

**CONSORTIUM OF
INDEPENDENT
REVIEW BOARDS**

CIRB

CIRB

April 21, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments on FDA's Request for General Information: Reporting of Adverse Events to Institutional Review Boards (Docket No. 2005N-0038)

Dear Sir/Madam:

The Consortium of Independent Review Boards ("CIRB") is pleased to provide comments on the issues raised in the Food and Drug Administration's ("FDA") notice concerning the reporting of adverse events to institutional review boards ("IRB").¹ The Organization appreciates the Agency's recognition of the problems associated with the current system and this important initiative to improve the process. CIRB is a consortium of independent IRBs located in the United States and Canada. The membership has a central mission of promoting the protection and rights of human research subjects, while providing an understanding of how independent IRBs support this goal. Approximately 40% of clinical research in the United States is conducted in non-academic settings and independent IRBs review a majority of this research. Thus, as an organization of IRBs, CIRB has a significant interest in this matter. FDA has asked for comments on the IRB's role in reviewing adverse event reports, perceived limitations under the current system, and recommendations to enhance the IRB's role. CIRB provides the following comments.

I. THE IRB'S ROLE IN THE REVIEW OF ADVERSE DRUG OR DEVICE EVENT REPORTS

The IRB has a primary regulatory responsibility to assure the protection of the rights and welfare of human subjects participating in clinical research through the review of proposed research and the continuing review of approved research. To that end, an IRB is responsible for reviewing reported "unanticipated problems involving risks to human subjects or others"² ("unanticipated problems") in connection with two of the IRB's continuing review functions for approved

¹ 70 Fed. Reg. 6693 (February 8, 2005). These comments supplement the comments delivered by CIRB at the March 21, 2005 FDA public hearing on this matter.

² 21 C.F.R. § 56.108(b); 21 C.F.R. § 312.66.

clinical research: (1) assessment of the ongoing risk/benefit ratio of the study; and (2) assessment of the necessity to inform participants of significant new findings that might affect their continued participation in the research.

Both current IRB regulations and Federal Register notices documenting the rulemaking history fail to define “unanticipated problems.” For this and other reasons, in recent years, “unanticipated problems” has become equated with the phrase “adverse events.” As a result, IRBs have been significantly burdened by the receipt of, and the subsequent need to review, an ever-increasing number of adverse event reports that lack information useful to carrying out the IRB continuing review functions. As this adverse event review function continues to grow, IRB core review and continuing review functions are increasingly threatened, ultimately to the detriment of human subjects. Thus, CIRB generally agrees with the opinions of Gary L. Chadwick, Associate Provost and Director, Office for Human Subject Protection, University of Rochester, who stated at the March 21, 2005 FDA public hearing on this matter that IRBs are not responsible for the review of adverse event reports.

In rejecting the adverse event review function, CIRB does not reject the importance of this function to the reduction of risks to human subjects. Instead, CIRB notes that this critical function is already properly delegated to the sponsor of the investigation, who is responsible for evaluating safety and effectiveness evidence associated with the test article as it is obtained from the investigator.³ Thus, in addition to the threat to core IRB functions, detailed IRB review of adverse event information presents an unnecessary redundancy given that sponsors already are required to have systems in place, either internally or externally through internal data monitoring and/or data monitoring committees (“DMCs”), to adequately evaluate the significance of individual adverse event reports with respect to the safety of human subjects.⁴

Separate and apart from individual adverse event data, as will be discussed further below, CIRB believes that IRB receipt of certain aggregated safety information containing sponsor analysis and conclusions would be of significant value to the IRB in connection with its continuing review responsibilities. However, to stem the unnecessary flow of adverse event reports to IRBs, it is imperative that FDA provide direction on the meaning of “unanticipated problems,” whether

³ 21 C.F.R. § 312.56(c); 21 C.F.R. § 812.46(b).

⁴ For these reasons, CIRB disagrees with comments made at the March 21, 2005 Public Hearing on this matter suggesting that IRBs should be responsible for conducting adverse event review of “single-site” trials. The sponsor monitoring obligations set forth in FDA regulations are no different for single-site trials as compared to multi-site trials, and this obligation applies equally to sponsor-investigator studies. An organization may choose to provide both IRB and data monitoring services to a sponsor. However, these services are separate and distinct, and should not be merged.

through guidance or regulation. In section III below, among its recommendations, CIRB provides its current thinking as to the proper definition of “unanticipated problems.”

II. LIMITATIONS UNDER THE CURRENT SYSTEM

FDA seeks comment on the problems associated with the current system of reporting adverse events to IRBs. CIRB believes that the inherent limitations associated with “adverse event reporting,” including the differences in FDA regulatory definitions associated with reportable events, result in IRB receipt of reports that lack information critical to a meaningful review of reported events or problems. The increase in multi-site studies has compounded these limitations.

A. Current Adverse Event Reporting Environment

Usually, IRBs randomly receive reports about isolated single events. Many reports document non-serious events, expected events, or events unrelated to the study itself. Attempts to describe the type of events that should be reported to IRBs as “unanticipated problems” are frequently thwarted by sponsor and investigator IRB reporting procedures which, in the interest of caution, are broadly written to capture most if not all adverse events, including many that are expected, non-serious, and of questionable relatedness.

In connection with drug studies, IRBs generally cannot tell from these reports whether the adverse event involves a participant on placebo, study drug, or comparator. Additionally, the IRB usually has no knowledge regarding the participant’s underlying medical or medication history. With multi-site studies, even at the time of continuing review, IRBs usually do not know at any given time how many sites or participants are enrolled in a study, or how many participants have experienced a similar adverse event. They lack important data available to the study sponsor that track events across multiple studies, including earlier studies, studies conducted overseas, and studies conducted under the oversight of different local and central IRBs. As a result, IRBs are hampered in their ability to assess the significance of an individual adverse event in the overall study with respect to human subject risk.

B. Differences in Regulatory Definitions of Reportable Events

It is CIRB’s belief that the different regulatory definitions associated with reportable events play a significant role in creating the current unworkable system. As discussed at the outset, while IRBs expect to receive reports from investigators concerning “unanticipated problems,” IRBs, sponsors, and investigators have been given no guidance as to what qualifies as an “unanticipated problem.” Thus, these parties have sought guidance elsewhere; specifically in the context of other reporting requirements associated with untoward occurrences in the context of a clinical study. To highlight the confusion created by reliance on differing definitions, a review of these reportable event regulations is worthwhile.

Under current drug regulations, clinical investigators are to submit *safety reports* to sponsors in connection with “any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug.”⁵ Clearly, the reporting standard here is fairly low. The adverse effect may be non-serious, and it may be expected. In determining whether or not to report such an event, the investigator is limited only to assessing “relatedness” of the event to the study.

Sponsors of drug studies must submit *IND safety reports* to the FDA and all participating investigators in connection with “any adverse experience associated with the use of the drug that is both serious and unexpected” and “any findings in laboratory animals that suggests a significant risk for human subjects[.]”⁶ In this case, while the event must be serious and unexpected, the level of relatedness to the study is extremely low. Specifically, “associated with the use of the drug” is defined as “a reasonable possibility that the experience may have been caused by the drug.”⁷

Further complicating this matter, FDA clinical research regulations concerning medical devices require investigators to report to sponsors and IRBs *unanticipated adverse device effects* which is defined as

any serious adverse effect on health and safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.⁸

Finally, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (“ICH”) Guideline for Good Clinical Practice (“GCP Guideline”), adopted by FDA as a Guidance Document in 1997, raises further questions as to the type of events that should be reported to IRBs. According to the GCP Guideline, investigators should report to the IRB all serious and unexpected adverse drug reactions for which a causal relationship cannot be ruled out.⁹

⁵ 21 C.F.R. § 312.64(b).

⁶ 21 C.F.R. § 312.32(c).

⁷ 21 C.F.R. § 312.32(a).

⁸ 21 C.F.R. § 812.3(s); § 812.150(a).

⁹ ICH Guideline for GCP, § 3.3.8.

Erring on the side of caution, there is a tendency by the investigator and the sponsor to define “unanticipated events” using the lowest common denominators associated with the definitions described above. As a result, it is not unusual for an IRB to receive numerous reports concerning non-serious, expected, and/or tenuously related adverse events.

C. *Increase in Multinational, Multi-Site Studies*

Adverse events reports associated with multi-site studies provide even less information of value to the IRB as explained above in section II.A, particularly under conditions where the reported event did not occur at a site under the IRB’s jurisdiction. However, the sheer number of multi-site studies has exponentially increased the number of reports received by a reviewing IRB, and has transformed a minor problem into a significant problem.

III. RECOMMENDATIONS

CIRB believes that steps can be taken to markedly reduce the number of individual event reports received by IRBs, while ultimately enhancing human subject protections. Specifically, CIRB recommends (A) harmonization of FDA definitions to clarify “unanticipated problems” as the standard for submission of individual event reports to the IRB; (B) development of a requirement for the sponsor to provide investigators and IRBs with periodic aggregated safety data reports containing analysis of safety data and conclusions; and (C) development of a requirement to include a safety monitoring plan in most research protocols.

A. *Harmonization/Clarification of “Unanticipated Problems”*

CIRB recommends the development of specific guidance concerning the meaning of “unanticipated problems.” The definition of “unanticipated problems” should be as follows:

Problems involving risk to human subjects or others that occur at the clinical investigator’s site, and that are (1) serious; (2) unexpected; and (3) related to the study product, procedures, or concomitant treatments called for in the study protocol.

As to individual phrases and terms in this proposed definition, the phrase “problems involving risk to human subjects or others” should include both adverse events associated with the test article or test procedures, and non-product related issues such as confidentiality concerns and economic risks. The words “serious” and “unexpected” should have the same meaning specified

in the IND Safety Reports regulation.¹⁰ In terms of an assessment of relatedness, CIRB believes that the events should “probably or definitely” be related to the study. The term “probably” should be understood to mean “more likely than not.” This definition limits the reporting requirement to problems that actually occur at the clinical investigator’s site. Thus, as to reports of unanticipated problems, an IRB should receive reports concerning events that occur only at sites subject to the IRB’s jurisdiction.¹¹ Such reporting is essential to assure that the IRB has up-to-date information on the status of the study at the individual site where the event occurred.

To assure that “unanticipated problem” reports provide value to the continuing review process, investigators must be required to document their assessment of the required elements associated with the reports. Thus, if an investigator fails to make an assessment concerning the “seriousness” of an event, the IRB should return the report to the investigator as “incomplete.”

B. Aggregated Safety Data Reports

While not properly included within the definition of “unanticipated problems,” CIRB believes that periodic reports to the IRB of protocol-level aggregated safety data in a summarized form (“*aggregated safety data reports*”) would significantly enhance the IRB’s ability to perform its human subject protection function as it relates to the assessment of ongoing risk, particularly when the study at issue is a multi-site study. The frequency of such reports should be consistent with the degree of study risk. CIRB believes the level of report detail should be consistent either with the level of safety information detail contained in the sponsor’s Annual Report for an investigational new drug,¹² or with that called for in the Council for International Organizations of Medical Sciences (“CIOMS”) Working Group VI proposal on reporting drug safety data from clinical trials. By “protocol-level,” CIRB expects that such reports will include safety data from all study sites associated with an ongoing trial, whether or not the safety data are from sites under the jurisdiction of the IRB receiving the report.

In terms of the procedures associated with the delivery of such reports to an IRB, CIRB believes that aggregated safety data reports should be submitted to the IRB by the investigator under the

¹⁰ 21 C.F.R. § 312.32(a) (defining *serious adverse drug experience* and *unexpected adverse drug experience*).

¹¹ Clearly, there may be events that occur at sites not subject to the IRB’s jurisdiction which the sponsor deems sufficiently serious so as to require immediate notification and action on the part of all IRBs. In this case, however, it would generally be expected that these reports would be provided to the IRB in the form of a request to review a protocol amendment and/or a change to the study plan, a procedure, or the informed consent document.

¹² 21 C.F.R. § 312.33.

IRB's jurisdiction, or by the sponsor on behalf of all the investigators subject to the IRB's jurisdiction. CIRB believes that, in most cases, the aggregated reports will be developed by the sponsor, or in some cases, the DMC associated with the trial. However, CIRB believes that IRB receipt of such reports from the investigator is consistent with the current relationship structure set forth in FDA regulations. Further, this process assures that the investigator receives and has an opportunity to fully review the information in the aggregated safety data report.

C. Data Monitoring Plan

Recognizing that continuous adverse event review is imperative to assure the protection of research subjects, CIRB believes that most, if not all, research proposals should include a plan to monitor safety issues associated with a study.¹³ While it has been CIRB's experience that most sponsors already include safety monitoring plans in the protocols submitted to IRBs for review, standardization of this practice would be beneficial. The monitoring plan should be sufficiently rigorous to identify emerging problems and may include one or more of the following:

- (1) Recording and analysis of all adverse events and problems;
- (2) Periodic reporting of aggregate information, along with analysis and conclusions, to all investigators;
- (3) Site-specific aggregated reports developed by the investigator and submitted to the sponsor or the sponsor's designee and the IRB; and
- (4) When DMCs are associated with a research study, a commitment may be included to provide the investigator with a summary of the findings of each DMC meeting, including the DMC conclusions without modification. The investigator will, in turn, be required to submit the DMC report to the IRB, or, where the IRB has jurisdiction over multiple sites involved in the same study, the sponsor can submit the report to the IRB on behalf of all the investigators.

CIRB believes that implementation of these three proposals will improve the IRB's ability to conduct meaningful review of important study information that may impact the status of the study. With such information, the IRB will be in a better position to determine the need to take action, whether it is to require a change to the informed consent, the protocol, or the approval status of the study.

¹³ There may be cases where a data monitoring plan, as characterized herein, may be unnecessary. For example, data monitoring plans may be unnecessary for certain low risk Phase IV studies. However, this would not be the case where the motivation for the Phase IV study is to further explore the significance and scope of a particular adverse event or events.

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April 21, 2005

CIRB thanks the FDA for the opportunity to comment on this crucial matter and is hopeful that its comments are helpful to FDA as the Agency considers how to proceed.

Sincerely,

A handwritten signature in cursive script that reads "John S. Freeman". To the right of the signature is a circular stamp containing the initials "JRF".

John S. Freeman, Esq.
Chair

cc: CIRB Membership