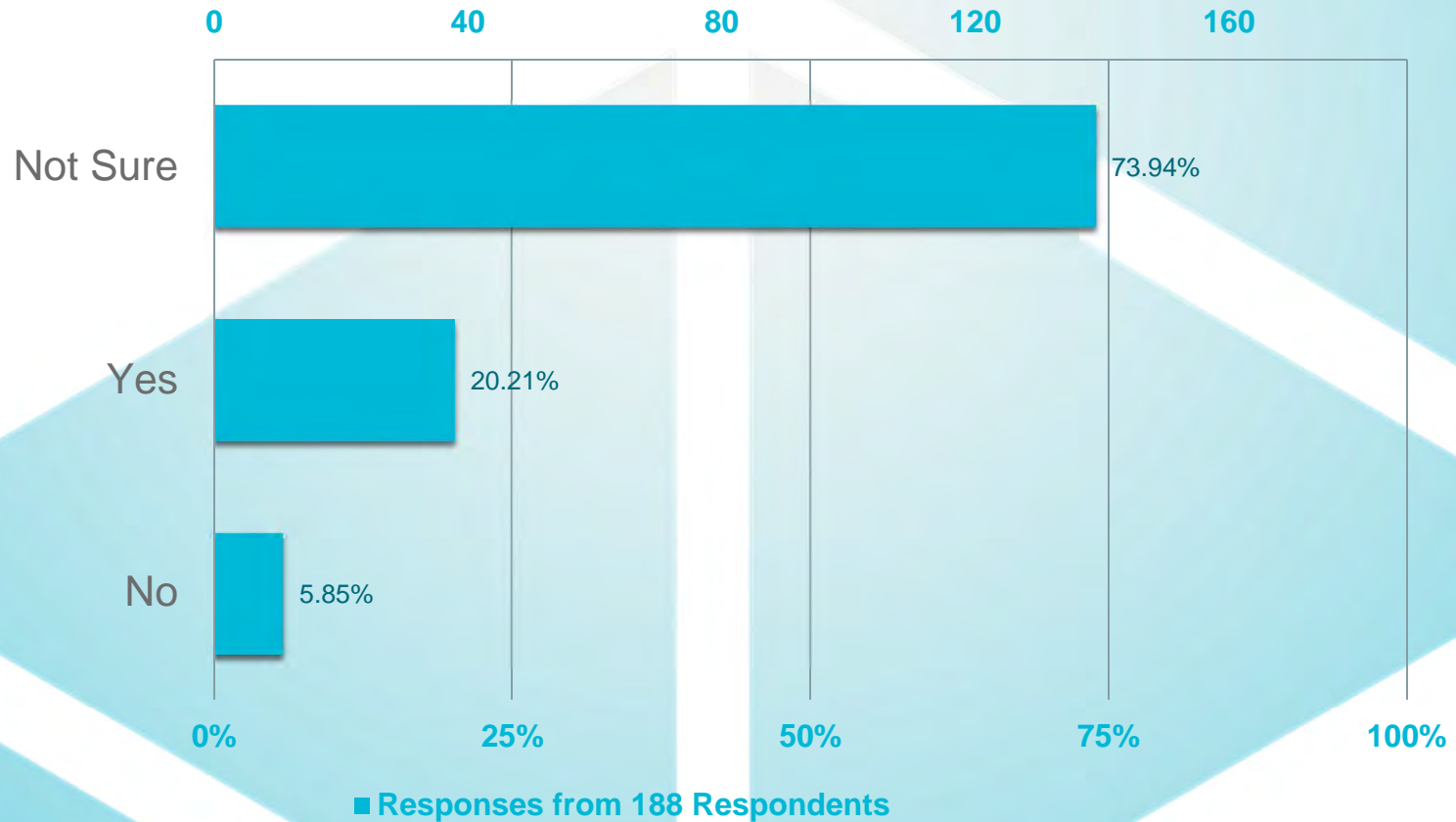
Other Study Staff



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?

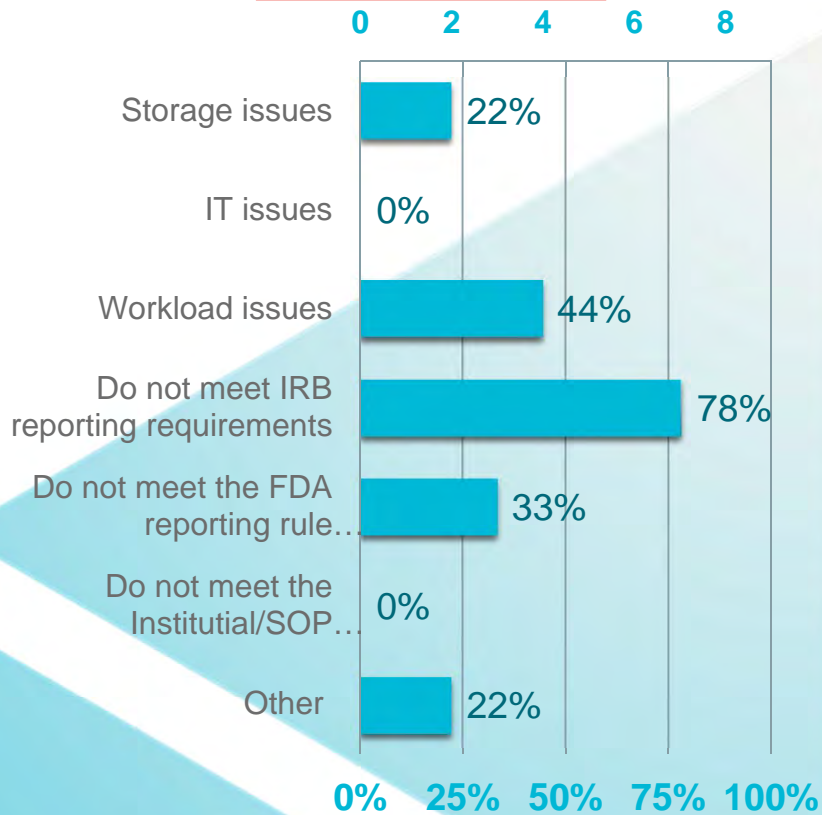


Has your site ever refused to receive or process IND safety reports?



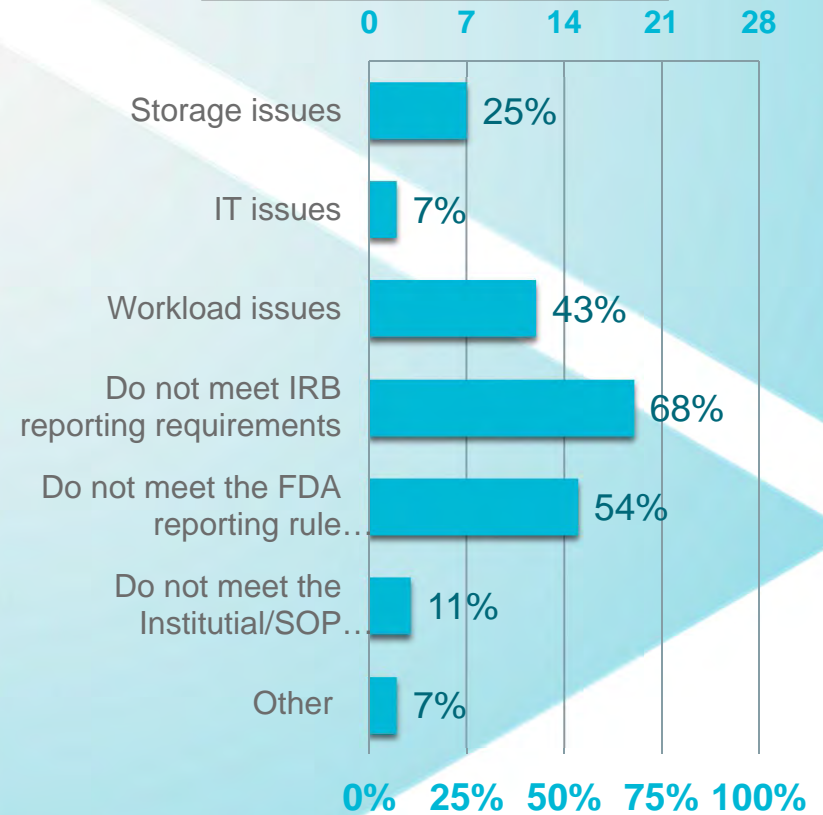
What is the reason your site has refused to process IND safety reports?

Investigators



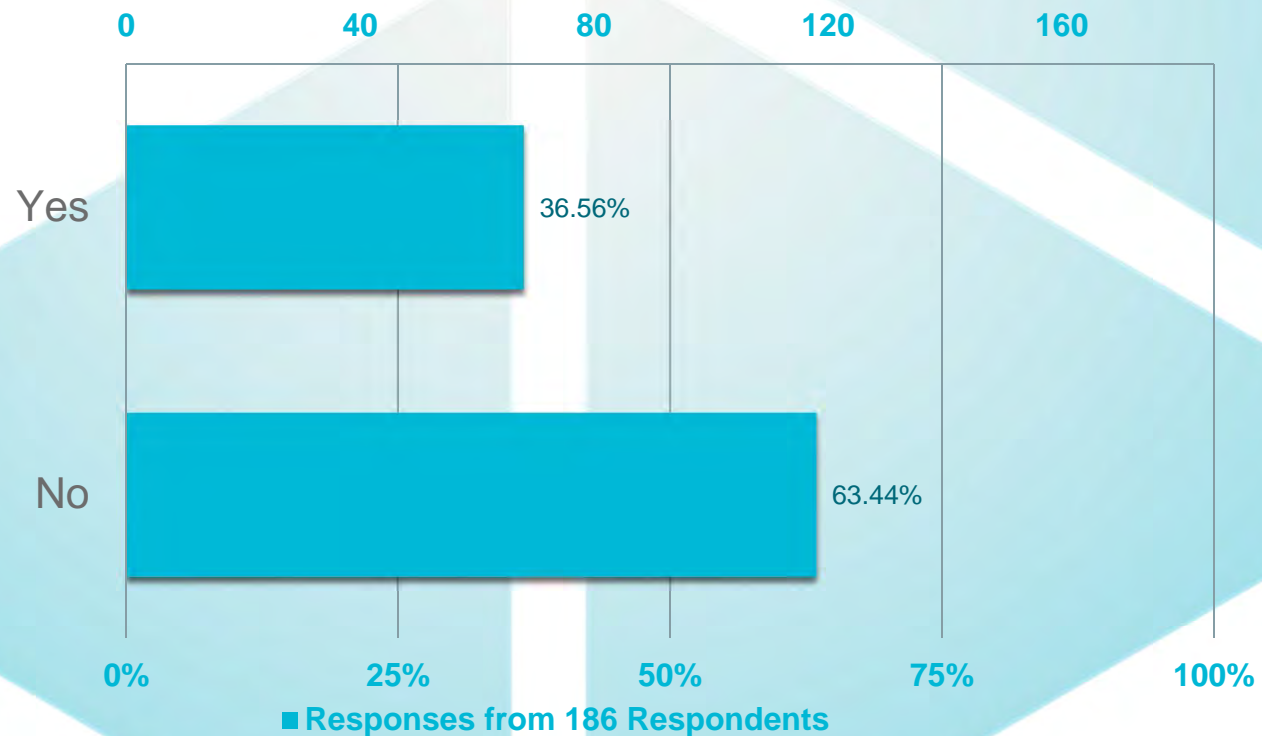
■ Responses from 9 Respondents

Other Study Staff



■ Responses from 28 Respondents

Is there variability in the practice of reviewing these reports based on the type of trial or other determining factor?



In your opinion, what do you feel is the main utility of the IND safety reports for the Investigators?



Please describe the factors that contribute to the variability in handling IND reports at your site.

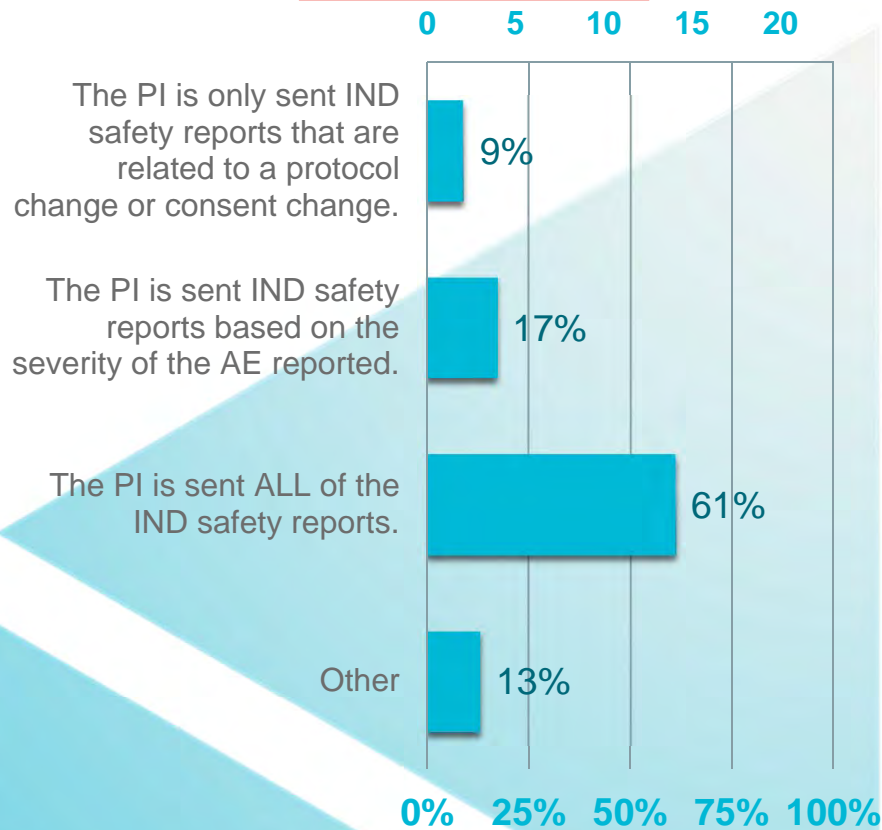
- ▶ Sponsor Requirements
- ▶ IRB Requirements
- ▶ PI Requirements
- ▶ First in human studies sent directly to PI
- ▶ Active treatment patients vs follow up only
- ▶ Trial type i.e., industry, NCI, IIT, cooperative
- ▶ Method of delivery i.e., hard copies, email, secure portals
- ▶ Reports are cumbersome and time consuming

What things about the current IND safety reporting system are especially useful?

- ▶ Notification of trends or unexpected AEs which aid in treatment decisions for current and future patients
- ▶ Safety/Ability to identify risks
- ▶ Defined attribution and causality
- ▶ Generate important changes to protocol and consent
- ▶ Determinations on whether or not a study is useful or should continue
- ▶ Electronic reports are more efficient, easy to track
- ▶ Summary reporting available

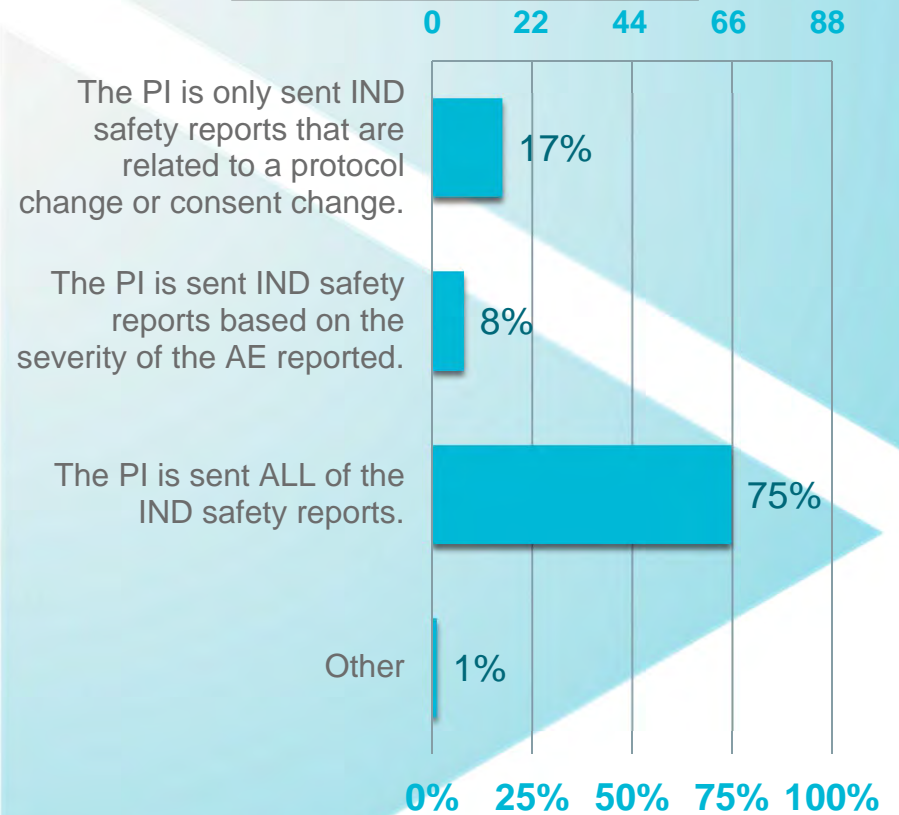
How does the initial reviewer determine which IND safety reports the Principal Investigator reviews?

Investigators



■ Responses from 23 Respondents

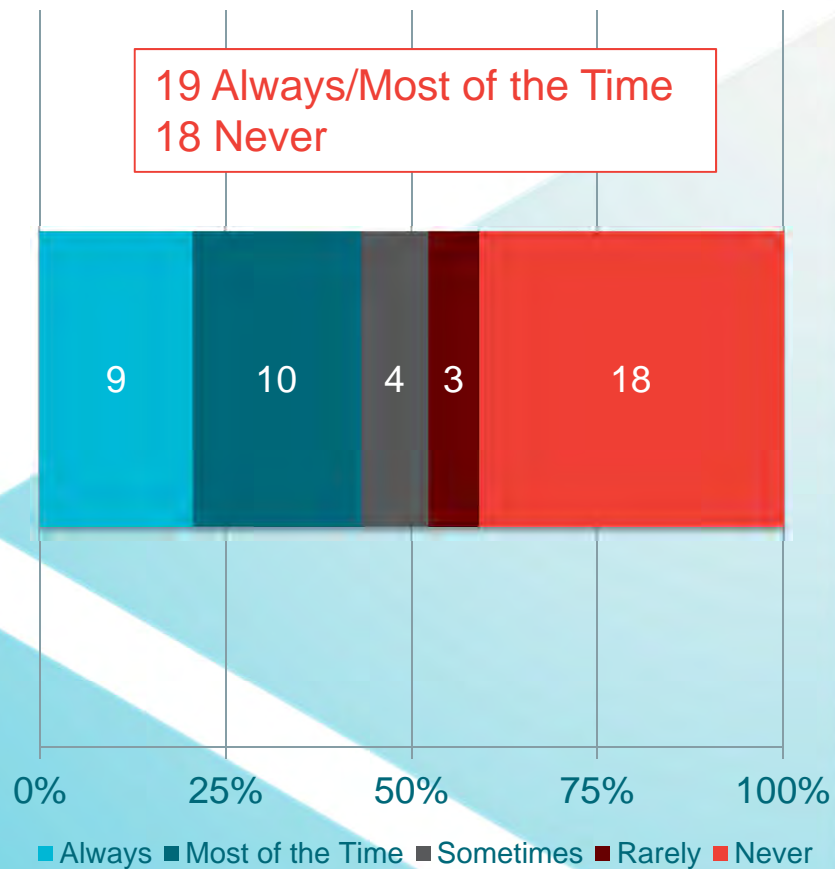
Other Study Staff



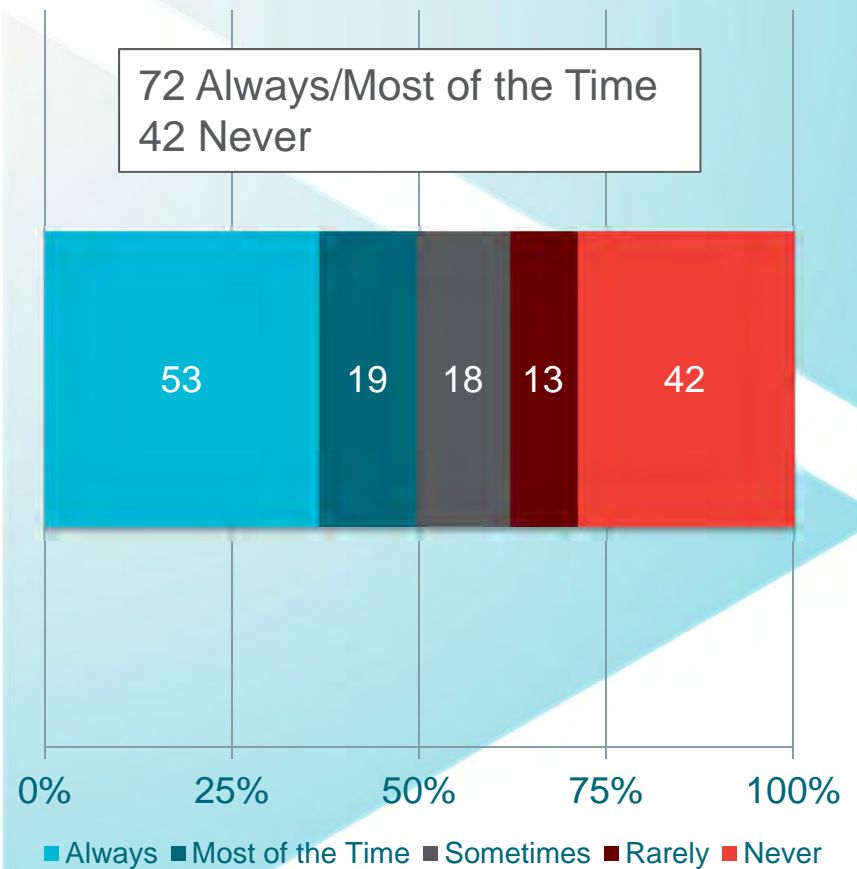
■ Responses from 89 Respondents

Upon receipt of IND safety reports at your site, does anyone initially review these reports before the PI in order to determine which reports the PI must review?

Investigators

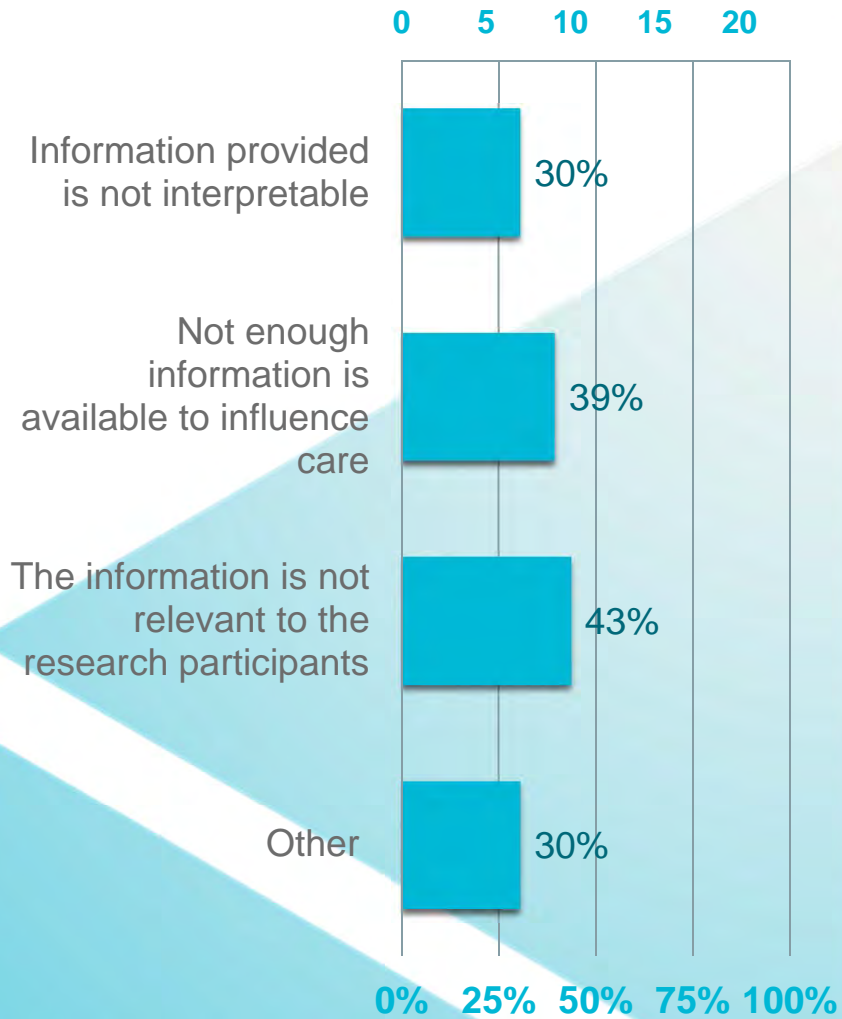


Other Study Staff



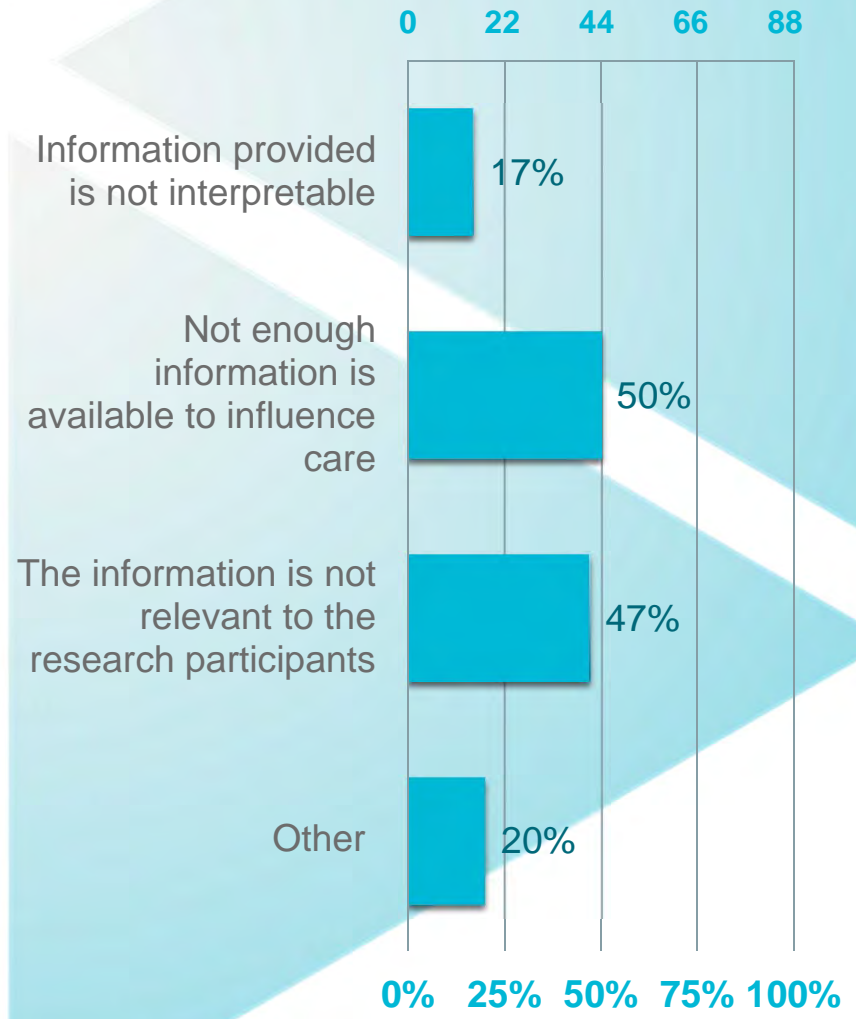
Why aren't these types of reports useful?

Investigators



Responses from 23 Respondents

Other Study Staff



Responses from 90 Respondents

CTTI IND Safety Advancement Sponsor Survey and Interview Findings

Rob Goodwin, Pfizer

July 21, 2015



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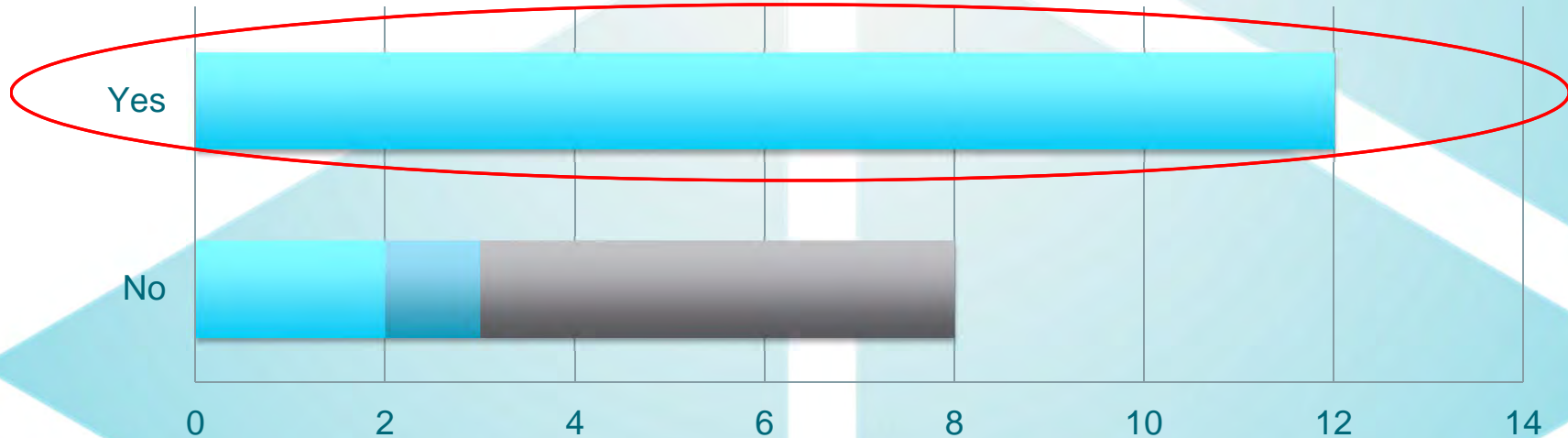
Methods

- ▶ 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:

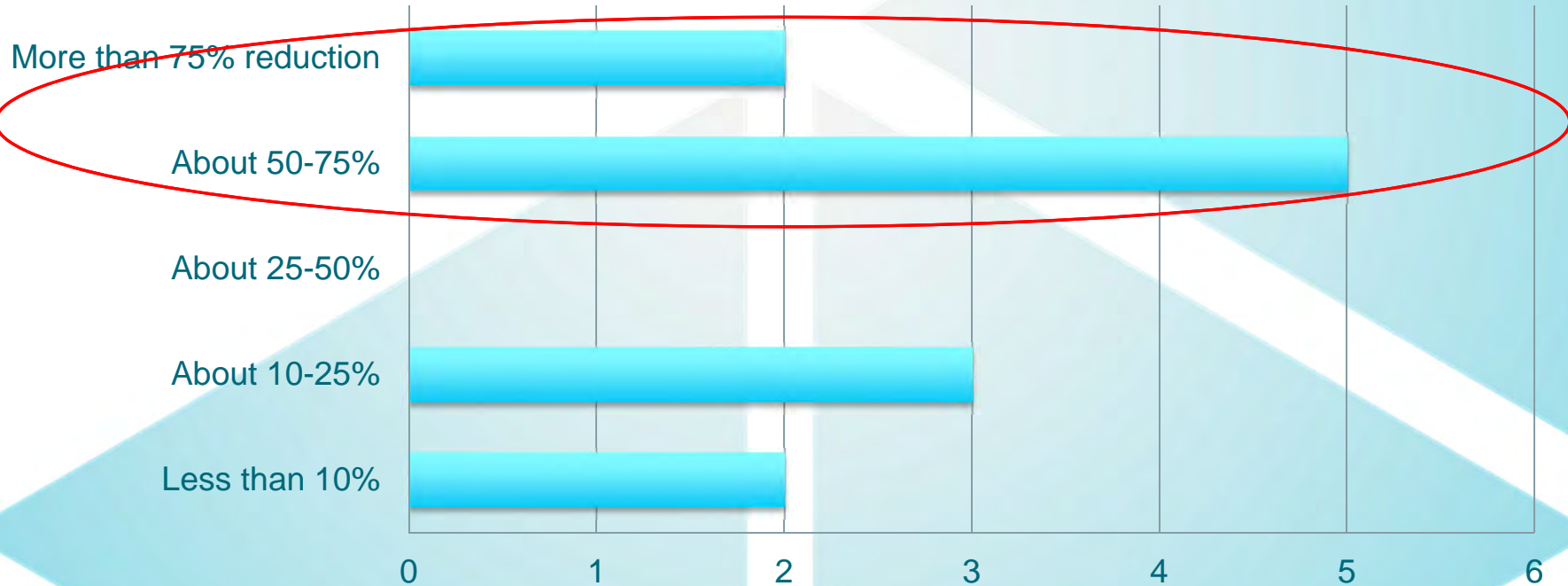
- ▶ Most of those interviewed said that their companies have cut down by at least 40 to 75 percent on their individual IND safety reports
- ▶ Two said that their companies achieved the 90 percent reduction goal

With your organization's implementation of the FDA final rule on IND safety reporting requirements (update of 21 CFR 312.32), did you see a reduction in the volume of initial safety reports distributed by your organization to US Investigators and FDA?



	No	Yes
Large	2	12
Midsize	1	0
Small	5	0

Approximately what percent reduction did you see?



	Less than 10%	About 10-25%	About 25-50%	About 50-75%	More than 75% reduction
■ Large	2	3	0	5	2
■ Midsize	0	0	0	0	0
■ Small	0	0	0	0	0

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



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

Exec 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)
- ▶ Conservatism: 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 were interesting... 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.

Thank you.



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Session III – Impact of FDA Inspection Practices on Expedited IND Safety Reporting

Objectives

- Clarify and discuss conduct of FDA inspections for expedited IND safety reporting
- Understand forces that have shaped the culture around expedited IND safety reporting
- Understand cultural issues sponsor organizations face in changing expedited IND safety reporting processes

Agenda

- FDA policy, processes and inspections: Expedited IND safety reporting
- Cultural issues and barriers to changing reporting practice: Sponsor perspective

FDA policy, processes and inspections: Expedited IND safety reporting

Chrissy Cochran, FDA/CDER

July 21, 2015



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U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

FDA Policy, Processes, and Inspections: Expedited IND Safety Reporting



Chrissy J. Cochran, PhD

Director (acting)

Division of Enforcement and Postmarketing Safety

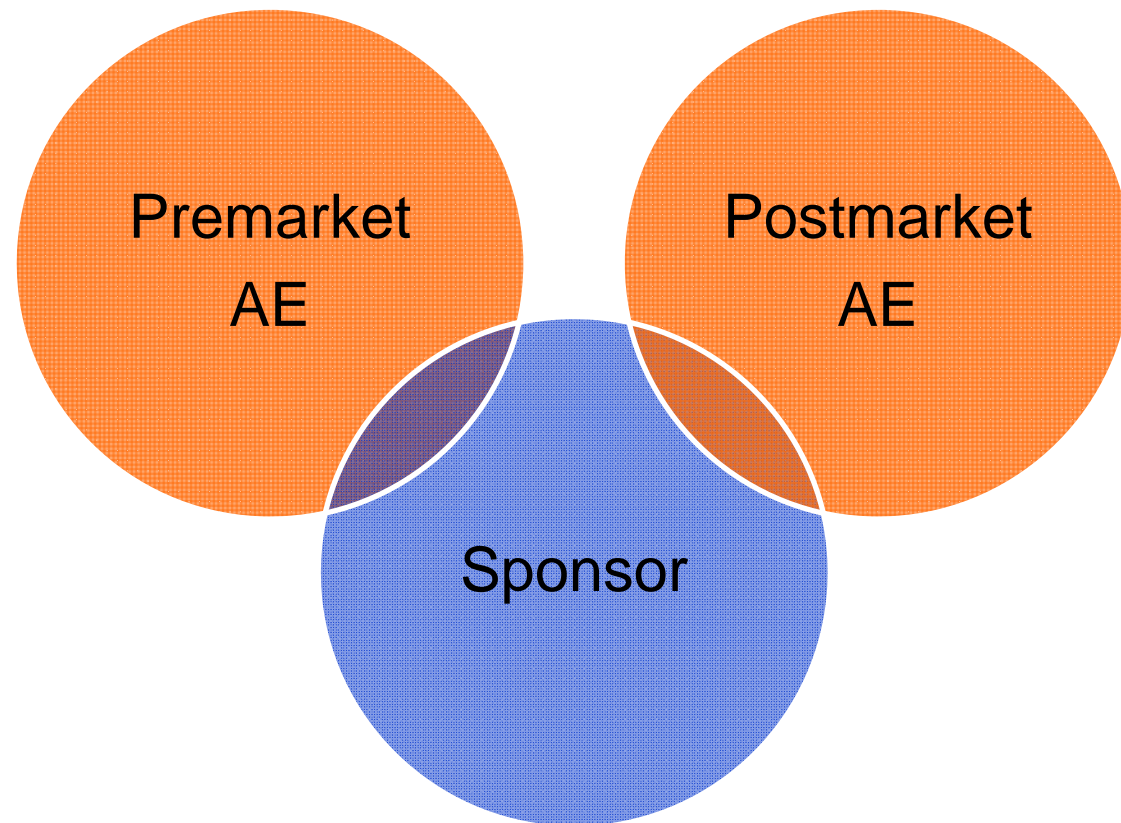
Office of Scientific Investigations

CDER/FDA

Issue

- Expedited IND safety reporting
 - Uninformative reporting
 - Underlying disease
 - Common occurrence in population
 - Study endpoints
- Time commitment
 - Sites
 - Sponsor
 - IRB
 - FDA
- Final Rule, Guidance
- Inspections

Sphere of influence



Expedited Safety Reporting

Pre - 21 CFR 312.32(c)(1)	Post - 21 CFR 314.80(c)(1)
Serious and unexpected suspected	Serious and unexpected
Clinical trials or any other source	Any source
15 calendar days	15 calendar days
Causal relationship	No causality assessment

References

- Safety Reporting Requirements for INDs and BA/BE Studies guidance
 - <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf>
- IND Safety Reporting Requirements final rule
 - <http://www.gpo.gov/fdsys/pkg/FR-2010-09-29/pdf/2010-24296.pdf>

What is the *most* compelling motivator to fully comply with the FDA final rule?

- Cut down on the “noise” in adverse events reporting in order to produce more meaningful reports (doing the right thing)
- Avoid being cited by FDA for safety reporting practices
- Create better relationships with the investigators

Cultural issues and barriers to changing reporting practice: Sponsor perspective

Rob Goodwin, Pfizer

July 21, 2015



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Culture Trumps Everything

- Based on the sponsor interviews and surveys, it is fair to conclude the most sponsors want to follow the IND rule
 - In fact, most believe they are making great strides
- There may be some true cultural challenges with full compliance to the rule, especially if there is some ambiguity
- PV functions see themselves as the protectors of patients and take the safety of anyone taking their medications very seriously
- This may lead to mentality that if there is any question, just report
 - There may also be a “lazy” factor associated with this in some cases

Perception or Reality

- There is a general fear that potential under-reporting could lead to inspection findings or worse
 - This would not include purposeful under-reporting
- This is based on years of past history
 - The lines to appear to be blurred between IND reporting and Post Marketing reporting
 - The rules are also very different if we review the IND rule which is geared to thoughtful reporting and current PADE reporting (especially for Patient Support Programs)
- Stronger FDA support (workshops, 1:1s) will drive stronger outcomes

What education is needed to change expedited IND safety reporting practice?

- Direct one-on-one interaction with FDA
- CTTI-hosted workshop with FDA participation
- CTTI-hosted webinar with FDA participation

Session IV – Implementation of the FDA Final Rule on Expedited IND Safety Reporting

Objectives

- Understand challenges and opportunities related to aggregate reporting of expedited IND safety reporting
- Describe some sponsor methods for determining what/when/how to submit expedited ICSR or aggregate reports
- Discuss what is needed in reports to be valuable and interpretable to FDA and investigators
- Identify future opportunities for educating sponsors

Agenda

- Overview of Expedited IND Safety Reporting
- Sponsor Experiences with Implementing the FDA Final Rule on Expedited IND Safety Reporting
- Investigator Perspective on Expedited IND Safety Reporting
- Round Table Discussion

Presenters/Panelists

- ▶ Patrick Archdeacon, FDA/CDER (moderator)
- ▶ Nina Stuccio, Merck Research Laboratories
- ▶ Kenneth Lipetz, Eli Lilly
- ▶ Maureen Fitzpatrick, Takeda
- ▶ Jeffrey Infante, Tennessee Oncology



Implementation of the FDA Final Rule on IND Safety Reporting: Overview of Purpose of Expedited Reports and Related Challenges

Patrick Archdeacon, MD
Medical Officer
Office of Medical Policy
Center for Drug Evaluation and Research, FDA
July 21, 2015

FDA Final Rule on Pre-marketing IND Safety Reporting

- US FDA published a new rule and draft guidance regarding IND pre-marketing safety reporting *
 - * Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans (21 CFR Parts 312 and 320; Federal Register, Vol. 75, No. 188)
- Published on 9/28/10, with an effective date of 3/28/11
 - 3/25/11: FDA notice of enforcement discretion with expectation of full compliance by 9/28/11

CFR 312.32(c)(1): IND Safety Reports

“The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigators’s IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than **15 calendar days** after **the sponsor** determines that the information qualifies for reporting...”

CFR 312.32(c)(1)(i): Serious and unexpected suspected adverse reactions

“The sponsors must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and adverse event, such as:

- (A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure...
- (B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed...
- (C) An aggregate analysis of specific events observed in a clinical trial that indicates these events occur more frequently in the drug treatment group....”

Merck Experience with Implementing the FDA Final Rule on Expedited IND Safety Reporting

Nina Stuccio, D.O.

Head, Medical Safety Review

July, 2015



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The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.

The presenter is a Merck Research Laboratories Employee.

Key Considerations Prior to Implementation

- ▶ Ensure adequate number of highly qualified Medical Safety Review Physicians
- ▶ Maintain consistent threshold for positive causality assessment as determined by Sponsor Medical Safety Review Physician
- ▶ Identification of clinically relevant follow-up information
- ▶ Impact on ROW Regulatory Agency reporting
- ▶ Impact on Investigator burden
- ▶ Stakeholder communication and change management
- ▶ Identification of events that require expedited reporting through periodic review of aggregate safety data

Identification of Adequate Number of Highly Qualified Medical Safety Review (MSR) Physicians

- ▶ Well supported recruitment effort
- ▶ Therapeutic Area alignment within MSR and key stakeholder groups (Clinical Development, Clinical Safety Risk Management)
- ▶ Diverse Clinical expertise and Industry experience
- ▶ Intensive training focused on level of evidence required to support Causality Assessment
- ▶ Ability to monitor and report key compliance, quality and performance metrics

Consistent Threshold for Positive Causality Assessment Achieved

- ▶ Medical Reviewers trained to ensure evidence exists to support a positive causality assessment
 - Clear documentation of rationale in Company Causality Assessment
 - Cases with insufficient information assessed as “not related”
 - Company Comments describe any planned action to be taken
 - IB update
 - Protocol amendment
 - Informed Consent update
 - Dear Investigator Letter

Identification of Relevant Follow-up Information Achieved

- Only follow-up case versions with actionable or clinically impactful information are submitted to FDA and US Investigators
- Technical ability to submit only case versions with clinically significant information to FDA and US Investigators
- Sponsor should define their parameters for clinically “relevant” follow-up

Impacts of Differential Reporting based on “As Determined” Causality Assessment

- Differential Expedited Reporting due to FDA IND Safety Reporting Rule (21CFR312.32) is technically possible
- For the purposes of IND safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event
- FDA reporting is determined by Sponsor’s independent assessment of causality ONLY
 - For ROW, causality assessment of "related" by either Investigator or Sponsor continues to determine reporting; FDA submission required only if Sponsor determines a causal relationship exists
- Significant reduction in volume of IND Safety Reports submitted to FDA and US Investigators
- ROW Agencies and Investigative Sites continue to receive all SUSARs as reported by Investigators

Positive Impact on Investigator Burden

- Several Investigators have reported positive impact on the volume of IND Safety Reports
 - Most reports now meet criteria for IRB submission
- Reactive communication distributed to sites regarding Merck's enhanced IND Safety Reporting process

Successful Stakeholder Communication and Change Management Initiated

- ▶ Live discussions to communicate enhanced implementation of IND Expedited Reporting Rule with key stakeholders in advance
 - Clear explanation of FDA expectations and implementation timelines
 - Important to acknowledge what is changing vs. what is **not** changing
 - Emphasis on ability to comply with expedited reporting regulations in all applicable regions

- ▶ Potential Stakeholders include:
 - Clinical Development Teams
 - Safety Surveillance Scientists
 - Regulatory Affairs
 - Regional Safety Affiliates and Local Operating Companies
 - Data Management
 - Information Systems Leads
 - Legal, Compliance and Quality Leads
 - External: Investigators and IRBs

Expedited Reporting of Adverse Events Identified during Aggregate Data Review

- Medical judgment and Risk Management Safety Team discussion determines whether expedited IND reporting is required
- Two situations:
 - Ongoing blinded study
 - Completed studies (unblinded)
- A quantitative framework used to aid the medical review and safety evaluation
 - Pre-specification of AEs of special interest
 - Characterization of the background event rates
 - Calculation of event rates and probability of risk elevation to quantify the “reasonable possibility”
 - Reliance on medical judgment and the quantitative evidence to determine actions (e.g. continue monitoring, **expedited IND reporting**, external DMC/internal DMC review, RSI update)

Enhanced Compliance with FDA IND Safety Reporting Rule

- ▶ Following recent implementation, achieved very significant reduction (> 90%) in initial and follow-up cases submitted to FDA and US Investigators within 6 weeks
- ▶ Helps ensure only clinically meaningful and interpretable individual case reports will be submitted in the US
- ▶ Recent implementation of process to identify events that require expedited reporting through aggregate review of safety data will enable full alignment with IND Safety Reporting Rule

Thank you.



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Nina Stuccio, D.O.

Head, Medical Safety Review

Merck Research Laboratories

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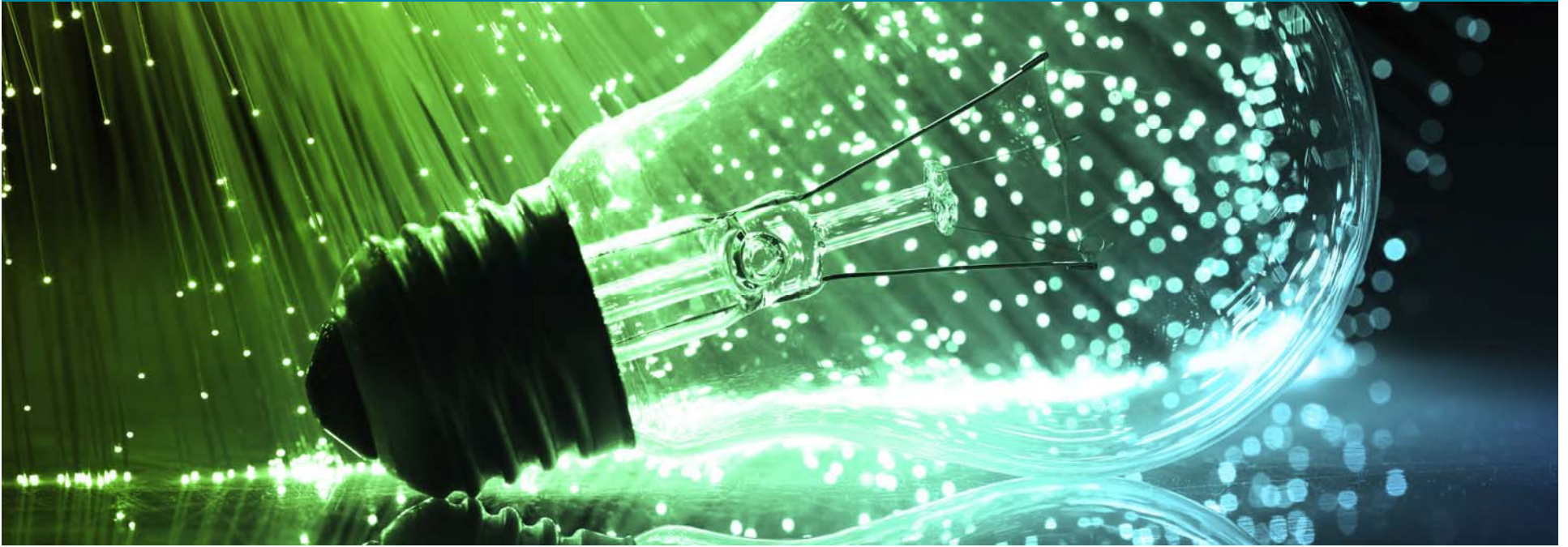
Eli Lilly and Company Best Practices: Sponsor Experience with Implementing the FDA Final rule on Expedited IND Safety Reporting (21CFR 312.32)

Kenneth Lipetz PhD, MBA, HCLD
Global Patient Safety Medical Business Advisor
GPS Medical Process Owner
GPS Medical and Benefit Risk Management
Eli Lilly and Company

July 21, 2015



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The presenter is an Employee of Eli Lilly and Company. Salary and travel support comes from Eli Lilly and Company.

Objectives

- ▶ Highlight the planning and cross-functional processes created to meet the updates to the IND safety reporting regulation (effective 28MAR2011)
- ▶ Outline the aggregate review structure/process
- ▶ Results and Lessons learned

Abbreviations

- ▶ DSMT: Development Safety Management Team
- ▶ DSST: Development Safety Surveillance Team
- ▶ PLSR: Program Level Safety Review
- ▶ PV: Pharmacovigilance
- ▶ SIRC: Safety Internal Review Committee
- ▶ SMT: Safety Management Team
- ▶ SRC: Safety Review Committee
- ▶ TLSR: Trial Level Safety Review

Project Core Implementation Team

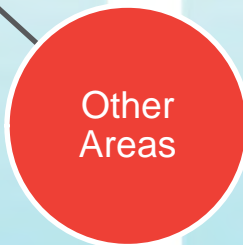
Final Rule Published
September 29, 2010



- PV Physicians
- PV Surveillance Sci.
- PV Pharmacoeconomics



- Quality
- PV Expedited Reporting
- PV Medical Reviewers
- PV Case Management
- PV Business Alliance



- Legal
- Regulatory
- Toxicology
- Clinical Development
- Clinical Operations

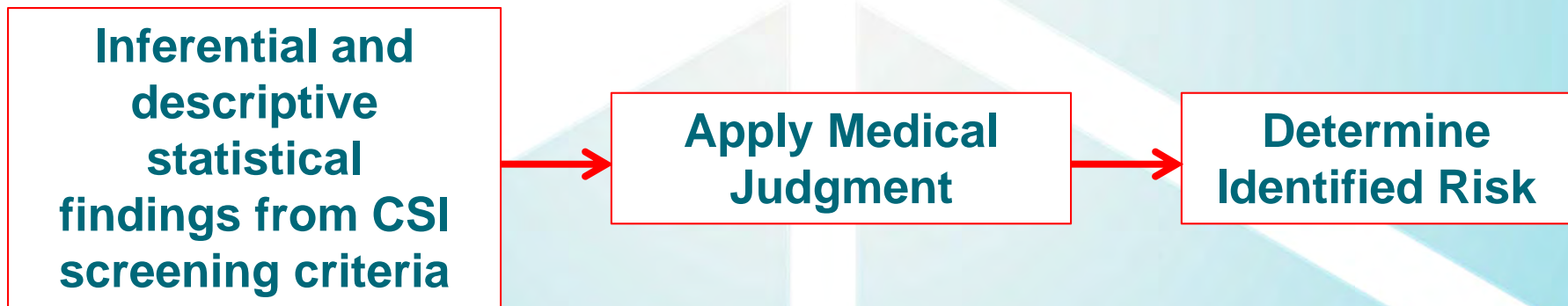


Updated processes needed

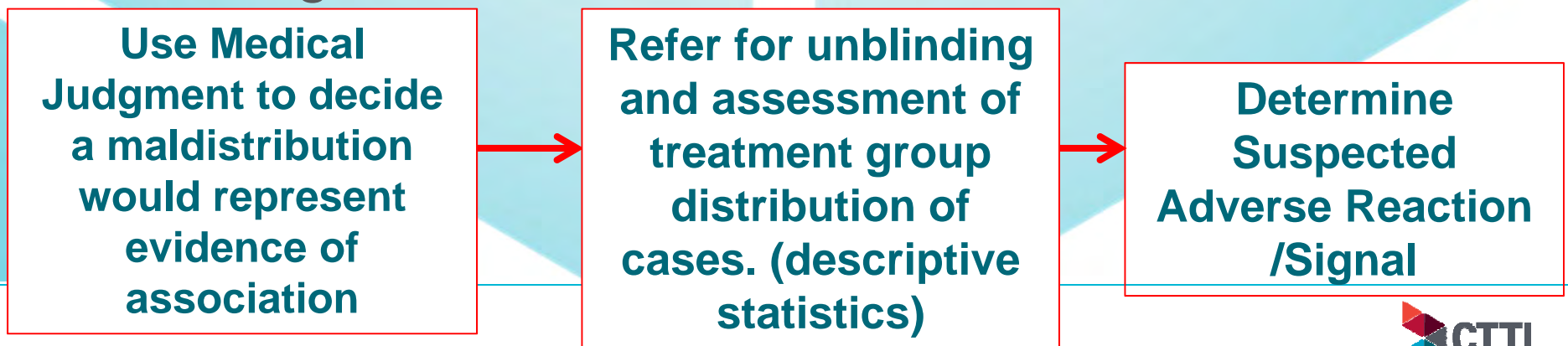
- Identify and document known consequences of underlying diseases or common events in the study population
- Process for company assessment of relatedness for ICSRs
- Aggregate review process that aligns with unblinding policy
- Literature review process for pre-marketed compounds
- Upgrade investigator portal system to allow distribution option based on country
- Regulatory process to expedite aggregate reports via eCTD

Evidence for Reasonable Possibility of Causality

DCSI/CSI Paradigm (unblinded data)



Suspected Adverse Reaction/Signal (blinded data)
Paradigm Shift



Aligning an FDA Suspected Adverse Reaction Definition with Lilly PV Definitions

- ***Suspected Adverse Reaction*** has attributes both of a ***Risk*** and a ***Signal***
- Lilly GPS considers a suspected adverse reaction to represent at least a safety signal (i.e., is worthy of further exploration and continued surveillance using appropriate pharmacovigilance techniques)
- In some circumstances a suspected adverse reaction may rise to the level of a potential or identified important risk

When do we start implementing the IND reporting rule?

- ▶ Prior to study start, DSST and DSMT pre-specifies events (reasonably anticipated SAEs (aka common comorbidities) threshold rates) anticipated for the study (or even the program)
 - These are documented in the Investigator's Brochure or the protocol
- ▶ Serious Adverse Events that can reflect natural history of the target condition
- ▶ Anticipated SAEs common to the study population
- ▶ Periodic assessment of anticipated SAEs (predetermined intervals) as specified in the protocol(s), IB, TLSR plan, and PLSR plan

Potential triggers for DSMT referring an event to SIRC for unblinded assessment

- DSMT reviews cases for consistency, confounders, alternative causes, timing, dechallenge
- DSMT considers biological plausibility
- DSMT concludes that important maldistribution between treatment groups disfavoring LY will establish a suspected adverse reaction/signal

- ▶ Other SAEs occurring at an unexpected rate even if not specified in the protocol and prove notable at the time of a blinded TLSR or PLSR
- ▶ Clusters of notable SAEs referred to the DSMT by the Case Management medical reviewer or prove notable at the time of review by the DSST/DSMT
- ▶ Other safety concerns determined important by the DSMT

SIRC and Maintaining Team Blind

Safety Internal Review Committee (SIRC)

- ▶ Co-chairs decide who will be the SIRC members for a drug.
- ▶ SIRC members are 2 PV physicians, PV surveillance scientist and PV statistician (≥ 2 levels removed from investigational drug's clinical trials and development program).
 - One PV physician is designated as the lead.
- ▶ Review unblinded data and information provided by the team.
- ▶ Look for a numerical incidence imbalance between treatment groups. SIRC looks for a numeric imbalance
- ▶ Statistician prepares properly stratified (by study) summary stats (e.g., Mantel Haenszel odds ratio);
 - the exposure table must provide time-based exposures (e.g., patient-days) rather than only the number of patients in each group
 - these are used to ensure that the crude pooled numbers are not off base

Important SIRC Process Rules

- ▶ When cases are derived from blinded as well as non-blinded (or unblinded) studies, all cases should be considered when the SIRC determines the distribution of cases between treatment groups
- ▶ A lack of consensus within the DSMT should be escalated to line management and, if necessary, to SRC
- ▶ Anticipate and prepare for the reaction of investigators and the IDMC to the finding of an SAR

IND Summary

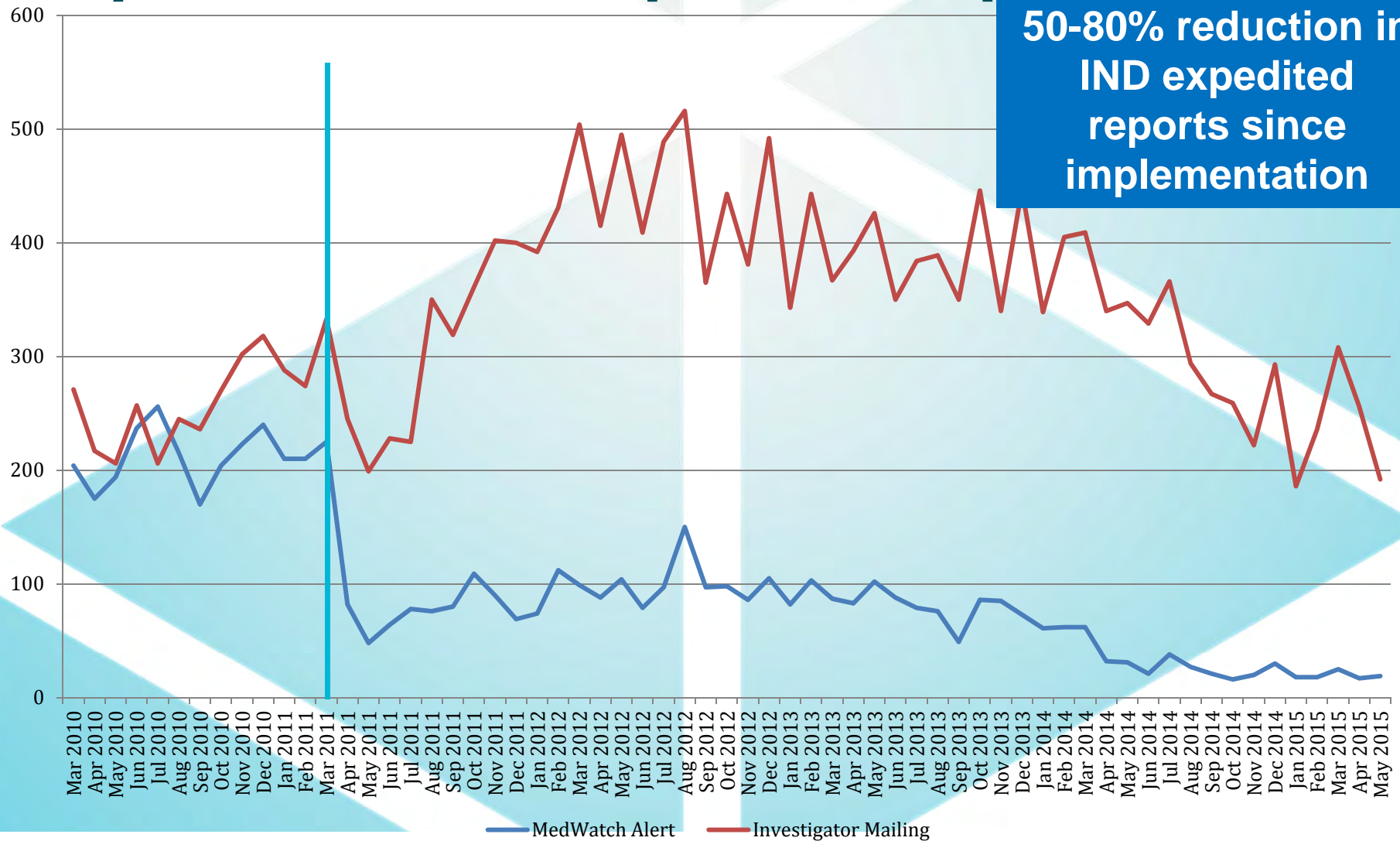
The First Two Years – 28 March 2011 through 12 April 2015

Overall Summary of Aggregate Reviews 28 March 2011 – 12 April 2015

Total assessments	45
Number of molecules	15
Number of DECAs	27
Nonblinded assessments	7
Unblinded assessments	38
Positive for SAR	24
No. of repeat assessments	15
Repeat assessment Positive	12

Impact on ICSR expedited reporting

50-80% reduction in IND expedited reports since implementation



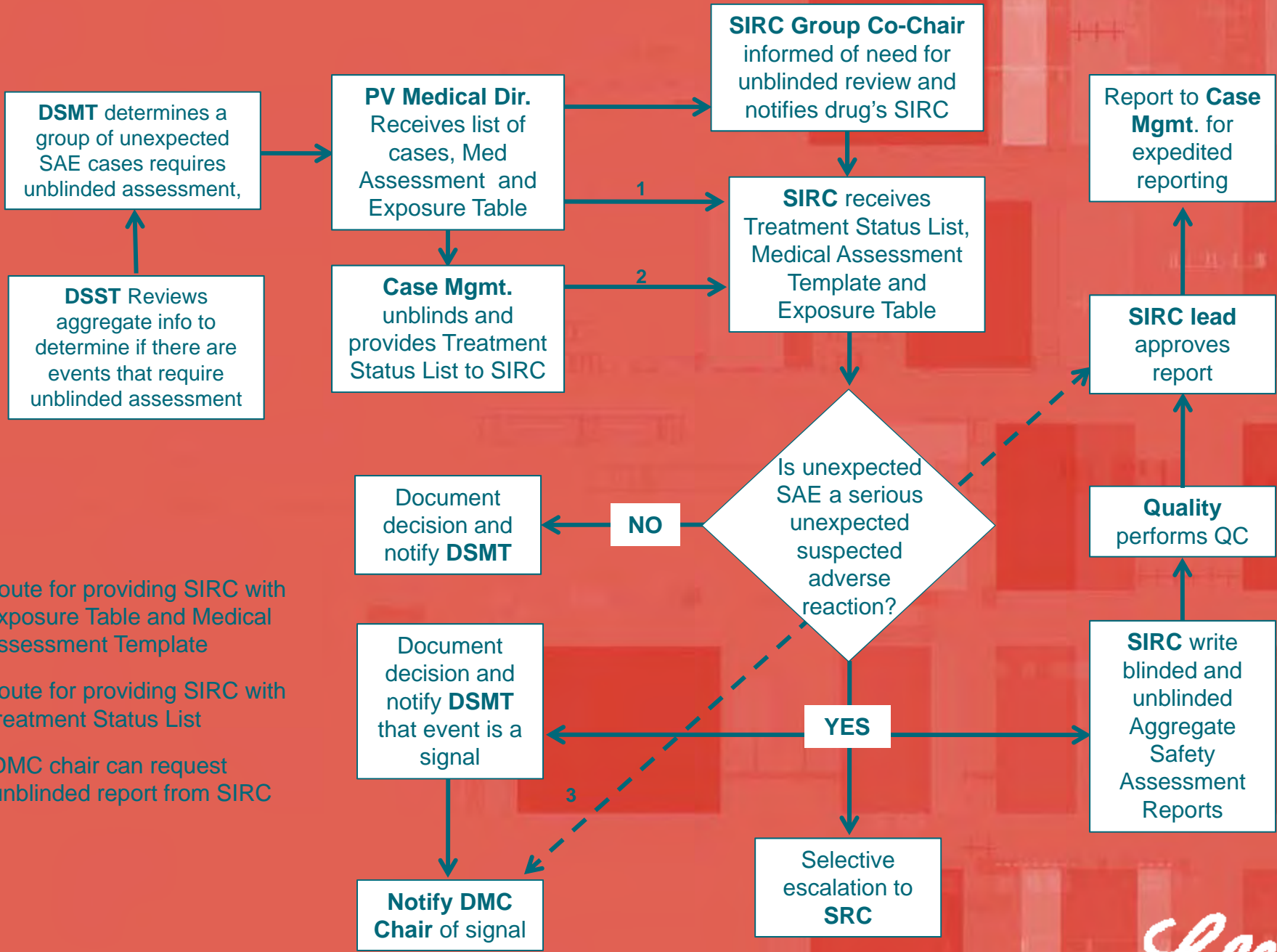
Back-up Slides

**Sponsor Experience with
Implementing the FDA
Final rule on Expedited
IND Safety Reporting
(21CFR 312.32)**

Reasonable Possibility

▶ Within 21 CFR 312.32(c)(1)(i), FDA makes clear the meaning of reasonable possibility and provided the following examples:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
- **An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group**



¹route for providing SIRC with Exposure Table and Medical Assessment Template

²route for providing SIRC with Treatment Status List

³DMC chair can request unblinded report from SIRC



Thank you.



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SCRI[®]

Sarah Cannon Research Institute

Investigator Perspective

21 July 2015

Advancing Therapies for Patients

Jeffrey R. Infante M.D.

Director Drug Development

Sarah Cannon Research Institute/Tennessee Oncology, Nashville TN



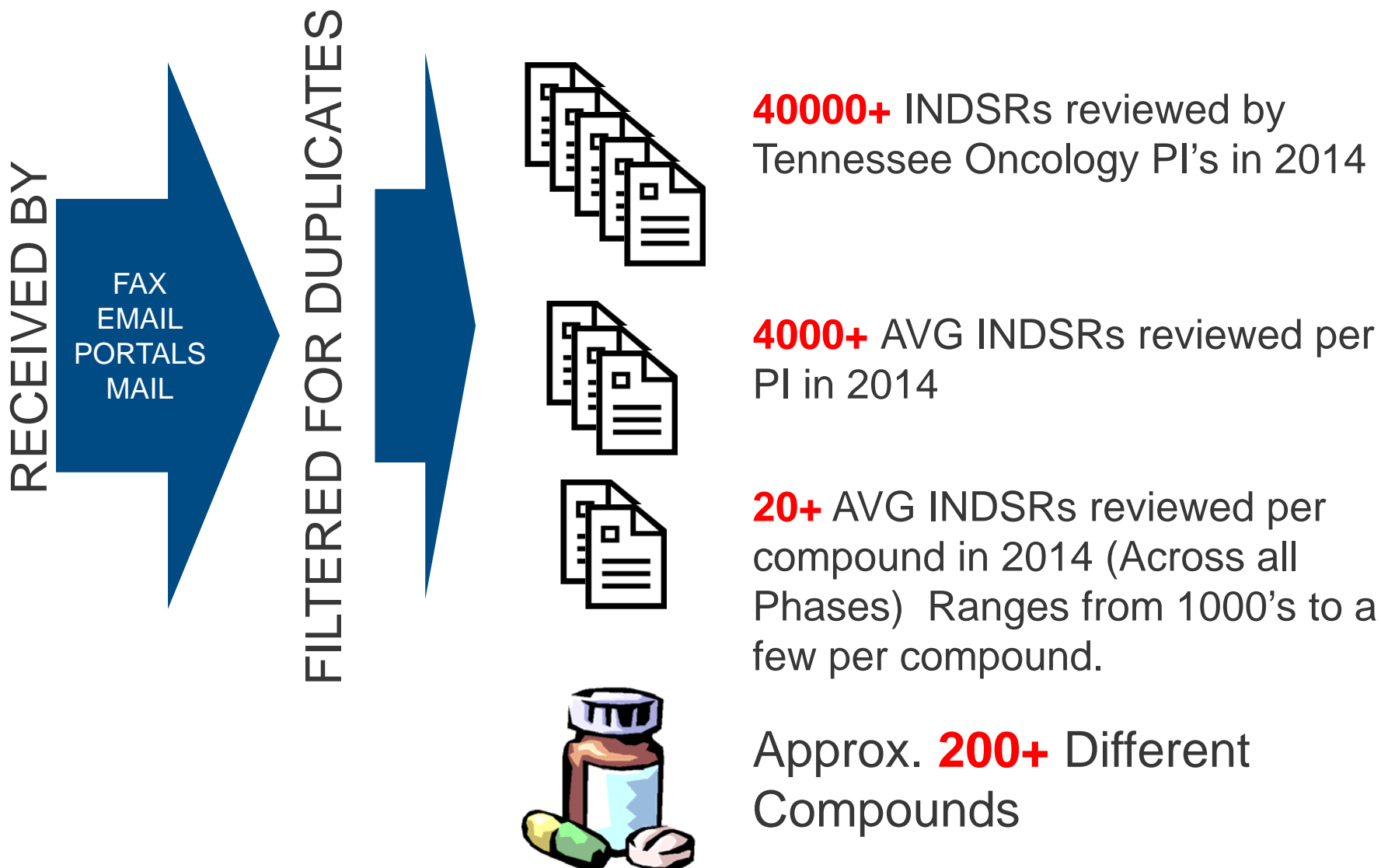
Investigator Perspective: Goal of INDSR Process

- Assimilate information on the investigational product behavior from all trials
- With goal of informing or altering treatment decisions at the bedside for all the individual physicians participating in the trials



The physician desires information that is concise and actionable

Truth is Lost in the Volume



SCRI INDSR System Example



June 19th – July 3rd ▶ 773 reports

INDSR Form

Pending Acknowledgement --> Please Select An INDSR To Acknowledge It

Page: 1 of 39 Total: 773 Items

X	Drug	MCN	Study	Event	Event Date	INDSR Version	Comments	URL
			GU 88	Bronchiolitis	3/13/2015	Not Provided		View INDSR
			MEL 34	Bronchiolitis	3/13/2015	Not Provided		View INDSR
			MEL 37	Bronchiolitis	3/13/2015	Not Provided		View INDSR
			MEL 49	Bronchiolitis	3/13/2015	Not Provided		View INDSR
			GU 88	Rhabdomyositis	12/8/2014	Not Provided		View INDSR
			MEL 34	Rhabdomyositis	12/8/2014	Not Provided		View INDSR
			MEL 37	Rhabdomyositis	12/8/2014	Not Provided		View INDSR
			MEL 49	Rhabdomyositis	12/8/2014	Not Provided		View INDSR

Additional Actions Batch INDSR Submission



Potential Small Wins

- Distribute events per drug – not for each study
- Report only events ▶ protocol / informed consent change
- Report only related events based on sponsor assessment (not PI assessment)
- Allow only one follow up report –hold until final outcome
- One Portal for all Sponsors

The Current Truth:

With the exception of Dear Dr. letters and protocol amendments:

In 10 years of practice, never has an INDSR informed or altered bed side management of a patient



Welcome to the CTTI IND Safety Advancement Project Expert Meeting, Day 2

July 22, 2015



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Session V – Desired Attributes of Electronic Portals for Expedited Safety Reporting

Objective

- Solicit feedback on proposed recommendations for ideal attributes of electronic reporting portals for expedited IND safety reporting

Agenda

- Presentation of proposed recommendations
- Small group discussion of proposed recommendations
- Report out

Desired Attributes of Electronic Portals for Expedited Safety Reporting

Krupa Patel
Merck & Co., Inc.

July 22, 2015



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Electronic Reporting Workgroup

Rationale

- Improve and streamline access to reports
- Eliminate reporting redundancy

Objectives

- Come up with proposed recommendations for sponsors for an electronic portal to deliver reports to investigators

Process

- Identified site barriers to accessing electronic portals
- Defined preferred specifications/attributes for electronic portals
 - Mined survey data
 - Reviewed internal data
- Gained understanding of other similar efforts (TransCelerate, NCI)

Key Stakeholders

- TransCelerate
- NCI
- Investigators
- Sponsors and CROs

Proposed Recommendations

Overall System Functionality

- Browser independent
 - Should work seamlessly with any commonly used browsers
- Operating system independent
- Performance - Quick report download time
 - Enabled via external hosting/cloud based technology
- Simplified process to manage security
 - End-user control over password management
 - Biometric identification in lieu of passwords
 - Ability to integrate with various identity access applications
- Access via mobile devices

User Interface

- Intuitive, easy-to-navigate interface
- Few “clicks” required to access safety reports directly
- Direct access to safety report via hyperlink contained in an email notification (*after authentication*)
- Flexibility within the portal for use with varied institutional processes

Proposed Recommendations

Report Notification, Acknowledgement and Verification

- Batch notifications as per investigative site user's preference
- Provide ability for PI to delegate accessing reports via portal to another site staff
 - Ensuring delegation is properly documented in Site personnel responsibility log
- One click /step acknowledgement
 - Click on a link to the report, check a box or check-all option
- Ability to acknowledge once per product report, not per trial; but capture acknowledgement under each trial
- Capture end to end audit trail
 - Ability to print or save for future reference by both the sponsor and investigative site
- Ability to document alternative method of delivery of reports within the portal if the site cannot access the portal and requires hard copy

Proposed Recommendations

Report Management & Analysis

- Ability to print reports or download multiple reports with one click to a compact disc, computer or electronic investigator site file
- Ability to sort reports by event # to easily identify Initial vs. Follow-up report types
- Ability to search and display safety reports using custom dates and/or event name
- Ability to export single report as well as aggregated data
- Ability to drill down to single report/write-ups from aggregated listing

Proposed Recommendations

Investigator Sign-off

- Consistent with US FDA guidance, we do not recommend PI or delegate sign-off (eSignature or wet signature)
 - Consider acknowledgement via portal by PI or delegate to be sufficient

Training

- Improved education for investigative sites
 - On portal functionality
 - Usability testing for portal-related educational material
 - Best practices for managing report access via portal
 - Any impact to work flow for study staff working on multiple trials for same compound, ownership of task, ensuring PI is informed, tracking/printing/saving while not duplicating
 - Any impact to IRB requirements related to safety report access, PI sign off?
 - Ensuring notifications are not sent to Delete or SPAM folder
- Improved education/awareness for site monitors (CRAs)
 - What was required for paper process may not apply to electronic process

Do not send same report via multiple ways – portal, fax, mail!!

Thank you.



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Discussion Questions

- ▶ Would these recommendations solve your current challenges with Sponsor safety mailing systems/processes? If not, what other recommendations would you like to have considered?
- ▶ How would these recommendations work with your organization's current processes/procedures?
- ▶ What are some of the benefits you see for your organization if these recommendations were implemented?

Session VI – Innovative Opportunities for Communicating Safety Information

Objectives

- Consider alternative methods for reporting of IND safety information, including related challenges and opportunities
- Understand alternate safety reporting processes that would be of value to investigators

Agenda

- Describe and Discuss Different Types of Safety Communication
- Investigator Perspective on Periodic Reporting
- Sponsor Experiences with Periodic Reporting
- Discussion

Presenters/Panelists

▶ Michael Jones, Eli Lilly (moderator)

▶ Name, FDA

▶ Maria Luisa Bonura, Pfizer

▶ Marsha Millikan, Eli Lilly

▶ Name, Affiliation



Established Vehicles for Communicating Safety Data

Patrick Archdeacon, MD
Medical Officer
Office of Medical Policy
Center for Drug Evaluation and Research, FDA
July 22, 2015



Communicating Clinical Data from Drug Studies to Regulators

- IND Safety Reports (expedited)
- Investigator Brochure
- Information Amendment
- Periodic Reports
 - IND Annual Report
 - Development Safety Update Report (DSUR)
 - Periodic Benefit-Risk Evaluation Report (PBRER)



IND Safety Report

- Received by regulators and by all clinical investigators of trials using the investigational agent
- Intent to communicate urgent new safety information (for that reason, must be expedited as 7 or 15 day reports)
- Should contain evidence that reasonably demonstrates causal link between drug and unexpected serious adverse event

Investigator Brochure (IB)

- Contents of IB are described in Section 7 of ICH E6 (Guidelines on Good Clinical Practice)
- Compilation of the clinical and nonclinical data on the investigational product that is relevant to the study for the product in human subjects
- IB should be reviewed at least annually and revised as necessary. More frequent revision may be appropriate.
- Tabular summaries of adverse drug reactions for all the clinical trials.
- Typically include a Company Core Data Sheet (CCDS), which contains the Company Core Safety Information (CCSI) – also the reference safety information (RSI) for the IB

Information Amendment (CFR 312.31)

- “A sponsors shall report in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety report, or annual report...”
- “An information amendment is required to bear prominent identification of its contents (e.g.... ‘Information Amendment: Clinical’), and to contain the following: ... An organized submission of the data in a format appropriate for scientific review.”
- “Information amendments to the IND should be submitted as necessary but, to the extent possible, not more than every 30 days.”



IND Annual Report

Annual report submitted to regulators; brief report including:

- Summary of each study, including total number of subjects enrolled, tabulated by age group, gender, and race
- Narrative or tabular summary showing the most frequent and most serious adverse experiences by body system
- A summary of all IND safety reports submitted during past year
- A list of all subjects who died during participation in the investigation, with the cause of death for each subject
- A list of subjects who dropped out during the course of the investigation in association with any adverse experience
- A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions

For full itemization of all required elements of IND annual report, please see 21 CFR 312.33



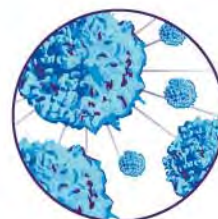
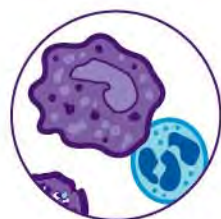
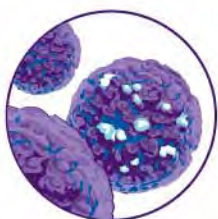
Development Safety Update Report (DSUR) – ICH E2F

- Annual report to regulators; may also go to IRBs and IECs
- Focus of data and findings from clinical trials
- Based on reference safety information (RSI) in IB
- Modular format, broken into 20 defined sections
 - Section 3: Actions Taken in the Reporting Period for Safety Reasons
 - Section 4: Changes to RSI
 - Section 7: Data in Line Listings and Summary Tabulations
 - Section 7.2: Line Listings of Serious Adverse Reactions During the Reporting Period
 - Section 7.3: Cumulative Summary Tabulations of SAEs, including both blinded and unblinded (completed trials and unblinded for expedited reporting) trial data
 - Section 8: Significant Findings from Clinical Trials During the Reporting Period
 - Section 8.2: Ongoing Clinical Trials – evidence of new safety signals
 - Section 18: Overall Safety Assessment
 - Section 18.1: Evaluation of the Risks, including newly identified safety issues



Periodic Benefit-Risk Evaluation Report (PBRER) – ICH E2C(R2)

- Based on Company Core Data Sheet (CCDS), which contains the Company Core Safety Information (CCSI) – also the reference safety information (RSI) for the IB
- Modular format, broken into 20 defined sections
 - Section 4: Changes to RSI
 - Section 6: Data in Summary Tabulations
 - Section 6.1 Data in Summary Tabulations from Clinical Trials (including blinded and unblinded data)
 - Section 15: Overview of Signals: New, Ongoing, or Closed
 - Section 16: Signal and Risk Evaluation
 - Section 16.1 Summary of Safety Concerns: based on the safety specification (if one exists)
 - Section 16.2 Signal Evaluation -- include signals categorized as potential or identified risks, as well as signals that have been rejected as false signals
 - Section 16.3 Evaluation of Risks and New Information – provides an interpretation of new information
 - Section 16.4 Characterization of Risks
 - Section 16.5 Effectiveness of Risk Minimization (if applicable)
- Periodicity of reports: varies but typically initially every 6 or 12 months



Sponsor Experience with Periodic Reports

M. Luisa Bonura, MD
CTTI IND Safety Advancement Project
July 22, 2015



WORLDWIDE SAFETY & REGULATORY

Worldwide Research & Development

Worldwide Research & Development

Type of Periodic Reports Containing Safety Information

- Investigator Brochure
- Development Safety Update Report / IND Annual Report
- Clinical Trial Safety Update Report
- Study-specific newsletters or similar periodic communications from study management

Investigator Brochure

- Created at the start of human trials
- Summarizes the available body of knowledge on a given product under clinical investigation
- Reviewed and updated, as appropriate, at least annually
 - Out of cycle updates are made in case of substantial new data that has a significant impact on the benefit-risk profile of the drug or the ability of the investigator to support the clinical management of subjects in the study(ies).
- Section 7 *Summary of Data and Guidance for the Investigator* contains the Development Core Safety Information, including the list of expected Adverse Drug Reactions
- Target Audience: Investigators, Regulatory Authorities, Institutional Review Boards/Independent Ethics Committees

Development Safety Update Report (DSUR)

- Created annually. Starts with the anniversary of the first IND/Clinical Trial Application worldwide
- Includes information from the current reporting period, as well as cumulative analyses based on previous knowledge of the product's safety and contains unblinded information regarding the entire development program
- Topics presented and discussed include:
 - Update on the status of the clinical development program
 - Significant findings from sponsored clinical studies during the reporting period and from other clinical studies (e.g. safety information from non sponsored studies or co-development programs), literature and marketing experience, where appropriate
 - Non-clinical new data and their implications to the safety of subjects
 - Overall safety assessment
- Target audience: Regulatory Authorities, Independent Ethics Committees

Clinical Trial Safety Update Report (CTSUR)

- Generated at 6-monthly intervals, coinciding with the anniversary of the DSUR and the midpoint of the relevant reporting period
 - May be developed more frequently depending on the risk assessment of the ongoing interventional studies
- Includes
 - A line listing of all serious adverse events that are unexpected and considered related to the investigational product(s) by either the investigator or the sponsor, from all sponsored interventional clinical studies for the investigational product, for the reporting period.
 - A brief summary report and comment on the impact of the data presented on the benefit-risk for subjects included in the clinical trial(s) concerned
- Target audience: Investigators in sponsored studies, Independent Ethics Committees

CTSUR Line Listing

- Blinded for Investigators
- All unexpected SAEs related to all study drugs (i.e. investigational product under consideration, active comparators, placebo) used in the studies for the reference investigational product
- Data are presented by study and, within each protocol, by MedDRA System Organ Class (SOC) of the primary event
 - For each case the listing includes
 - Case I.D.
 - Subject I.D.
 - Country of occurrence
 - Patient age, sex and outcome
 - Suspect product(s), indication, total daily dose, dosage form, route of administration, treatment dates
 - Event term(s) (verbatim and MedDRA PT), onset date and latency.
 - Causality: Investigator and Sponsor



Study Newsletters

- No standard format or frequency
- Study-specific
- May contain recommendations or clarifications for managing specific adverse events
- Not used to communicate new safety information
- Target audience: Investigators in individual studies

Conclusions

- With the enforcement of the Final Rule on IND Safety Reporting, the number of expedited mailings of individual case safety reports is significantly reduced
- Sponsors may continue to streamline their internal processes to further limit the expedited mailings of individual reports
- There is no other formal and standard process to share safety information during the conduct of studies than through IB updates and investigators may learn of potential safety signals that don't reach the threshold of IND safety reporting only with the next IB update
- Periodic aggregate reporting may provide meaningful updates to investigators on the evolving safety profile of investigational products in between IB updates and complement the information provided expeditely for those reports that may have an immediate impact on the safety of the subjects participating in the studies



An Approach To Periodic Safety Reporting To Investigators

Marsha Millikan RPh
22-JUL-2015
CTTI Meeting

Lilly

Objectives

- ◆ Discuss investigator feedback that led to new solution of periodic reporting to investigators
- ◆ Describe the periodic investigator safety mailing process

Global feedback received from investigator sites

- ◆ Increased volume of investigator safety mailings has made communication of safety information challenging for investigator sites
- ◆ Expedited reports do not provide an assessment of the evolving safety profile of an investigational product
- ◆ Sites were requesting safety data in aggregate along with summaries of the safety profile

Investigator ICSR Process prior to January 2013

- ◆ Expedited ICSR reports
 - Investigators receive via electronic portal:
 - US investigators: Unexpected SAE assessed as possibly related by the company medical reviewer
 - OUS investigators: Unexpected SAE assessed as possibly related by company medical reviewer or investigator

Global Investigator Mailing Process Improvement effective 1JAN2013

- ◆ Six month SUSAR Line Listing (LL) Report distributed to all world-wide investigators via electronic portal

AND

- ◆ All Investigators receive ICSRs to comply with the FDA IND rule
 - In addition they may receive expedited aggregate reports for a specific topic per IND rule
- ◆ Investigators in a few “opt-in” countries* receive all ICSR SUSARs and not just the ones that met the IND final rule

*Germany, Hong Kong, Italy, Israel, South Africa, Thailand, Switzerland

Narrative Content Investigator LL Report

- ◆ Introduction: lists the time period for the review
- ◆ Summary of Safety Surveillance Activities during the reporting period
 - Results of Individual Case Review
 - Results of Assessment for Unusual Clusters of SAEs
 - Results of Assessment of Reasonably Anticipated SAEs
 - Other Significant Safety Findings

Line Listing Sections

- ◆ Summary Tabulation
 - Counts of SUSAR events per MedDRA System Organ Class (SOC)
 - Counts of SUSAR events with fatal outcomes per MedDRA SOC
- ◆ Blinded Line Listings organized by study
 - Includes Case ID, MedDRA term, Age, Gender, Country, Outcome

Investigator feedback and future solutions

- ◆ Reduced number of concerns coming from investigators (particularly in Europe)
- ◆ No actual feedback on whether investigators appreciate this periodic LL approach
- ◆ Propose periodic investigator LL reports as an alternative to investigators reading ICSRs
 - Possible waivers for companies?

Summary

- ◆ Decreased number of ICSRs to US investigators following IND rule later led to company decreasing ICSRs to global investigators
 - To meet OUS regulations, company began sending periodic line listing reports to global investigators every six months as well as ICSRs/aggregates to align with IND rule
- ◆ Future discussion: Can US investigator expedited ICSRs be replaced with 6 month LL reports (via individual company waiver process)

IND Expedited Safety Reports ...Investigator Perspective

Mohamed E. Salem, MD

Lombardi Comprehensive Cancer Center, Georgetown University

July 22, 2015



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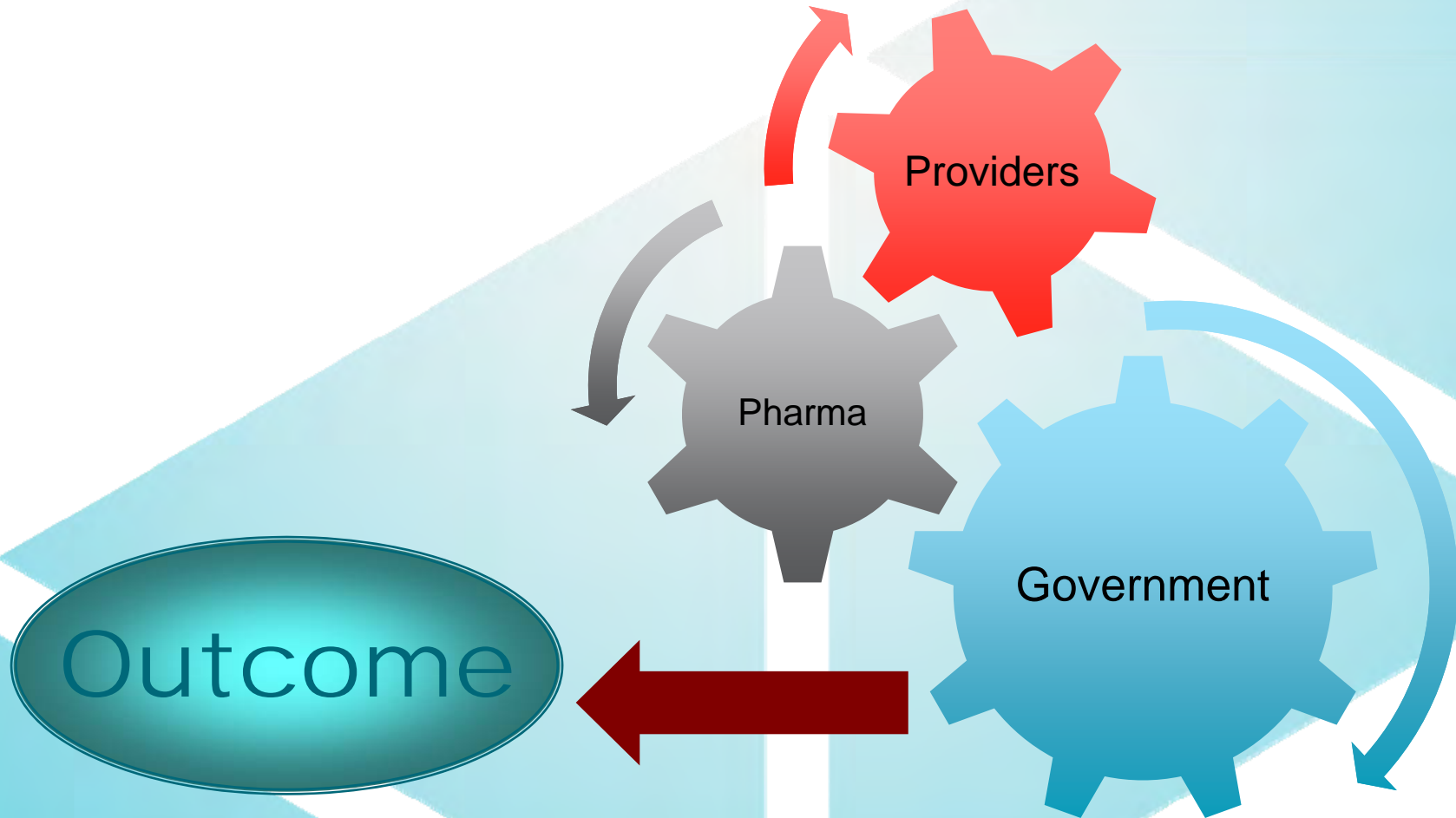
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What do patients really want?



Partnership



The image features a teal decorative background with various geometric shapes, including triangles and trapezoids, some overlapping. A prominent white rectangular box is centered on the page, containing the text 'Subjectivity'.

Subjectivity

Safety Reports

	YES	NO
Goal:	Safety	Reporting
	Quality	Quantity
	Concise and actionable	Too many reports
	Access to information	---

How do we get there?

- ▶ Clear Objectives
- ▶ System in place
- ▶ Communication
- ▶ Education
- ▶ Culture Change
- ▶ Address Fear Factor
- ▶ Metric System
- ▶ Feedback Mechanism

"Things that matter most must never be at the mercy of things that matter least."

~ Bill Crawford

Thank you.



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