

# **Improving the System of Reporting and Interpreting Unexpected Serious Adverse Events (SAEs) to Investigators conducting research under an Investigational New Drug Application (IND)**

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## **Workstream 2 Findings Summary**

**03 October 2010**



# Workstream 2 Team

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# Work Stream 2

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**Objective:** To quantify the personnel time required by investigators to receive, analyze, interpret, and communicate information in individual expedited safety reports and their perceived value of this information in updating the risk profile of investigational products.

**Method:** A sample of 12-15 investigators will be surveyed who represent three different therapeutic areas, from a mixture of academic and research practice sites, and who are engaged in at least two clinical trials during the time of their response to this project's questions.

**Deliverable:** A resource estimate for the current safety reporting system; and an assessment of the value of current practices in risk-benefit decision-making.

# Prospective Review

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- Investigators to prospectively quantify for 8 week period the number of individual expedited SAE reports they receive and the personnel time spent and level of personnel engaged in receiving, interpreting, documenting, and submitting these to their IRB.

# Retrospective Review

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- Investigators will retrospectively review all expedited SAEs received for a 3 month period prior to the beginning of this exercise and will address:
  - ◆ relevance of these reports to the investigators' overall understanding of the risk and benefits of the investigational product (IP) under study
  - ◆ any changes made to consent form or study conduct (e.g., recruiting approach, inclusion / exclusion criteria, protocol, subject monitoring, etc.) as a result of reports
  - ◆ Impact of reports on investigator vigilance in safety monitoring
  - ◆ any sponsor mechanisms used for aggregating, analyzing, interpreting and communicating SAEs

# Estimating Resource Requirements

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## ■ Data to be used

- ◆ Data from investigator sites collected in EXCEL charts on weekly basis prospectively, and WORD survey retrospectively, and faxed anonymously to central Duke site

## ■ Estimates

- ◆ Time and resources required by the current safety reporting system
- ◆ Subjective assessment of value of current system for decision-making regarding risks and benefits of investigational products (IP)

# Investigator (PI) as “Research Subjects”

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- **PIs in three Therapeutic Areas were initially targeted:**
  - ◆ Cardiology (5 of 6 respondents)
  - ◆ Oncology
  - ◆ Infectious Diseases
- **PIs in academic, clinical group, and gov’t institutions were solicited (details of respondents in next slide):**
  - ◆ 375 PIs were asked to participate via calls, e-mail, or letters
  - ◆ 63 agreements to complete the data forms were obtained and assigned a site ID and blinded data forms
  - ◆ Each of these 63 were contacted/reminded ~6 times
  - ◆ 5 prospective data sets were returned
  - ◆ 6 retrospective data sets were returned

# Retrospective Data Analysis Summary\*

Site	IRB Approval	Therapy Area	Current Studies	Current Patients	Number of INDs
Private Practice #1	Local/Community	Cardiology	3	18	2
Private Practice #2	Local/Community	Cardiology	25	520	3
Private Practice #3	Central/Commercial	GI	5	33	3
Academic Center #1	Academic/University	Cardiology	~100	NA	3
Academic Center #2	Academic/University	Cardiology	11	178	3
Community Hospital/Clinic	Local/Community	Cardiology	4	52	3



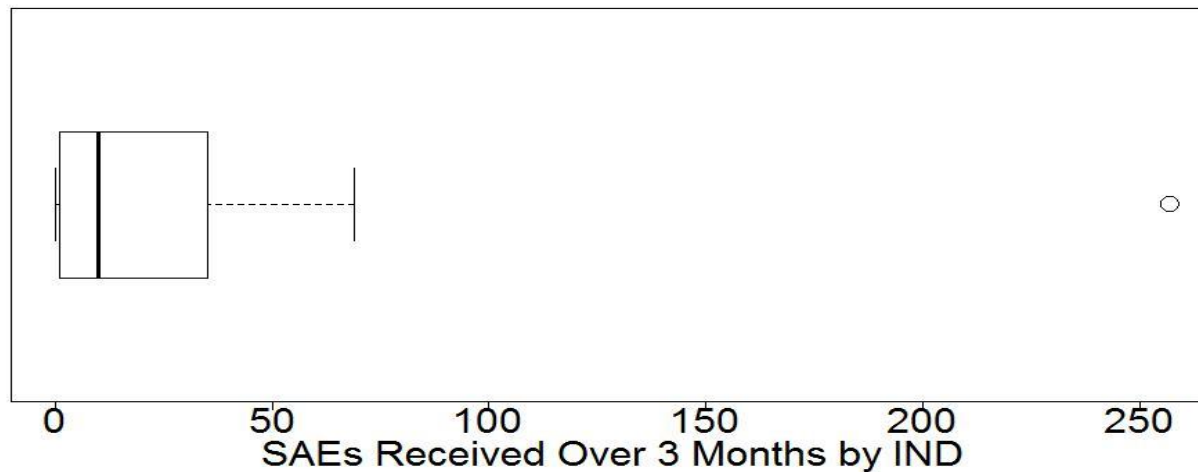
\*6 sites and 17 INDs in survey;  
528 SAEs over 3 month period

# Number of SAE Reports per IND

- Each site reported the number of SAE reports received over three months reporting period for each of 17 INDs:

Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Total SAEs
0	1	10	35	257	528

Retrospective SAEs Received



# Changes in Protocol Due to SAE Reports

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- Investigators asked how many SAEs resulted in a protocol amendment, or change in investigators' brochure, informed consent, or patient selection criteria
- None of the 528 SAEs reviewed were reported to have resulted in any of the above actions
- Changes could have occurred through DMC reports or other aggregated reports of SAEs or communication

# Other Safety Reporting

- Investigators asked what other safety reporting approaches were used, and data on 16 INDs were reported
- 9 of the 16 INDs had 14 other approaches; 7 of the 16 INDs had no other approach:

Other Safety Reporting	N*
Aggregate line-listings	2
Periodic Summaries of SAEs	2
Data Monitoring Committee (DMC) reports	8
Other	2

\* from 16 INDs reported

# Prospective Data Analysis Summary\*

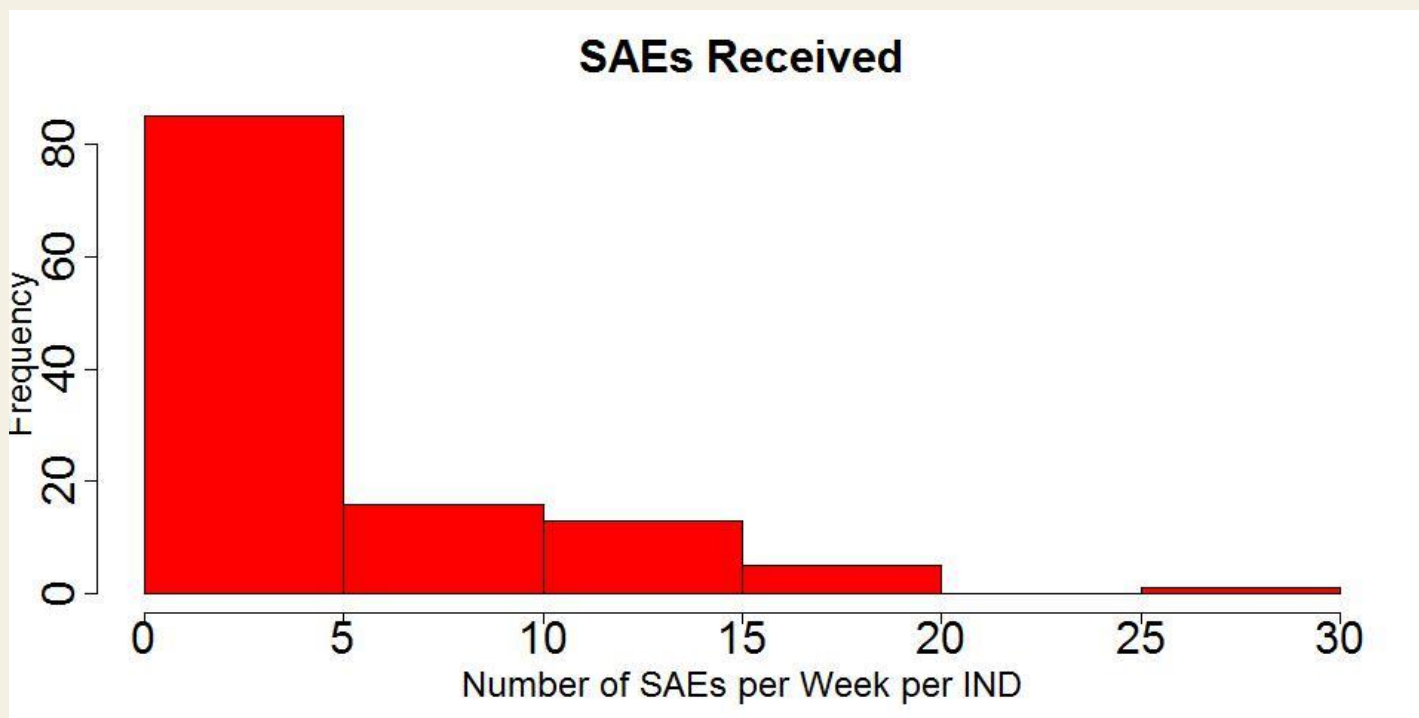
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- Prospectively recorded number of SAEs received and number of man-hours reviewing SAEs
- Man-hours recorded separately for MD, other HCP, and non-HCP (HCP=health care professional)
- Data recorded *daily* over 8 weeks but aggregated by calendar *week* for analysis
- Total of 120 weeks data analyzed from 15 INDs x 8 weeks from five different centers (subset of retrospective sites)

\*5 sites and 15 INDs in survey;  
472 SAEs over 8 week period

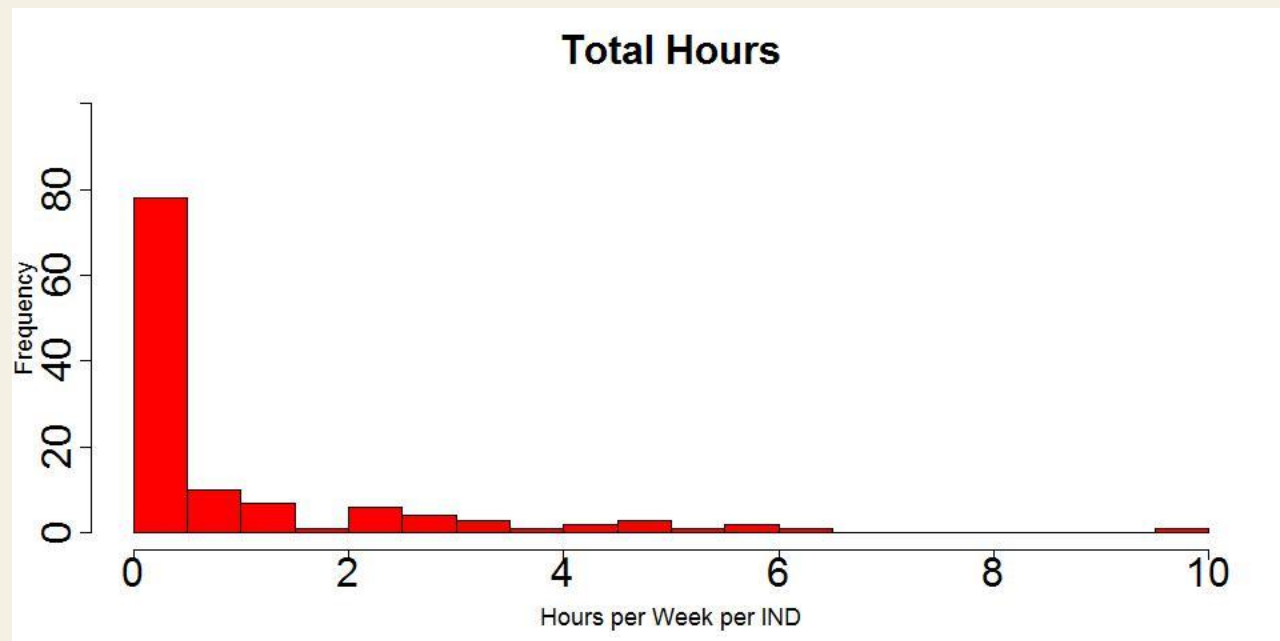
# Prospective Data: Weekly SAEs per IND

Variable	Min	Lower Quartile	Median	Upper Quartile	Max
#SAEs received/week/IND	0.00	0.00	1.00	7.00	29.00



# Prospective Data: Weekly Man-hrs per IND

Variable	Min	Lower Quartile	Median	Upper Quartile	Max
MD man-hours	0.00	0.00	0.00	0.08	4.83
Other HCP man-hours	0.00	0.00	0.00	0.25	1.44
Non-HCP man-hours	0.00	0.00	0.00	0.69	4.50
Total man-hours	0.00	0.00	0.16	1.12	9.66



# Estimating Resource Burden

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To estimate the resource burden per SAE received, we estimated or assumed the following:

- ◆ Time spent reviewing SAEs related to # SAEs
- ◆ The breakdown in time among MD, other-HCP, and non-HCP
- ◆ Cost of MD, other-HCP, and non-HCP time

# Time Reviewing SAEs Related to # SAEs

- As expected, there was a strong correlation between #SAEs during a week and the # total man-hours (0.844) expended; possibly somewhat less correlation with MD man-hrs expended
- This suggests decreasing MD intensity per SAE as #SAEs increase:

#SAEs vs. man-hrs expended	Pearson Correlation Coefficient
MD M-Hr	0.629
other HCP M-Hr	0.767
non-HCP M-Hr	0.763
<b>Total M-Hr</b>	<b>0.844</b>

# Hours Expended per SAE by IND

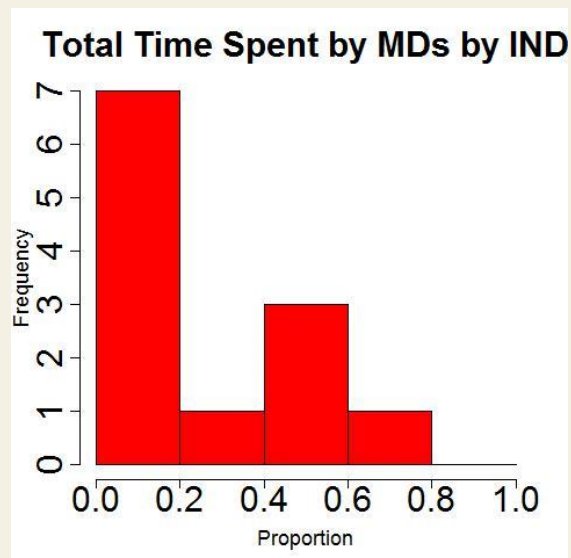
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- For each IND, # SAEs and total man hours spent reviewing SAEs was tabulated for the 8 week prospective period
- 3 of the 15 INDs had no SAE reports
- 12 of 15 INDs had the following hours expended per SAE:

Min	Lower Quartile	Median	Upper Quartile	Max	Total SAEs
0.0811	0.117	0.254	0.373	1.570	472

# Time Breakdown by Man-hour Category

- From data collected, median total man-hr consisted of 0.25 'MD', 0.20 'other HCP', and 0.55 'non-HCP'.
- Mix of the man-hour categories differed fairly substantially among INDs.
- For sensitivity analysis, range of man-hr mix is [0.1, 0.2, 0.7] to [0.5, 0.3, 0.2] as quartile estimates.
- As expected, MDs account for the greatest cost:



# Estimate of Resources per SAE

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- Median of 0.25 hr per SAE evaluated with CI of 0.12 to 0.38 hr/SAE
- Estimated hourly rates of \$150, \$60, and \$30 (with 1.3x benefits burden); weighted average = \$86/hr with sensitivity range \$62-\$129/hr
- For median mix of man-hrs, each SAE costs \$10-33 (0.12-0.38 hr) to process or median of \$22/SAE (0.25 hr)
- For low-MD mix, \$62/hr or \$15/SAE (\$7-24). For high-MD mix, \$129/hr or \$32/SAE (\$15-49)

# Free-form Responses to Questions\*

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- They send reports out of Europe where the drug is being marketed where it appears to be a lack of treatment effect rather than a true SAE.
- The volume of data received dilutes the true effect of anything we see.
- It would be useful to receive aggregate information that is possibly summarized in a chart format.
- It would be extremely useful to have the data come quarterly rather than faxes and e-mails daily.
- If the incidence of the event is not given, it would be hard to interpret ... the knowledge of event is important in awareness of future SAEs.
- I believe the individual reports are of little value.
- DSMC is changed with reviewing events and protecting patient's safety, individual investigators do not have vantage point to evaluate these

# Free-form Responses to Questions\*

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- It would be more valuable to have a “clinical events committee” evaluate reports in the big picture and provide the PIs with summary reports... Receiving reports individually with no “high level” view is not helpful.
- The current system covers most information but it would be better if the SAE reports were summarized according to the events and represented as charts/figures.
- If the sponsor could provide a summary document in a standard format (not sponsor-specific), it would be useful to know what events trends are across all studies with an agent, not individual events.
- We don't have the denominator of any of the events and it is difficult to assess.
- With sponsors who work in other countries where the drug is approved and marketed, the notifications are more like post market reports, and may not be relevant to patients who are still under an IND.

# Discussion of Results

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- **Retrospective and Prospective surveys had large number of SAEs with skewed distribution:**
  - ◆ Retrospective (6 sites, 3 months, 17 INDs, 538 SAEs)
  - ◆ Prospective (5 sites, 8 weeks, 15 INDs, 472 SAEs)
- **None of the sites reported that for any of their IPs that an SAE resulted in a protocol amendment, changes in IB, ICF, I/E criteria, etc.**
  - ◆ The estimate of the 95% CI for the proportion of SAEs that provide useful information is 0-0.006, based on this sample of 538 SAEs with no actionable effect (rule of 3\*,  $3/538=0.006$ )

\*Jovanovic & Levy, The American Statistician, Vol 51, 1997

# Discussion of Results

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- **Lack of SAE reports leading to changes to protocol, IB, ICF, etc. may imply:**
  - ◆ “Important” selected SAEs lost in flood of SAEs?
  - ◆ Individual SAEs are inefficient tool for signal detection?
  - ◆ Lack of appreciation of importance of selected SAEs?
- **A number of sites gave value to DMC report or “*Notification letter of unanticipated problem*” (analogous to UADE, “*unanticipated adverse device effect*” in 1/09 FDA guidance or “*suspected adverse reaction*” in 9/10 FDA draft guidance)**
- **Changes to IB, ICF, etc. may be conveyed separately from the individual SAE Reports**

# Discussion of Results

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- **Other safety reporting methodology perceived as valuable sources:**
  - ◆ Aggregate line listings
  - ◆ Periodic summaries of SAEs
  - ◆ Data Monitoring Committee (DMC) reports
  - ◆ Notification letters of unanticipated problems
- **Consistent use of these may be very helpful**
- **Investigators voiced frustration at large number of individual SAE reports, perceived of minimal value**
- **Request for aggregate, quarterly or summarized data**

# Limitations

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- **Though 375 PIs were solicited and 63 agreed to participate, only 6 provided survey data (target was 12-15).**
- **Five of six sites were cardiology PIs (6<sup>th</sup> was GI), while no representation of oncology or ID sites.**
- **Large variability in # SAE per IND and site.**
- **Variability presumed likely due to IND, rather than week or site, though insufficient data to confirm this.**

# Conclusions

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- Resource estimate of \$22/SAE evaluated with CI of \$10-\$33 (0.25hr median with CI of 0.12-0.38 hrs/SAE). Sensitivity analysis gives range of \$7-49/SAE.
- Low perceived value of individual SAE reports due to lack of context (incidence, relatedness) for events
- “Contextual” information is useful:
  - ◆ Data Monitoring Committee (DMC) reports
  - ◆ Notification letter of unanticipated problem (~*UADE* or *suspected adverse reaction* in FDA guidances of 1/09 and 9/10)
- Increased use of DMCs and FDA Guidance may assist investigators, sponsors, and IRBs focus on events likely to impact patient safety

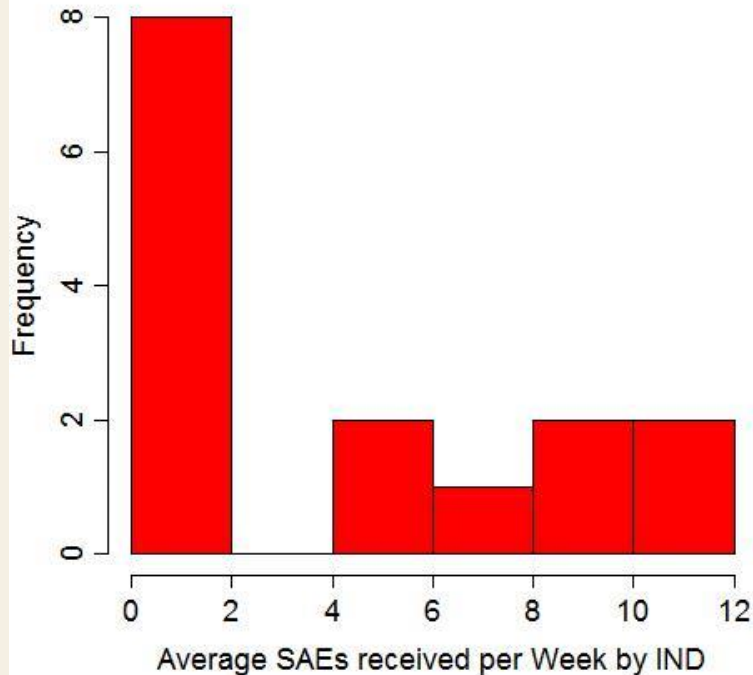
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# Back Up Slides

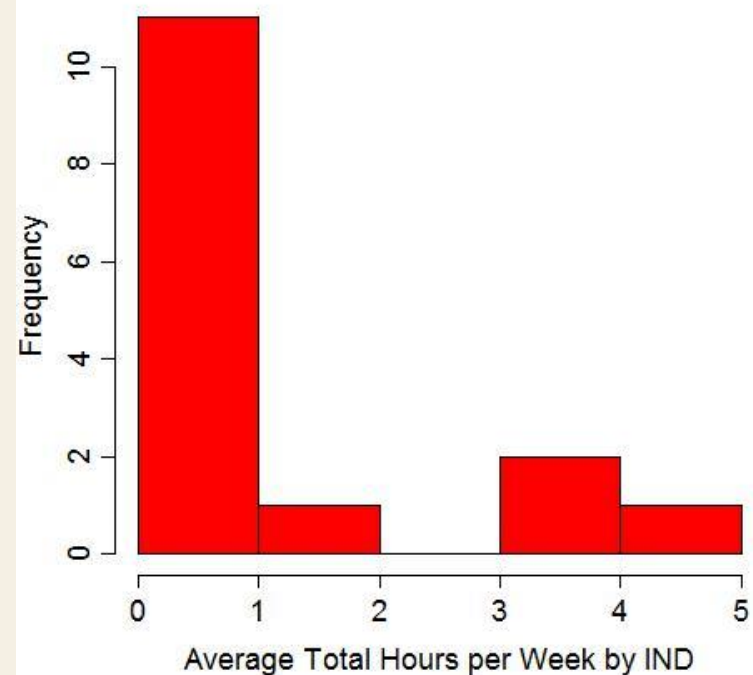
# Weekly SAEs & Man-hours by IND

Variable	Min	Lower Quartile	Median	Upper Quartile	Max
Avg. Weekly SAEs by IND	0	0.125	1.25	9.125	11.125
Avg. Weekly Man-hrs by IND	0	0.10	0.315	1.309	4.203

Average Number of SAEs Received by IND



Average Number of Total Hours by IND



# SAE Report Impact?

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- **No site reported that for any of their IPs or INDs that a SAE report resulted in any of these actions:**
  - ◆ Protocol amendment
  - ◆ Change to investigators' brochure
  - ◆ Change in informed consent form
  - ◆ Change in patient selection for study
  - ◆ Increased vigilance in safety monitoring
  - ◆ Change to informed consent requiring urgent re-consent
  - ◆ New study procedure or lab test
  - ◆ Elimination of study procedure or lab test
  - ◆ Study interruption (e.g., IND hold)
  - ◆ Study closure
  - ◆ Other

# Prospective Data Analysis Summary

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- Is the large variability due to differences in IND or week-to-week variability within each IND
- Examine the differences in the average SAEs and total man-hours per week among the INDs
- Large differences in the averages between the INDs suggest variability due to differences in IND

# Time expended / SAE by IND Prospectively

IND	Total Hrs	Total SAEs	Hrs/SAE
1	33.62	89	0.37775
2	26.87	73	0.36808
3	1.81	5	0.36200
4	0.00	0	.
5	0.00	0	.
6	31.01	89	0.34843
7	3.13	33	0.09485
8	4.15	50	0.08300
9	3.00	37	0.08108
10	10.47	75	0.13960
11	0.80	5	0.16000
12	1.60	10	0.16000
13	1.57	1	1.57000
14	2.52	5	0.50400
15	0.00	0	.

Min	Lower Quartile	Median	Upper Quartile	Max	Total SAEs
0.0811	0.117	0.254	0.373	1.570	472

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# *Retrospective Survey*

## *Free-form Questions and Responses*

# For IP 1-3, question F

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**F. For this investigational product, describe the content or characteristics of the individual SAE reports that you received over the 3-month period that were especially useful to you and why (please be specific)?**

- None. All were standard MedWatch forms
- SAE reports typically included literature review and query of company database
- Nice summary sheet is very helpful
- No useful characteristics
- Quarterly summary reporting

# Question F

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- The sponsor sends out SAE reports/notifications/safety alerts only if the event is determined to be serious, unexpected and related to the study drug.
  - ◆ In the SAE reports for this study, the causality of all arterial and venous thrombotic events are very useful since the study is trying to find out if the investigational drug has effects on heart muscle damage, complications and endothelial progenitor cell production in heart attack (STEMI) patients.

# Question F

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- The sponsor informs investigators by sending a notification letter of relevant information of Unanticipated Adverse Drug Effect (UADE) that could adversely affect the safety of study subjects.
  - ◆ The letter summarizes the clinical history related to the event. It also narrates the ongoing review of the event and any further discussions on changes to the protocol, informed consent, or investigators brochure.
  - ◆ This report is useful since the study drug is well documented; therefore, any SAE information in UADE submitted to Food and Drug Administration (FDA) and the Data Safety Monitoring Board (DSMB) is anticipated to be rare.

# Question F

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- The SAE reports come with Council for International Organizations of Medical Sciences (CIOMS) Form that show the details of the SAE as reported to FDA.
  - ◆ There are some details that I find very useful like renal failure information to ensure patients get immediate care.
- In general, the sponsor sends out chronological Suspect Adverse Reaction Reports (SUSARs) using CIOMS Form.
  - ◆ The adverse events are considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. ...
  - ◆ The information in SUSARs are all useful the severity and the relation of the SAE to the investigational drug.

# For IP 1-3, Questions G

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**G. For this IP, describe the content or characteristics of the SAE reports that you received over the 3-month period that were NOT useful to you and why (please be specific)? (1/4)**

- The vast majority of the Medwatch reports did not meet the definition of a SAE (serious, unexpected, AND related/possibly related), and should never have been sent out to the sites.
- Also, because this drug was FDA approved for another indication, Medwatch reports were sent to sites that contained limited info (ie. patient called and left a message on hotline to report a side effect, but no additional or follow-up was obtained from the patient, patient complained because the drug didn't do what it was supposed to, etc.).
- Unfortunately, because we received the Medwatch, we needed to go through our process of assessing the event, and each event needed to be reported to the IRB according to current IRB policy (ie. either promptly or at the time of continuing review).

(Site had 257 SAEs for Invest. Prod. #1 /3 months)

# Question G

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- The letter that accompanied the report that stated what the changes were in the follow up reports.
- This sponsor sends multiple reports daily by fax, some reports are updated 3 and 4 times.
  - ◆ So you never really know what the total number of events relative to the total patients being exposed.
  - ◆ Also they send reports out of Europe where the drug is being marketed where it appears to be a lack of treatment effect rather than a true SAE.
  - ◆ The volume of data received I think, dilutes the true effect of anything we would see.

# Question G

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- The SAE reports were often regarding cancer trials. While it could be potentially helpful, it was difficult to extrapolate adverse events to our population (Cardiac Transplant).
- In general the forms all contain the same information but each sponsor seems to use their own form – it seems that this format and the information layout could be standardized.
  - ◆ Each form must be scanned to determine where the information you may be interested in can be found on that particular form.
- SAEs not related to the study drug because things happen out of the control of the study and it is not related to the study then it is just extra paperwork.
- The SAE reports we receive for this study concisely narrate the clinical history of the event and the information are all useful.

# Question G

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- Our (investigational) site received a box (pile of papers) of all the SUSARs for 1 year.
  - ◆ Aside from using it for ready reference in the site, it is useless because these reports were already sent electronically all throughout the year.
  - ◆ Paper/hard copies were already compiled after review and submission to the IRB. It takes time to read, review, report and file the SAE reports we received but then again, these reports are all useful content-wise.

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# *Retrospective survey*

## *General Questions*

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**A. What specific type(s) of information do you need to receive promptly to ensure the proper care of patients in the study and why (please be specific)?**

- Any information that will help our PI determine whether or not the event was serious, unanticipated, and related/possibly related.
- There were severe unanticipated events.
- Only issues which have been determined to be related to the investigational product and may affect the participant's willingness to participate (Safety)

## A. What specific type(s) of information do you need to receive promptly to ensure the proper care of patients in the study and why (please be specific)? (con't)

- Name of injury because we know exactly what to look for.
- It would be useful to receive aggregate information that is possibly summarized in a chart format? and,
  - ◆ it would be extremely useful to have the data come quarterly rather than faxes and emails daily.
- For investigational product
  - ◆#1 we need to look at any hypertensive crisis and left ventricular thrombus identification.
  - ◆#2, renal failure information is crucial to ensure that patients get immediate care and advice.
  - ◆#3, bleeding events information needs to reach us possibly during its occurrence.

## B. How do you respond to SAE reports when the treatment is blinded?

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- Treat the report as if the subject was on open-label drug.
- Usually you can't make any judgment in context on a blinded study.
- It is impossible to determine anything meaningful.
- Assume everyone is on it.
- Do not treat blinded or unblinded reports any differently
- Initially, we respond to SAE reports by managing patient acute condition.
  - ◆ Any decision for patient to be unblinded comes later after series of discussion with corresponding personnel.

## **C. How do you respond to SAE reports when the incidence of the event is not described in the report (e.g., the cumulative number of similar events is not known, the overall number of patients exposed is not known, etc.)?**

- Require sponsor to provide us with that info.
- Again, you usually cannot, this is the province of the DSMC.
- This is the biggest obstacle in determining the significance of any report.
- Assume it is a potential real problem.
- Difficult to respond to this
- If the incidence of the event is not described in the report, it would be hard to interpret but the knowledge of incidence itself is important in the anticipation and awareness of future SAEs.

## D. What is your overall opinion of the value of the individual SAE reports that you receive?

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- The value of the report depends whether or not the sponsor provided the information necessary for our PI to determine whether or not the event was a SAE.
- Minimal value.
- Minimal to none.
- Good to know what to watch for but overall it is overdone because once it gets to be a problem the IB is changed and updated.
- Overall, we consider the individual SAEs very important since it is very necessary to have an idea about the “unknown” side effects of the investigational drug and also to anticipate for specific SAEs.

## D. What is your overall opinion of the value of the individual SAE reports that you receive? (con't)

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- I believe the individual reports are of little value.
  - ◆ Each company sends their reports in a different format with different information provided, so we spend a great deal of time sifting through the information to glean out the pertinent facts.
  - ◆ Our IRB does not require reporting except for related, and unexpected events.
  - ◆ However, sponsors are requesting that we submit them all and that the IRB acknowledges them all.
  - ◆ So this “sponsor” requirement causes a great deal of work for our regulatory staff, our physicians who must read and sign them and for our IRB to sort through what information is relevant or not.

## **E. If you could re-design the system, what would you suggest to improve efficiency, better define the risks and benefits of investigational drug products, and/or better protect patients? (1/4)**

1. Don't split sections up (i.e. describe event or problem: that box isn't big enough, so the rest of the info is located on another page)
2. Each AE should be on it's own form, not lumped together on 1 form
3. AE terms should be consistent (i.e. don't call it angina on 1 patient and chest pain on another).
4. Follow-up reports: highlight or "track change" any new information added to the previous form. In a lot of cases it's not obvious, leading to time spent trying to figure out what info is new.
5. Follow-up reports: make sure the correct follow-up number is listed on the form.



CLINICAL  
TRIALS  
TRANSFORMATION  
INITIATIVE

6. Include # of times this event has previously occurred and # of patients who've been treated to date so we can calculate whether or not the frequency has increased.

## **E. If you could re-design the system, what would you suggest to improve efficiency, better define the risks and benefits of investigational drug products, and/or better protect patients? (2/4)**

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- DSMC is changed with reviewing these events and protecting patient's safety, individual investigators do not have vantage point to evaluate these
- It would seem more valuable to have a committee similar to a “clinical events committee” which is charged with the responsibility to evaluate the IND reports in relation to the big picture and provide the PIs with summary reports on an interim basis. Receiving reports individually with no “high level” view is not helpful.
- The relatedness is usually buried in the narrative. It would be nice if this was a “box” and was addressed in a standardized way with every IND.

**E. If you could re-design the system, what would you suggest to improve efficiency, better define the risks and benefits of investigational drug products, and/or better protect patients? (3/4)**

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- Don't have so much paperwork. Send out periodic logs unless it is an immediate problem that requires us to notify the subjects.
- We think the current system covers most of the points and information that we need but it would be better if the SAE reports were summarized according to the events and represented as charts/figures.

## **E. If you could re-design the system, what would you suggest to improve efficiency, better define the risks and benefits of investigational drug products, and/or better protect patients? (4/4)**

- If the sponsor could provide a summary document in a standard format across sponsors, it would be useful to know what events trends are across all studies with an agent, not individual events.
  - ◆ We don't have the denominator of any of the events and it is difficult to assess whether an action should be required based on the limited information we receive.
  - ◆ Also, some sponsors who do work in Europe and other countries where the drug is approved and actively being marketed, the notifications are more related to post market reports, and may not be relevant to our patients who are still under an IND.
  - ◆ I hope this makes sense.