CONSORTIUM OF
INDEPENDENT REVIEW BOARDS

April 2, 2010

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

Re: **Docket No. FDA-2009-D-0605 – Comments on Draft Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review After Clinical Investigation Approval**

Dear Sir or Madam:

As noted in our correspondence dated March 15, 2010, the Consortium of Independent Review Boards ("CIRB®") appreciates the opportunity to comment on the Food and Drug Administration's ("FDA" or "Agency") draft guidance document, entitled "IRB Continuing Review After Clinical Investigation Approval" ("draft guidance"). As FDA knows, CIRB is a consortium of independent institutional review boards ("IRBs") located in the United States and Canada that provide IRB services to institutions external to their individual member institutions. With most of the research under the oversight of independent IRBs being regulated by FDA, CIRB has a significant interest in this draft guidance document.

CIRB is pleased that FDA has issued this draft guidance and believes that it will be very helpful to the IRB community. While CIRB supports the FDA draft guidance as a whole, we respectfully request that FDA consider the following comments as it prepares to finalize the draft guidance.

A. Role of the Sponsor During the Continuing Review Process

CIRB appreciates the fact that FDA recognizes in the draft guidance that study sponsors play an important role in connection with the continuing review process, particularly as it concerns multi-site trials. CIRB agrees that sponsors can provide much, if not all, of the information identified on page 5 of the draft guidance as necessary for the IRB to conduct continuing review of multi-site trials. As noted by FDA, "[s]ponsors are in the unique position of having information for the entire study that may assist IRBs in reviewing the studies and protecting subjects." *See* p. 3 of the draft guidance. Assuming that the individual study sites have provided all required information to the IRB throughout the reporting period

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and continue to comply with their reporting obligations to the IRB (e.g., reporting of unanticipated problems), CIRB supports this position and believes that it assures a more complete and efficient review that is consistent with the IRB's mission of protecting the welfare of human subjects involved in clinical research.

B. Review of the Informed Consent Information

CIRB wholeheartedly agrees that review of the adequacy of the informed consent process is a critical aspect of the continuing review function. In particular, CIRB believes that in the context of a multi-site trial that involves a central IRB alone, this can be accomplished by reviewing the approved informed consent document template and any approved variations of the document at the individual study sites.

C. "Closing out" of Study Sites

CIRB would appreciate clarification as to when an IRB involved in a multi-site trial can "close out" a study site. Under the discussion of "Expedited Review Category (8), the last paragraph of page 10 of the draft guidance states the following:

> For trials that meet the provisions of category (8)(a) or (c) and are subject to a review agreement with a CIRB, consideration may be given to closing out the study at all sites except for the CIRB, provided that does not breach the terms of any review agreement(s). That is, the CIRB could provide continuing review for the study using expedited review procedures when the research activity is limited to long-term follow-up of subjects (category 8(a)) or analysis of the data (category 8(c)). Similarly, for multi-site trials that do not involve use of a CIRB, when the remaining research activity is limited to long-term follow-up or data analysis, only the site(s) engaged in the long-term follow-up or ongoing data analysis would need to have continuing IRB review, and it could be handled via expedited review.

While we believe that we understand FDA's intent here, we ask that the Agency provide some clarification, as we believe that this paragraph will create confusion among members of the clinical research community. In particular, the guidance states that consideration can be given to "closing out the study at all sites except for the CIRB." This incorrectly implies that an IRB can be "closed out". It also implies that study sites can be "closed out," even if the sites continue to conduct long-term subject follow-up, or continue to provide access to identifiable[1] data. CIRB does not agree with these premises and believes that FDA did not

[1] On page 11 of the draft guidance, FDA states, "Once the data collection from all trial sites is complete and the overall study results base has been locked, so that the only remaining activity is analysis of the aggregate data by the study sponsor, continuing review is generally no longer needed." CIRB understands FDA's reference to "aggregate data" as data that does not contain patient identifiable information. Based upon this understanding, CIRB agrees that when the site or sites are no

intend to suggest use of the term "close-out" in this matter. Further, it is unclear whether, in a multi-site trial that only involves a centralized IRB, the centralized IRB can "close out" study sites that are no longer involved in data analysis or long-term follow-up of subjects. Central IRB "close out" of individual sites is common in a multi-site trial, even while the study as a whole remains open due to ongoing research activity at other individual study sites.

It may be helpful to provide FDA with CIRB's understanding of when a study site can be "closed out" under expedited review category (8). CIRB has identified 3 scenarios identified below.

> First, it is CIRB's understanding that when a multi-site trial involves the use of both a centralized IRB and local IRBs, consideration may be given to having the local IRBs "close out" the study at their individual sites, if the agreement allows, even while the centralized IRB keeps the study and certain study sites open for purposes of providing continuing review when study sites are conducting long-term follow-up of subjects or analysis of identifiable data. Thus, in this case, the sites will be considered "closed" from the local IRB's perspective, but "open" by the central IRB for purposes of providing continuing review.
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> Second, when a multi-site trial involves a centralized IRB alone (i.e., without any local IRBs), then it is our understanding that the centralized IRB only needs to conduct continuing review of the study and the study sites that are involved in long-term follow-up of subjects, or analysis of identifiable data, and may "close out" the other study sites that are no longer engaged in these or any other research activities.
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> Finally, in a multi-site trial that does not involve a centralized IRB, each local IRB is required to keep the study site open and conduct continuing review as long as its particular site is engaged in research activity, which includes long-term follow-up of subjects or analysis of identifiable data.

Assuming FDA agrees with CIRB's understanding of when a study site can be "closed out," we would appreciate clarification of the draft guidance to reflect this understanding more clearly. If FDA disagrees, we request that it notify CIRB, because CIRB may have additional comments.

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longer collecting data from research subjects, and the only data being reviewed/analyzed is de-identified aggregate data, IRBs may "close out" a study.

D. Process for Conducting Continuing Review

On page 5 of the draft guidance, FDA has included a list of information that it recommends IRBs consider during the continuing review process. This includes,

> any new and relevant information, published or unpublished, especially information about risks associated with research; for example, a summary of any unanticipated problems and available information regarding adverse events.

Id. As we understand it, the type of "new and relevant, published or unpublished" information that FDA generally is referring to is information that the sponsor is required to submit in its Annual Reports to the Agency.[2] *See* 21 C.F.R §312.33 and § 812.150(b)(5).

CIRB agrees and further asserts that it is not the IRB's role to analyze study data. The IRBs should only receive information that has been appropriately evaluated and put into context by the study sponsor, a data monitoring committee, or the investigator. Thus, IRBs may receive new and relevant information in the form of unanticipated problem summaries, sponsor Annual Reports, Data Safety Monitoring Reports, and other similar documents that properly evaluate new information. Receipt of data by the IRB that has not been properly evaluated is inappropriate and serves of little value to the IRB in conducting its continuing review function.

E. Determining Continuing Review Dates

On page 13, paragraph 3 of the draft guidance, FDA states "it may be less confusing to researchers if the same anniversary date for continuing review can be preserved, year to year." CIRB agrees and requests clarification on the acceptable time frame for applying a continuing review approval action that occurs on a date before the anniversary date to the anniversary date itself. Thus, for example, if a study is approved on January 30, 2009, and the anniversary date is set for January 30, 2010, but the board's continuing review and approval occurs two weeks earlier on January 15, 2010, CIRB believes it would be appropriate for the IRB to assign an anniversary date in 2011 of January 30.

F. Use of term "CIRB"

In the draft guidance, FDA uses the term CIRB as an acronym for "centralized IRB process." While it may be clear within the context of the draft guidance document that "CIRB" refers

[2] As noted in the draft guidance much of the information that FDA recommends that the IRB review "is often included in annual reports prepared by the study sponsor." *See* p. 5 of draft guidance.

to "centralized IRB process," we are concerned that FDA's use of the term "CIRB" may be the source of confusion among members of the clinical research community. CIRB is the registered trademark acronym for the Consortium of Independent Review Boards.[3] As an association that has been in existence since 1993, CIRB is well known in the research community as an association devoted to assuring the protection and rights of human research subjects, while promoting an understanding of how independent IRBs support this goal.

Therefore, in order to avoid any confusion, and to prevent inadvertent infringement of CIRB's registered trademark, we respectfully request that FDA use another term when referring to centralized IRBs in its draft guidance document.

In closing, CIRB would like to once again express its deep appreciation to FDA for the opportunity to comment. We hope that FDA will take these comments into consideration prior to finalizing the draft guidance. We look forward to continuing to work with FDA to assure the protection and welfare of human subjects involved in clinical research.

Sincerely,

Cami Gearhart
Chair

cc: CIRB Board

[3] CIRB, Reg. No. 3,267,111, registered July 24, 2007