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What to Do with External Safety Reports?

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Introduction

Investigators conducting clinical trials of experimental drugs sponsored by pharmaceutical companies frequently receive IND safety reports describing serious adverse events that occurred at other study sites. The reports often lack important details and can be repetitive. Sometimes a report is accompanied by a cover letter stating that the sponsor does not believe the adverse event is related to the study and there is no need to change the protocol. Sometimes the cover letter says something to the effect that "we're sending you this report because the FDA requires us to; please file it." Often, the sponsor directs the investigator to send the report to the IRB overseeing the study at the site; however, some may qualify this with a phrase like "if required by your local IRB policies." What should an investigator do with these reports?

In a haystack of noisy adverse events, it is often very difficult to detect the needle of a safety signal that justifies changing a protocol. It requires experience, sophisticated statistical techniques, agreement on what, in fact, constitutes such a signal, and access to all the relevant data. In Phase 3 studies, this task typically falls to a data and safety monitoring board (DSMB); in other studies, it can be performed by a safety monitor or other appropriate group designated by the sponsor. Investigators, particularly in multi-site studies, seldom have the expertise, resources or access to data) available to a DSMB.

The Conundrum

Neither FDA regulations nor ICH-GCP (E6) guidelines state that an investigator is responsible for reading or analyzing individual safety reports, but it is not uncommon for trial monitors or auditors to expect to see that an investigator has signed or at least initialed the reports. (This raises the question of what an investigator's signature on a report means in the absence of a statement such as "read and understood".[1])

Furthermore, many institutions, including prestigious medical centers, have policies that require investigators to review the reports and determine whether to transmit them to their IRBs. (See Table 1.) We believe these policy statements are problematic for several reasons:

- An individual investigator does not know how many people are taking the drug, either as part of the study overseen by the investigator or in other studies. Therefore, it is impossible to estimate an incidence rate. (This is often called the "denominator problem.") Without an incidence rate, it is very difficult to determine whether a given report indicates a pattern of concern or is just an isolated event.
- Training in human research protections and good clinical practice does not prepare investigators to analyze an external safety report and detect a signal that something serious has happened. (Indeed, if individual investigators were actually responsible for detecting safety signals, recruiting sites for clinical trials would be problematic.)
- Investigative sites usually do not have standard operating procedures that describe how to analyze individual IND safety reports. (However, UC San Francisco does appear to have a systematic process for analyzing the reports.[2]) They certainly do not have the expertise, data (sometimes unblinded as to arm) and resources of a DSMB.

- Many safety reports sent to investigators are *inherently* unanalyzable (and effectively useless) because important information is withheld. This happens frequently with safety reports from randomized, double-blinded studies that compare experimental medications to standard drugs or placebos.

Proposed Resolution

Binders full of safety reports, sponsors' unrealistic expectations, and problematic institutional policies add up to a conundrum for the investigator. A solution to the problem comes from a straightforward reading of *Guidance for Clinical Investigators, Sponsors, and IRBs. Adverse Event Reporting to IRBs – Improving Human Subject Protection*, issued by the FDA in January 2009.[3]

The *Guidance* makes it clear that investigators should not forward to the IRB a safety report that does not describe an unanticipated problem:

> In general, an AE {adverse event} observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, ***only*** if it were unexpected, serious and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol, such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure). An individual AE occurrence ***ordinarily*** does not meet these criteria because, as an isolated event, its implications for the study cannot be understood. [Emphasis in original.]

The *Guidance* further states that sponsors should analyze individual safety reports, assess their significance, and advise investigators accordingly:

> Accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, an investigator participating in a multicenter study may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor.

These statements, as well as similar guidance issued by the Office of Human Research Protections in 2007[4], validated the position that many IRBs had already taken and incorporated into their policies: they would no longer accept "undigested" safety reports that were not accompanied by a clear statement from the sponsor or the investigator that the seriousness of the reported event necessitated a significant change in the protocol or the consent document. The elements of the *Guidance* were incorporated into a revision of the FDA regulations issued in September 2010 and effective March 2011.[5] A major theme of the revised regulation was that the FDA expects sponsors to analyze individual safety reports and interpret them in the context of relevant additional information about a drug under study:

> In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. [21CFR312(c)(1)]

The *Guidance* does not discuss whether investigators should review IND safety reports for their own edification. Nevertheless, we can assume that, if an IRB would find a safety report uninformative, so would an investigator. The *Guidance* and the revised regulation did make exception for certain one-time events that are so alarming as to require immediate notification and action, such as a case of Stevens-Johnson Syndrome.

We propose that investigators should only review a safety report that is accompanied by a sponsor's analysis and conclusion that the safety issue meets the regulatory criteria for reporting. We further suggest that institutions develop operating procedures or policies that describe how they process external safety reports; further, investigative sites should consider how — or whether — paper copies of non-informative reports should be stored. Additionally, a site's position on the matter should be explained clearly to a sponsor's representatives before a study begins, for example during contract negotiations or at the site initiation visit. (We have had modest success incorporating our position into clinical trial agreements.)

The following policy statements have been implemented at our institutions:

> **Baptist Clinical Research Institute**
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> A safety report from a sponsor must contain an explicit statement that the information qualifies for reporting (to the IRB). In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information… If the reporting criteria are met, then the investigator will transmit the safety report to the IRB with an assessment of the implications of the report for the conduct of the trial at Baptist. If the reporting criteria are not met, the cover letter transmitting the safety report is labeled with the notation "Does not meeting reporting criteria. No further action taken." The cover letter is stored with regulatory documents, and the safety report is destroyed within 30 days of receipt. (August 2012)
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> **Vanderbilt Ingram Cancer Center**
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> The following information should be included in the OSR [Outside Safety Report] or provided by the industry sponsor: A clear explanation of why the adverse event or series of adverse events have been determined to be an unexpected problem; the implications for the conduct of the study (e.g., requiring a change to the protocol, such as revising the inclusion/exclusion criteria, addition of a new monitoring requirement, change to the informed consent, or change to the investigator brochure).
>
> OSRs that meet the above criteria will be submitted to the Vanderbilt IRB to process the change in the conduct of the study; the Principal Investigator will review the updated Investigator Brochure and informed consent and provide a summary of the events to the IRB at the time of continuing review.
>
> OSRs that do not meet the above criteria will not be reviewed, retained or forwarded by the Principal Investigator. (March 2011)

A brief Internet search did not yield any policies as explicit as ours about doing essentially nothing with IND safety reports in the absence of specific guidance from sponsors. However, the policy statements of Georgia Health Sciences, University of North Carolina, and University of Rochester have similarities. (See Table 2.)

Conclusion

If the investigators are analyzing the safety data, why do we need DSMBs? We need DSMBs because investigators usually cannot analyze the data — they do not have the data or the expertise or the statistical tools. It is time to end the costly and time-consuming charade.

Investigators have plenty do just conducting the study and dealing with any local safety issues.

Table 1. Policy Statements that Require Investigators to Review IND Safety Reports.

Institution	Policy Statement*
University of Iowa	IND/Outside Safety Reports under FDA Regulations for Investigational New Drugs Federal regulations do not require immediate reporting to the IRB of IND/outside safety reports for events that do NOT meet the criteria outlined above UNLESS… If after review, The University of Iowa Principal Investigator believes the information indicates a change to the risks or potential benefits of the study being conducted at Iowa. (April 2006)
Emory University	Guidance for Reporting External Events to the IRB. External UPs may be reported by the sponsor to Emory investigators in the form of a safety report (IND safety reports or MedWatch reports), DSMB reports, new publications in the literature, sponsor-imposed suspensions, or participant complaints. The Emory PI should review these reports and consider whether they represent UPs. (Sep 2008)
Dana Farber Cancer Institute	Policy on Receipt and Review of IND/IDE Safety Reports. It is the responsibility of the Principal Investigator to review all IND/IDE safety reports provided by an outside sponsor (or themselves if they are the sponsor) within 60 days of receipt. (Jan 2009)
Dartmouth-Hitchcock Cancer Center	Data Safety Monitoring and Reporting of Adverse Events. [Requires] principal investigator to review adverse event reports s/he receives from the sponsor or agency. (Mar 2009)
Johns Hopkins	Submission of IND Safety Reports. Investigators should review all IND safety reports sent by the sponsor. (Aug 2010)
University of Michigan Comprehensive Cancer Center	Standard Practice Guideline 638. The principal investigator is responsible for assessing all safety reports and determining whether or not they are "Unanticipated Problems" requiring IRB review and consent revision. (Aug 2011)
University of Arkansas for Medical Sciences	UAMS requirements for reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs) and IND safety reports. [Same as University of Iowa's policy.] (Mar 2012)
UCSF Helen Diller Comprehensive Cancer Center	Safety Reporting Policy. The IND Safety Coordinators are responsible for processing and maintaining all safety reporting information sent to the Principal Investigators conducting ISTs or clinical trials for pharmaceutical companies, including IND safety reports. IRB reporting of external IND safety reports is required when the UCSF PI determines that the event described: Changes the study risks or benefits OR necessitates modification to the CHR-approved consent document(s) and/or the CHR-approved application or protocol. (Jan 2012)
LSU Health Shreveport	Submission of IND Safety Reports. Investigators should review all IND safety reports sent by the sponsor. (2012)

* Institutional web sites accessed December 2012

Table 2. Policy Statements that Do Not Require Investigators to Review IND Safety Reports.

Institution	Policy Statement*
University of Rochester	Guidance for Reporting Reportable Events to the RSRB. Common examples of reportable matters are accompanied by: • "Dear Investigator" letter notifying the site of a trend based upon adverse events reported in the entire study. • DSMB reports that require an action to the study (e.g., terminating the study, terminating an arm of the study, adding risks to the consent form, etc.). • Annual Manufacturer HUD Reports. (Jun 2010)
Georgia Health Sciences University	The individual reports are not required to be submitted to the HAC but must be kept on file by the investigator. If submitted, IND safety reports will be returned to the research team. However, a summary must be submitted to the HAC at the time of initial and continuing review. (Oct 2008)
University of North Carolina	Handling non-reportable adverse events and IND safety reports. Individual IND safety reports from external sites are generally not reportable to the IRB because their implications for the study cannot be understood. External events should not be reported to the IRB unless accompanied by an aggregate analysis that establishes their significance and a corrective action plan that addresses the problem. All individual AE and IND Safety Reports shall be maintained by the Investigator. (2012)

* Institutional web sites accessed January 2013

References

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3. Food and Drug Administration. Guidance for Clinical Investigators, Sponsors, and IRBs. Adverse Event Reporting to IRBs - Improving Human Subject Protection. 2009.
4. Office for Human Research Protections. Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events. 2007.
5. Food and Drug Administration. 21 CFR 312.32. IND Safety Reporting (Revised). 2010.

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