Improving the System of Reporting and Interpreting Unexpected SAEs to Investigators Conducting Research Under an IND

Summary of WS1: IND Sponsor Practices

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SAE Project Workstream 1
Focus on IND Sponsor Practices

- SAE Project:
  - Generate empirical evidence for possible modification of the current reporting system to more efficiently and effectively inform investigators of these events, thus optimizing protection of study participants.
- Workstream 1
  - Document the current range of practices for safety monitoring and reporting of unexpected serious adverse events (SAEs) to US-based investigators of IND research
  - Survey investigated sponsor practices for IND research
    - Safety monitoring
    - Safety decision-making
    - Safety reporting

Methods

- Survey of industry[1] sponsors of IND research
  - Voluntary, anonymous, non-compensated
  - Web-portal based, all questions mandatory (n = 79[2])
  - Data collection period = 22Oct2009 – 08Jan2010
- Approximately 50 companies approached (drug safety unit)
  - Majority from WCI PVNet and PVConnect industry forums[3]
    - Additional invitees from CTTI membership
  - 10 complete responses received (~20%)
    - 1 incomplete response, results not included in analysis
- Similar surveys sent to NIH & academic IND sponsors
  - Results not included in this analysis

(1) *Self-identified as either "biotechnology" or "pharmaceutical" companies; medical device companies not invited to participate*
(2) *Question logic applied resulted in some questions not posed based on earlier responses*
(3) *WCI (World Class International) is a life sciences consulting firm that manages two industry pharmacovigilance forums; they agreed to the survey to be presented to their membership*

Organization of Survey Review

- Key Results
  - Profile of Respondents
  - Safety Data Management
  - Safety Monitoring and Analyses
  - Safety Reporting
- Discussion
  - Respondent Profile and Interpretation
  - Use of Specialized Resources and Structures
  - Individual SAE vs. Aggregate Reports
  - Reporting Patterns
  - Investigator Feedback to Sponsors
- Recommendations

Results

Profile of Respondents

- Respondents representative of
  - Pharmaceutical companies
  - with large IND research programs
- Main therapeutic areas for IND research
  - Oncology (9)
  - Endocrinology and Metabolism (8)
  - Neurology/Psychopharmacology (6)
  - Anti-infective/Infectious disease (6)

Table 1.

Characteristic	A	B	C	D	E	F	G	H	I	J
Description	Pharma	Pharma	Pharma	Pharma	Biotech	Pharma	Pharma	Pharma	Pharma	Biotech
Current INDs	21-50	51+	21-50	51+	51+	51+	51+	2-5	51+	51+
Current IND Studies	51+	51+	51+	51+	51+	51+	51+	2-5	51+	51+
Countries involved in IND Studies	21+	21+	21+	21+	21+	21+	5-20	2-5	21+	5-20
Size (FTE) of Clinical Research Group	101+	101+	101+	101+	101+	101+	101+	<10	101+	101+
Separate Drug Safety Unit	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Safety Data Management: Written Procedures

- All have specific written procedures for multiple aspects of IND safety evaluation and reporting

Table 2.

Written Procedures	Respondents (n)	Respondents (%)
SAE data entry and report construction	10	100
Evaluation of individual SAEs	9	90
Evaluation of all safety data for a specific study	6	60
Evaluation of all safety data under a single	4	40
Evaluation of all safety data across INDs for a single molecule	6	60
Reporting SAEs to regulatory agencies	10	100
Reporting SAEs to investigators	10	100
Reporting SAEs to IRBs (where sponsor has responsibility)	9	90

- Primary regulations influencing company IND safety procedures
  - US CFR and FDA Guidelines (100%)
  - ICH GCP (90%)
  - EMA CTD and Eudralex Volume 10 (80%)
  - OHRP Guidances (50%)
  - NIH institution guidelines (40%)

Safety Data Management: Use of DCCs

6 respondents use external data coordinating centers (DCC) for IND safety data

- 5 use public/academic DCCs
  - Primary drivers: thought leadership, credibility, federally-funded network
  - Services: review of individual SAEs
- 4 use private/CRO DCCs
  - Primary driver: augment resources
  - Services: Process, review, submission, and distribution of SAEs
- Only 1 respondent (of 10) uses any DCC for aggregate safety data analysis

Table 3.

Primary Drivers for Use of a DCC	Respondents	
	Public/ Academic (n = 5)	Private/ CRO (n = 4)
Thought leadership	4	0
Greater resources (lack of internal resources at company)	1	4
Corporate strategy	2	2
Credibility/visibility with academic research organizations	3	0
Ability to share data across other INDs	0	0
Collaboration with federally-funded network in a single DCC	3	0
DCC Safety Data Management Services Utilized	**Public/ Academic (n = 5)**	**Private/ CRO (n = 4)**
Processing of SAEs (data entry and report construction)	1	2
Review of individual SAEs	4	2
Database for SAEs	1	0
Submission of SAEs to regulatory agencies	0	2
Distribution of SAEs to investigators, IRBs, and others	1	2
Analysis of aggregate safety data	1	0

Safety Analyses: Use of Clinicians

- Internal clinicians consistently accountable for review and assessment of IND safety data
  - Predominantly use internal drug safety physicians/clinicians
  - All 10 undertake routine clinical review of SAEs regardless of "expectedness"
  - 9 of 10 do so for "unrelated" SAEs as well

Table 4.

Primary Accountability	Respondents (n)		
	Individual SAE Review	Cross-IND Safety Data Review	Investigator SAE Notification Decision
Physician/Clinical lead for study	1	3	0
Other study team physician/clinician	0	1	0
Drug safety physician/clinician	9	6	9
External physician/clinician	0	0	1
Non-clinician study team member	0	0	0
Internal company review board	0	0	0
DMC/DSMB	0	0	0
None	0	0	0
Other	0	0	0

Safety Analyses: Use of DMCs/DSMBs

- All respondents use Data Monitoring Committees for safety data review of some portion of their IND research
  - 20% (2 of 10) identified that they used a DMC for more than half of their studies under IND
  - Most common reasons for DMC use are research in life-threatening diseases and vulnerable populations

Table 5.

Primary Drivers to Use a DMC	Respondents (n)	Respondents (%)
Life-threatening diseases	10	100
Vulnerable population (pediatric, geriatric, etc.)	10	100
Known/suspected investigational product toxicity	8	80
Morbidity/mortality endpoints	8	80
Planned interim analyses	6	60
Length of study	3	30
Low therapeutic ratio	3	30
Long duration of study drug exposure	2	20
Company/institution requirements to use for all studies	1	10
Other	0	0

Safety Analyses: Aggregate Reports/Analyses

- Aggregate safety data reports, summaries, or analyses for submission routinely produced by 8 of 10 respondents
  - Content focused on unexpected SAEs related to study-drug
  - Distribution predominantly to FDA and other regulatory agencies (75%)
    - Limited distribution to investigators in US (25%)
  - 5 (88%) produced annually; 3 (38%) produced quarterly

Table 7.

Data Contained in Aggregate Safety Data Reports/Summaries/Analyses	Respondents	
	(n)	(%)
Unexpected SAEs Related to Study Drug	8	100
Expected SAEs Related to Study Drug	5	63
SAEs Unrelated to Study Drug	4	50
Summary analysis/position on risk/benefit	3	38

Table 8.

Recipients of Routine Aggregate Safety Data Reports/Summaries/Analyses	Respondents	
	(n)	(%)
FDA	6	75
Other Regulatory Agencies	6	75
Investigators of the molecule, regardless of IND, in the US	2	25
Investigators of the molecule, regardless of IND, outside the US	3	38
All co-development partners	5	63
Other groups separately sponsoring INDs for the molecule	3	38
IRBs in the US	1	13
IRBs or Ethics Committees outside the US	3	38

Safety Reporting Scenarios

Several scenarios for safety reporting were investigated across multiple variables:

- Type of SAE safety data
- Type of recipient
- Type of report
- Drug associated with SAE
  - Investigational product vs. comparator/non-investigational

Safety Reporting: Investigational Product SAEs

- Unexpected SAEs related to study drug almost always:
  - Sent to FDA as individual expedited reports
    - ~60% send in aggregate as well
  - Sent to US investigators (across INDs) as individual expedited reports
    - Only rarely provided in aggregate
- Expected SAEs related to study drug, and unrelated SAEs, were
  - Usually sent to FDA, almost exclusively in aggregate
  - Were not usually sent to investigators, either as individual or aggregate reports
- Individual expedited reporting limited to unexpected, related SAEs

Table 9.

IND Safety Reporting: Investigational Product	Respondents (of 10)					
Type of Report and Recipient	Unexpected, Related		Expected, Related		Unrelated	
	Fatal	Non-fatal	Fatal	Non-fatal	Fatal	Non-fatal
Individual expedited report						
FDA	10	10	1	0	1	1
US Investigator - same	9	10	1	0	0	0
US Investigator - different IND, same molecule	8	8	0	0	0	0
Periodic summary/listing						
FDA	6	6	9	9	8	4
US Investigator - same	2	2	1	3	2	2
US Investigator - different IND, same molecule	2	2	2	1	1	2

Safety Reporting: Active Comparator and Non-Investigational Product SAEs

- Companies that report SAEs for active comparators or non-investigational compounds do so in a similar pattern to investigational product SAEs
  - Only approximately half as many do so
- If reported, these are predominantly reported only to the FDA
- Reporting to investigators rare (no more than 20% for any scenario)
  - Including individual expedited reporting of unexpected, related SAEs

Table 10.

IND Safety Reporting: Active Comparator and Non-Investigational Product Safety Reporting	Respondents (of 10)					
Type of Report and Recipient	Unexpected, Related		Expected, Related		Unrelated	
	Active	Non-Inv.	Active	Non-Inv.	Active	Non-Inv.
Individual expedited report						
FDA	4	6	1	0	0	0
US Investigator - same	2	2	1	0	0	0
US Investigator - different IND, same molecule	0	0	0	0	0	0
Periodic summary/listing						
FDA	4	4	5	5	6	3
US Investigator - same	2	0	1	0	1	0
US Investigator - different IND, same molecule	1	0	2	0	1	0

Safety Reporting: IND Waivers

- 7 respondents have actively discussed exceptions to safety reporting to IND investigators with the FDA
  - 6 of those respondents indicated they have had such discussions for a minority (less than 25%) of their studies under IND
  - Those same 6 respondents also reported having received some waiver from the FDA as well

Investigator Interactions & Feedback

- 9 respondents send SAEs to investigators within expedited timeframes
- 7 respondents identified that in the last 12 months they have received concerns from investigators regarding the SAEs/safety reports
  - Predominant concern: Too many reports (7 of 7, 100%)
- 5 respondents have taken on IRB reporting responsibilities; of these 5…
  - All were of the 2009 FDA Guidance on Adverse Event Reporting to IRBs
  - All had IRBs spontaneously communicate changes in their requirements and expectations for safety reporting, citing the FDA Guidance
  - 4 also had *investigators* communicate changed expectations for safety reporting to them, citing the guidance on IRB reporting
  - 2 changed reporting patterns (by time of survey conduct)

Table 12.

Concerns from Investigators Regarding SAEs/Safety Reports	Respondents	
	(n)	(%)
Too many reports	7	100
Too few reports	1	14
Not enough information on individual reports	1	14
Too much information on individual reports	1	14
Information not relevant for their patients	5	71
Analysis missing; implications unclear	3	43

Discussion

Discussion

Respondent Profile and Interpretation of Results

- 10 responses received (~20% of the invited industry participants)
  - Suggests results are limited in their ability to completely describe the full range of practices by all companies sponsoring IND research
- However, respondent profiles generally representative of those industry sponsors that presumably generate large volumes of investigator safety reports
  - Large pharmaceutical companies (some biotechnology and mid-sized companies)
  - Large clinical research programs in number and scope
  - Conduct clinical studies in many currently active therapeutic areas(1)
- Substantial breadth and depth of the dataset from the 79-question survey (all 10 were complete responses)
- Results are likely able to provide a reasonable cross-section of the nature of safety data management practices by the larger population of companies
  - Where responses to questions (or a series of related questions) are similar across most respondents, the extrapolation to the larger population of companies sponsoring IND research is more reliable.

(1) From ad hoc *comparison with correlated NIH institutional funding in recent years*

Discussion

Use of Specialized Resources and Structures

1. Drug safety unit distinct from general clinical research group
   - Further, roles for SAE review and notification decisions are predominantly assigned to drug safety physicians or clinicians.
2. Written procedures across multiple aspects of safety data processing
   - Such documentation expected given regulation of clinical research
   - Most respondents also appear to be subject to multiple domestic (eg NIH, OHRP) and international (eg EMA) regulations
     - Written procedures may be necessary to create order across different requirements.
3. Maintenance of separate safety database from the clinical trials database
   - Requires reconciling data between databases (processes varied across respondents)
   - Opportunities to evaluate and report safety data in a specialized fashion, prior to completion of clinical trial conduct and dataset “cleaning”
4. Use of external bodies for significant portions of safety data management
   - All respondents use external DMCs
   - Public DCCs used by 5 (of 10), primarily for evaluation of safety data
     - Typically to ensure thought leadership, credibility, and access to a network
   - Private DCCs used by 4 (of 10), as augmentation of resources
     - For a broad range of data management activities.

These 4 mechanisms of specialized resources & structures for IND safety data management are utilized repeatedly and almost universally

Discussion

Focus on Individual SAE Reports vs. Aggregate Reports/Analyses

- Efforts and deliverables focused heavily on individual SAEs
  - Less emphasis and more variation in aggregate analysis/interpretation/reporting

	Individual SAEs	Aggregate Safety Data
Procedures	90-100% penetration of written procedures for individual SAE processing and reporting	40-60% penetration of written procedures to evaluate safety data across a study, IND and multiple INDs
Clinical Monitoring	90% have accountability for SAE report review with drug safety clinicians/physicians	Cross-IND safety review spread across drug safety, team members, & study team lead clinicians/physicians
External Resources	50% use DCCs (public or private) for individual SAE evaluation	10% (1 of 10) uses a DCC for aggregate safety data analysis
Safety Reporting	80-100% report unexpected SAEs related to study drug within and across INDs to FDA & investigators	10-90% report expected SAEs related to study drug and SAEs unrelated to study drug, predominantly in aggregate

- Aggregate analyses produced, but more restricted scope and distribution
  - 9 sponsors produced an Analysis of Similar Events for SAEs
    - But not produced where not required by CFR 312.32(1)
  - 8 produced routine aggregate safety data reports
    - Most (5) annually, some (3) quarterly
    - Only 3 include summary risk-benefit analyses
    - Only 2 provide to US investigators

Discussion

Safety Information Reporting Patterns By Recipient

- Where judgment is perceived acceptable, consistently greater safety reporting to FDA as compared to US investigators
  - For all 17 SAE reporting scenarios, information is provided to FDA in equal or greater frequency than to investigators
    - In many cases, particularly periodic summaries, the discrepancy is marked
  - Similar pattern for aggregate reports, though less distinct
    - Of 8 respondents who produce such reports 6 (75%) provide them to FDA, but only 2 (25%) provide them to US investigators
- When reporting to investigators, most respondents provide such to US investigators across INDs for the same molecule

Possible rationale for these patterns include:

- **Fewer regulatory requirements to notify investigators of safety data**
- **Bias to provide any externalized investigator notifications to FDA, but not *vice versa***
- **Desire not to burden or bias investigators with reports that are difficult to interpret**

Discussion

Investigator Feedback on Sponsor Safety Reporting Practices

- Most (7 of 10) respondents have received complaints from investigators in the past 12 months regarding SAE reports
  - Issues cited were of high volume and low relevance/explanation
  - Complaints of too few reports and level of information observed, but by fewer companies
- Incidental finding of dissatisfaction
  - For companies who report to IRBs on behalf of investigator, most (4 of 5) received spontaneous communications from investigators to change safety reporting to them, citing the 2009 FDA Guidance for IRB safety reporting
- Possible reasons for investigator dissatisfaction:
  - Focus on individual vs. aggregate safety data reporting
  - Infrequently provided summary conclusions with safety data
  - Reporting safety data to US investigators across INDs

Even though sponsors send fewer reports to investigators, the volume and nature of those reports may still be sub-optimal

Recommendations

Recommendation 1: Encourage Greater Aggregate Reporting

- Aggregate reports are produced by sponsors, sometimes provided to FDA, typically not provided to US investigators
- Consider methods to leverage industry sponsor infrastructure for safety monitoring, including external oversight bodies (DMCs, DCCs)
- Encourage improvements in breadth, frequency, standardization, and conclusions for aggregate safety reports
- Build regulations/guidance to encourage analyses and distribution
  - Involve investigators and sponsors in development
  - Seek international harmonization given other regional agency aggregate reporting requirements

Recommendation 2: Limit Investigator Burden of Unwanted Reports

- Jan 2009 FDA Guidance on IRB safety notifications did not include investigator safety notifications
  - Concerns voiced by investigators similar to those referenced in Guidance and pre-Guidance Town Hall meeting
  - New Premarketing Safety Rule aligns individual safety report notifications between investigators and IRBs
- Evaluate value of individual safety reports for identifying changes to safety profile or IND study conduct as an individual report or series of reports
  - Conclusive risk-benefit statements
- Continue individual reporting to FDA

Thank You

Backup

Safety Analyses: SAE Analyses of Similar Events

- 90% (9 of 10) respondents produce analyses of similar events for individual SAEs routinely for unexpected SAEs related to study drug
  - Fewer respondents produced such analyses for
    - Expected SAEs related to study drug (n=3); or
    - Unrelated SAEs (n=1)
  - Data reviewed for SAE analyses of similar events always included serious safety data across INDs
    - Use of other data more varied

Table 6.

Data Reviewed for SAE Analyses of Similar Events	Respondents	
	(n)	(%)
Serious safety data for all INDs for that molecule	9	100
Non-serious safety data for all INDs for that molecule	1	11
Clinical data outside of INDs (i.e. from studies outside the US)	6	67
Manufacturer or co-development partner data	4	44
Post-market safety data (if molecule is marketed)	5	56
Scientific literature	4	44

Safety Reporting: Relevant Non-IND Safety Reporting

- Most treat unexpected SAEs related to investigational product received from co-development partners or investigator-sponsored studies similar to such SAEs from their own IND studies for FDA reporting
  - However, many also provide such SAEs as individual expedited reports to US investigators, unlike their treatment of SAEs from internal INDs
- Spontaneous unexpected and related SAEs from outside the US and from literature reports are also typically submitted to the FDA as expedited reports(1)

Table 11.

Relevant Non-IND Safety Reporting	Respondents (of 10)				
Type of Report and Recipient	Unexpected, Related				
	Co-Dev.	ISS	US Spont.	Ex-US Spont.	Literature
Individual expedited report					
FDA	8	8	4	8	9
US Investigator - same	8	5	1	5	3
US Investigator - different IND, same molecule	6	3	1	4	3
Periodic summary/listing					
FDA	6	5	2	4	5
US Investigator - same	1	2	0	1	0
US Investigator - different IND, same molecule	2	0	0	0	0

(1) Spontaneous reports originating in the US are the exception and are generally not reported to the IND; however they may be reported to the NDA or BLA but the questionnaire did not allow that determination