CONSORTIUM OF INDEPENDENT REVIEW BOARDS

CIRB **CIRB**

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By Overnight Delivery
Via E-Mail ohrp@osophs.dhhs.gov

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Re: Draft Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others

Dear Dr. Carome:

The Consortium of Independent Review Boards ("CIRB") is pleased to provide comments on the Office for Human Research Protections (OHRP) Draft Guidance entitled: *Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others* ("*Draft Guidance*"). As OHRP knows, CIRB is a consortium of independent institutional review boards ("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 75% 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 independent IRBs operating under several different models, CIRB holds an important perspective on human subject protection issues. CIRB provides the following comments.

CIRB thanks OHRP for addressing the daunting issues currently associated with the adverse event reporting process. In 2005, CIRB provided its opinions on adverse event reporting at the Food and Drug Administration's ("FDA") March 21, 2005 public hearing on the matter, and in

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written comments to FDA dated April 21, 2005.[1] CIRB's oral and written comments in response to FDA's request are incorporated by reference into this document.

CIRB generally agrees with the principles set forth in the *Draft Guidance*. The *Draft Guidance* attempts to provide a mechanism to assure review of all adverse events associated with a regulated clinical study by the appropriate bodies (i.e., sponsors, data monitoring committees ("DMCs")), while limiting adverse event reporting to investigators, institutions, and IRBs to those events properly deemed "unanticipated problems involving risks to subjects or others" ("Unanticipated Problem(s)"). With the modifications recommended below, CIRB believes that implementation of this *Draft Guidance* across all federal agencies would aid in reducing the review burden currently experienced by investigators, institutions, and IRBs, allowing these parties to shift additional resources to other core human subject protection functions.

I. Harmonization with FDA and Other Federal Entities

The OHRP Backgrounder preceding the *Draft Guidance* states that the research community has been requesting, for a number of years, harmonized adverse event reporting guidelines and requirements that apply to all federal agencies. This is because the research community recognizes that harmonization is key to reducing the current adverse event reporting and review regulatory burdens.

Because FDA has oversight authority over most pharmaceutical and medical device studies conducted in the U.S., unless FDA adopts similar guidance, the impact of the *Draft Guidance* will be of limited value. CIRB believes the *Draft Guidance* principles are consistent with most, if not all, FDA regulations. However, FDA statements and clarifications, preferably as co-authors of a guidance with OHRP, would be helpful to IRBs and the research community in connection with some matters. For example, FDA should provide guidance on a definition of "unanticipated problems involving risks to subjects or others" that is similar to that set forth in the future final version of the *Draft Guidance*. Because FDA has not yet defined this term, sponsors and clinical investigators are inclined to adopt policies that require submission of all adverse events to the IRB, regardless of IRB policies or any OHRP statements or guidances.

The research community and IRBs would further benefit from FDA clarification of the level of relatedness required for reporting Unanticipated Problems (i.e., the level of known relationship of the adverse event to participation in the study). This clarification should be harmonized with OHRP guidance. As will be stated elsewhere, for the purpose of reporting Unanticipated

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[1] CIRB, Comments on Reporting of Adverse Events to Institutional Review Boards (Docket No. 2005N-0038), submitted April 21, 2005 and entered as Electronic Comment No. 28 (EC28), *available at*, http://www.fda.gov/ohrms/dockets/dockets/05n0038/15.htm.

Problems to the IRB, CIRB believes the level of relatedness should be fairly high; that is "probably or definitely related" to participation in the study.

Other federal bodies besides OHRP and FDA have also addressed the adverse event reporting requirements. For example, the National Cancer Institute ("NCI") issued a guidance in December 2004 on this subject.[2] The NCI adverse event reporting requirements are quite stringent. The reporting of "severe and undesirable", life-threatening/disabling, and fatal adverse events is required even if the events are determined unrelated or doubtfully related to the intervention.[3] Data from the NCI's adverse event database are accessed by the NCI's Central IRB in connection with NCI-funded studies.[4] The NCI Central IRB does not reveal the extent or level of its review of the NCI adverse event database. Thus, without clarification from NCI Central IRB, investigators of NCI-funded research and local IRBs may believe that IRBs are required to review unrelated adverse events deemed "severe and undesirable." Because many forms of cancer result in severe and fatal events regardless of intervention, such a requirement would undermine OHRP's efforts to reduce the adverse event reporting and review burdens currently experienced by investigators and IRBs.

The examples provided above are intended to impress upon OHRP the need to develop a guidance that is jointly issued or jointly adopted by all federal agencies. Until such action occurs, finalization of the *Draft Guidance* will have a limited impact on current adverse event reporting problems.

II. External Adverse Events versus Internal Adverse Events

CIRB appreciates OHRP's acknowledgement that a distinction should be made between External Adverse Events and Internal Adverse Events. Further, CIRB welcomes OHRP's support for the principle that sponsors (or granting agency)/DMCs should not routinely forward reports of External Adverse Events to all participating investigators, institutions, and IRBs in a multisite study unless the events are determined to be Unanticipated Problems. CIRB also finds helpful OHRP's recommendation that Unanticipated Problem reports issued by the sponsors/DMCs to all investigators, institutions and IRBs should contain (1) a clear explanation of the basis for the

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[2] *See* Cancer Therapy Evaluation Program, National Cancer Institute, Guidelines: Adverse Event Reporting Requirements (December 15, 2004).

[3] *Id.*

[4] See NCI Central Institutional Review Board Initiative Frequently Asked Questions (**www.ncicirb.org/CIRB_FAQ.asp**) (last accessed on 12/30/05).

Unanticipated Problem determination, and (2) a description of proposed or implemented actions in response to the Unanticipated Problem.

Despite CIRB's general support for the recognition of a need to process Internal Adverse Events and External Adverse Events differently, it is concerned that the proposed *Draft Guidance* definitions of these two types of adverse events could reduce the impact of OHRP's objectives. Based upon a review of the *Draft Guidance* as a whole, it becomes clear that OHRP intends to distinguish between adverse events that are reported to a principal investigator directly by the subject, another collaborating local investigator, or the subject's healthcare provider (typically, Internal Adverse Events) versus those adverse events reported to the principal investigator by a study sponsor or coordinating center (typically, External Adverse Events).

However, distinguishing between the two types of events by reference to the IRB's jurisdiction, as set forth in section II of the *Draft Guidance*, may create unnecessary confusion, and could defeat OHRP's suggested procedures for addressing such events. Specifically, in a multisite study, one IRB may have jurisdiction over many clinical sites. Thus, if an investigator receives a report from a sponsor about an adverse event experienced by a subject that is not associated with the investigator's clinical site, in determining whether to treat the event as an internal adverse event versus an external adverse event, the investigator must ascertain whether his or her clinical site shares the same IRB of record as the clinical site from which the adverse event report was generated.

Further, as part of their continuing review responsibilities, many IRBs require clinical sites subject to their jurisdiction to report events that may not meet the Unanticipated Problem definition when the events are associated with subjects enrolled at these sites. A number of these IRBs currently refer to such events as Internal Adverse Events. The proposed *Draft Guidance* definition of Internal Adverse Event could create confusion, unnecessarily burden the investigator in determining the need to report sponsor/DMC issued Adverse Event Reports, and result in duplicate reports of the same event to the IRB.

As a result, to provide clarity to the research community, and to prevent unnecessary reporting, CIRB recommends that the distinction between the two types of events be based upon the authority or jurisdiction of the principal investigator. For example, a definition of *External Adverse Events* could be as follows: "individual adverse events experienced by subjects enrolled in multicenter clinical trials at clinical sites not under the principal investigator's authority." Further, CIRB recommends that *Internal Adverse Events* could be defined as "those adverse events experienced by subjects enrolled at clinical sites subject to the principal investigator's authority." The principal investigator would then be responsible for following the necessary procedures associated with each type of event and reporting to the IRB of record those events determined to be Unanticipated Problems, or as required by more stringent IRB procedures, if any.

As a related matter, the *Draft Guidance* proposes that an External Adverse Event meeting the proposed definition of Unanticipated Problems be reported to all investigators and IRBs associated with a multisite study. CIRB recommends that External Adverse Events should fall outside the scope of Unanticipated Problems reporting. Instead, such events should only be reported to all IRBs in connection with a "request for change to the approved research" in accord with 45 C.F.R. § 103(b)(4).

III. Defining Unanticipated Problems

As Part III of the *Draft Guidance* explains, the phrase "unanticipated problem involving risk to subjects or others" is undefined in the Department of Health and Human Services (HHS) regulations. *See* 45 C.F.R. 46.103(b)(5). While CIRB appreciates OHRP's initial steps towards providing a necessary definition, CIRB found the proposed definition, along with the accompanying examples, to be vague and confusing.

A. Definition of "Problem"

As an initial matter, CIRB notes that the *Draft Guidance* is lacking a definition for "problems" as distinguished from Unanticipated Problems. As CIRB stated in its previously mentioned April 21, 2005 written comments to FDA, the difficulties associated with the current adverse event reporting environment are largely due to the many different definitions and terms associated with reportable events. The *Draft Guidance* provides an opportunity to harmonize the meanings of such terms. Thus, CIRB recommends that OHRP offer a definition of "problems" that includes reference to "adverse events", as that term is defined in the Draft Guidance, plus other unfavorable social, behavioral, psychological events.

B. Definition of "Serious"

Second, CIRB recommends the inclusion of a definition for "serious" because this is a key term in defining an Unanticipated Problem. CIRB recognizes that FDA's definition for the term "serious adverse drug experience" is included in Appendix A of the *Draft Guidance*, which provides examples of definitions of adverse events and similar terms. FDA defined a serious adverse drug experience as:

> Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious

> adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.[5]

CIRB generally agrees that the FDA definition captures the kind of events that should be characterized as serious adverse events. However, the FDA definition is limited in application to drug related adverse events. Further, the text of the *Draft Guidance* does not specifically adopt the FDA definition of "serious adverse drug experience" as the definition of "serious". Therefore, for clarity, CIRB recommends that a definition of "serious", which is consistent with current regulatory definitions for the term, be added to Section I of the *Draft Guidance*.

C. Relationship of Adverse Event to Study

Third, CIRB believes that, for the purpose of reporting serious, unexpected adverse events to the IRB as Unanticipated Problems, the relationship level to the study should be "probably or definitely related". As a general matter, OHRP should keep in mind that, under FDA regulations, serious, unexpected adverse events for which there is a "reasonable possibility" of study article causation are reported by the sponsor to all investigators and the FDA. *See* 21 C.F.R. 312.64(b). Thus, the sponsor is already responsible for thoroughly reviewing such reports and determining whether a change to the protocol is necessary. Clearly, the sponsor is in a better position than the IRB to understand the impact of a "possibly related" event on the study and whether there is a need for a change to the approved research, particularly when the event is associated with a multisite study. Therefore, CIRB believes that duplicative review of "possibly related" events by the IRB provides no additional protections to human subjects participating in the study. Generally, such events do not require changes to the IRB-approved research. On the other hand, those serious, unexpected events that are "probably or definitely related" to participation in the study would more likely require some type of change to the protocol, the informed consent document, or some other aspects of the approved research, and thus warrant immediate submission to the IRB as Unanticipated Problems or, in the case of External Adverse Events, as recommended by CIRB in Section II above, as a "request for a change to the approved research".

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[5] *See* Appendix A(10) of the *Draft Guidance,* referencing 21 C.F.R. §§ 310.305(b), 312.32(a), and 314.80(a).

D. Clarification of Unanticipated Problems Category 3

Fourth, CIRB recommends the following changes to the *Draft Guidance*'s third proposed category of adverse events meeting the Unanticipated Problems definition:

> 3) Other unexpected adverse events, regardless of seriousness, that may unfavorably alter the IRB's analysis of the risk versus potential benefit of the research and, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document.

Use of "seriousness" in place of "severity" assures consistency in terms. Further, the addition of "unfavorably" to qualify "alter the IRB's analysis" provides clarity to this category.

E. Removal of Example 2 in Appendix D

As a final comment on the definitions and examples associated with Unanticipated Problems, CIRB strongly recommends removal of Example 2 in Appendix D to the *Draft Guidance*. Example 2 describes a processing error that results in a subject receiving an experimental agent that is 10-times higher than the dose dictated in the protocol. The subject never experienced detectable harm or adverse effect. Following an appropriate time period, it was learned that this error resulted in no risk to the subject, and clearly, the error did not result in risk to others in the study. Nonetheless, the *Draft Guidance* states that this event provides an example of a reportable Unanticipated Problems that do not involve an adverse event. CIRB disagrees that this type of event should be broadly disseminated to all research sites and IRBs in a multisite study. Whether this event should be reported to the IRB with jurisdiction over the site is a different matter, as some IRBs may want to receive a report about this type of Internal Adverse Event after proper review by the investigator.

IV. *Draft Guidance* Proposed Procedures for Handling Adverse Events

Under Section VI.B.3, the *Draft Guidance* states that the IRB or another appropriate institutional official is generally responsible for reporting Unanticipated Problems to the supporting HHS agency and OHRP. CIRB disagrees that the IRB generally has this responsibility. This responsibility may be specifically delegated to the IRB by the institution. However, in multisite studies, it would appear to be more appropriate for the institution to delegate this reporting responsibility to a DMC. Thus, CIRB recommends that the proposed procedures be modified to reflect the institutional responsibility to assure reporting of Unanticipated Problems to the supporting HHS agency and OHRP, and to recognize appropriate delegation of this responsibility.

V. Appendix A to *Draft Guidance*

As a final comment, CIRB notes that Appendix A, which presents examples of definitions of adverse events, includes the definition of adverse event adapted from the International Conference on Harmonization guideline E2A. For clarity, CIRB suggests that this Appendix A definition also reference the ICH guideline E6, which is the decisive document on international Good Clinical Practice standards.

CIRB believes that OHRP has taken the right course in its development of the *Draft Guidance*. With the modifications suggested above, along with a concerted effort among the applicable agencies to issue this guidance jointly, at the *Draft Guidance* has the potential to reduce the current burdens associated with adverse event reporting to IRBs, and subsequent IRB review.

Sincerely,

John Freeman

John Freeman
Chair

AMB:
cc: Dr. Andrew C. von Eschenbach – NCI, Director; FDA, Acting Commissioner
Dr. David Lepay – FDA, Good Clinical Practice Program, Director
CIRB