Guidance for Industry

Using a Centralized IRB Review Process in Multicenter Clinical Trials

DRAFT GUIDANCE

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Procedural

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I. INTRODUCTION

This guidance is intended to assist sponsors, institutions, institutional review boards (IRBs), and clinical investigators involved in multicenter clinical research in meeting the requirements of 21 CFR part 56 by facilitating the use of a centralized IRB review process. The guidance (1) describes the roles of the participants in a centralized IRB review process, (2) offers guidance on how a centralized IRB review process might consider the concerns and attitudes of the various communities participating in a multicenter clinical trial, (3) makes recommendations about documenting agreements between a central IRB and the IRBs at institutions involved in the centralized IRB review process concerning the responsibilities of a central IRB and each institution's IRB, (4) recommends that IRBs have procedures for implementing a centralized review process, and (5) recommends how a central IRB should document its reviews of clinical trial sites not affiliated with an IRB. This guidance applies to clinical investigations conducted under 21 CFR part 312 (investigational new drug application or IND regulations).

This guidance is intended to help facilitate IRB review of multicenter research using a centralized IRB review process (a single central IRB or a small number of central IRBs) in situations where centralized review would not compromise human subject protections and could improve efficiency.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Good Clinical Practice Program in the Office of the Commissioner (OC), and the Office of Regulatory Affairs (ORA) at the Food and Drug Administration.

II. BACKGROUND

Clinical investigations that are subject to the requirements of IND regulations must be reviewed and approved by an IRB in accordance with the requirements of 21 CFR part 56. The IRB requirements evolved at a time when most clinical trials were conducted at a single study site or at a small number of sites. In the intervening years, there has been substantial growth in the volume of clinical research generally, the volume of multicenter trials, and the size and complexity of late-stage clinical trials. These changes have placed considerable burdens on IRBs and on sponsors and clinical investigators who are seeking IRB review for multicenter trials.[2, 3]

In a multicenter trial, an IRB at each center typically conducts a complete review of the protocol and informed consent. Multiple reviews by multiple IRBs can result in unnecessary duplication of effort, delays, and increased expenses in the conduct of multicenter clinical trials.[4, 5, 6] Greater reliance on a centralized IRB review process, in appropriate circumstances, has the potential to reduce IRB burdens and delays in the conduct of multicenter trials.

Use of a centralized IRB review process is consistent with the existing IRB regulations. Section 56.114 (21 CFR 56.114 Cooperative Research) provides, "institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort." When this rule was proposed, the preamble to the proposed rule indicated that the purpose of this section is "to explicitly reduce duplicative review of multi-institutional studies."[7] The preamble to the final rule also stated that "the purpose of this section is to assure IRBs that FDA will accept reasonable methods of joint review."[8] Physical proximity of an IRB to a research site is not necessarily of significance, provided that the IRB is competent to understand the local context of the research. As stated in 21 CFR 56.107(a), this would require sensitivity to community attitudes, familiarity with the standards of professional conduct and practice where the research takes place, and knowledge about local laws and regulations applicable to the study (see Section IV).

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[2] Department of Health and Human Services (DHHS), Office of the Inspector General Report, *Institutional Review Boards: A Time for Reform*, June 1998.

[3] Burman WE, RR Randall, DL Cohn, RT Schooley, Breaking the Camel's Back: Multicenter clinical trials and the local institutional review boards, *Ann Intern Med*, 134(2): 152-157, 2001.

[4] Burman W, P Breese, S Weis, N Bock, J Bernardo, A Vernon, The Effects of local review on informed consent documents from a multicenter clinical trials consortiu*m*, *Controlled Clin Trials*, 24(2003) 245-255.

[5] Silverman H, S Chandros Hull, J Sugarman, Variability among institutional review boards decisions within the context of a multicenter trial, *Crit Care Med* 29(2), 235-241, 2001.

[6] McWilliams R, J Hoover-Fong, A Hamosh, S Beck, T Beatty, G Cutting, Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study, *JAMA*, 290(3), 360-361, 2003.

[7] See 44 *Fed. Reg.* 47688, 47700 (8/14/79).

[8] 46 *Fed. Reg.* 8958, 8970 (1/27/81).

A centralized IRB review process is an agreement in which multiple study sites in a multicenter trial rely, in whole or in part, on the review of an IRB other than the IRB that ordinarily would be responsible for review of research conducted at that location (i.e., the IRB for the institution with which the site is affiliated). A site may rely entirely on the central IRB for initial and continuing review of a clinical trial, or it may rely primarily on the central IRB, but use the IRB with which it is affiliated for certain aspects of the review (e.g., review of informed consent for local concerns). A study site in a multicenter study that does not have its own IRB (e.g., a physician office site that is not affiliated with an institution with an IRB) would rely on the central IRB that is providing IRB review for multiple sites in the study.

III. ROLES IN ENSURING IRB REVIEW

The following sections describe one model for defining the roles and responsibilities of the various parties who would be involved in a centralized IRB review process.

A. Institution

We recommend that institutions that participate in multi-center clinical investigations develop policies for determining when and which studies conducted in the institution would be appropriate for centralized review and how initial and continuing IRB review would be conducted for such studies. An institution may permit a central IRB to be entirely responsible for initial and continuing review of a study, or the institution may apportion IRB review responsibilities between a central IRB and its own IRB.

B. Sponsor

For drug and biological product studies, 21 CFR part 312 provides that a sponsor is responsible for obtaining a commitment from each investigator that the investigator will ensure that requirements relating to IRB review and approval in part 56 are met with respect to that portion of the research conducted by that investigator (21 CFR 312.53(c)(1)(vi)(d)). Sponsors can also initiate plans for use of a centralized IRB review process and facilitate agreements and other necessary communications among the parties involved.

C. Investigator

Under 21 CFR part 312, an investigator is responsible for ensuring that there will be initial and continuing review by a qualified IRB of research conducted by that investigator. If the investigator is performing this portion of a multicenter study in an institution with its own IRB and the investigator is subject to that institution's policies, those policies would dictate how the investigator will ensure IRB review within the context of a centralized review process. Under those policies, the investigator might ensure review by a central IRB or by the institution's IRB, or with review responsibility apportioned between a central IRB and the institution's IRB.

D. Central IRB

For all sites that agree to participate in a centralized IRB review process, the central IRB is the IRB that conducts reviews applicable to multiple sites involved in a single study, in a manner consistent with the requirements of part 56. The central IRB and the IRB for an individual study site may also agree to apportion certain review responsibilities.

IV. ADDRESSING LOCAL ASPECTS OF IRB REVIEW

The implementation of a centralized IRB review process involves addressing a number of issues related to the local community. The requirements for IRB membership in 21 CFR 56.107(a) specify that the membership of an IRB must have sufficient experience, expertise, and diversity to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. This requirement is intended to implement a recommendation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research that IRB members be "men and women of diverse backgrounds and sufficient maturity, experience, and competence to assure that the Board will be able to discharge its responsibilities and that its determinations will be accorded respect by investigators and the community served by the institution or in which it is located."[9] In addition, IRB membership must "be able to ascertain the acceptability of the proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice" (21 CFR 56.107(a)). Thus, IRB review, through diversity of IRB membership, is intended to provide meaningful consideration of various local factors in assessing research activities, including the cultural backgrounds (e.g., ethnicity, educational level, religious affiliations) of the population from which research subjects will be drawn, community attitudes[10] about the nature of the proposed research, and the capacity of the institution to conduct or support the proposed research. Inter-community differences could influence, among other things, assessments of whether mechanisms of subject selection will be equitable, whether adequate provision is made to minimize risks to vulnerable populations, and the adequacy of the informed consent process.

The preamble to the final rule indicates that where a centralized IRB review process is used (21 CFR 56.114), the review should consider the ethical standards of the local community. [11] Therefore, a centralized IRB review process should include mechanisms to ensure meaningful consideration of these relevant local factors. Possible mechanisms include:

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[9] 44 *Fed. Reg.* at 47690.

[10] *Local community attitudes* is usually interpreted to refer to the attitudes of the local community where research will be conducted. However, it could also refer to a community of otherwise similarly situated individuals, such as a community of individuals with the same disease. For purposes of a discussion of special issues that arise in the context of central IRB review of multicenter research, when we refer to *community attitudes*, we are referring to any considerations that may be unique to the various local communities from which research subjects will be drawn.

[11] 46 Fed. Reg. at 8966.

- Provision of relevant local information to the central IRB in writing by individuals or organizations familiar with the local community, institution, and clinical research
- Participation of consultants with relevant expertise, or IRB members from the institution's own IRB, in the deliberations of the central IRB
- Limited review of a central IRB-reviewed study by the institution's own IRB, with that limited review focusing on issues that are of concern to the local community

Other mechanisms may also be appropriate. IRB meeting minutes or other records should document how relevant community issues were considered in the review.

Guidance issued by the Department of Health and Human Services, Office of Human Research Protections (OHRP)[12] identifies certain factors that should be considered by central IRBs in assessing the local research context for research supported by DHHS. The factors identified in that guidance may be reasonable factors for all IRBs to consider, to the extent they are relevant to the proposed research, when assessing local community attitudes.

V. IRB RECORDS; DOCUMENTING AGREEMENTS FOR CENTRALIZED IRB REVIEW

IRBs and institutions are required to prepare and maintain adequate documentation of IRB activities (21 CFR 56.115(a). If an institution, its IRB, and a central IRB agree (under 21 CFR 56.114) to participate in a centralized IRB review process, we recommend that they document that agreement and ensure that all other parties involved receive copies of the agreement (e.g., the institution, the institution's IRB, the central IRB, investigators at the sites, the sponsor).[13] If the agreement apportions IRB review responsibilities between a central IRB and the institution's IRB, the agreement should delineate the specific responsibilities of the central IRB and the institution's IRB for the initial and continuing review of the study.

VI. WRITTEN PROCEDURES

IRBs are required to follow written procedures for the conduct of initial and continuing review of clinical research and for reporting findings and actions to the investigator and the institution (21 CFR section 56.108(a)). For central IRBs and IRBs at institutions that participate in a

[12] OHRP guidance, *IRB Knowledge of Local Research Context*, updated July 21, 2001, currently available at http://www.hhs.gov/ohrp/humansubjects/guidance/local.htm. Although this guidance applies only to clinical research that is supported by DHHS funding, FDA believes the factors presented will be helpful for IRBs reviewing non-DHHS funded research in their consideration of local community attitudes.

[13] When research covered by a Federalwide assurance (FWA) approved by the Office for Human Research Protections (OHRP) is to be reviewed by a central IRB, the central IRB must be designated under the FWA (45 CFR 46.103(b)(2)). Procedures for respective responsibilities for IRB review activities must be documented in writing (45 CFR 46.103(b)(4)). OHRP has a sample IRB Authorization Agreement on its website at www.hhs.gov/ohrp/humansubjects/assurance/iprotsup.rtf that may be to allocate responsibilities between IRBs, or the institutions may develop their own agreement.

centralized IRB review process, these written procedures should be sufficient to ensure adequate IRB review when a centralized IRB review process is used.

Central IRB procedures could address the following, for example:

- How the central IRB plans to communicate (e.g., with relevant institutions, the institutions' IRBs, and investigators) to accommodate a centralized IRB review process
- How the central IRB ensures that its deliberations consider relevant local factors for communities from which research subjects will be drawn (see Section IV)
- How the central IRB assesses the capability of a geographically remote site to participate in a study (e.g., whether the site has medical services appropriate to the complexity of the study)

For agreements that apportion IRB review responsibilities between a central IRB and an institution's IRB, we recommend that the institution's IRB have written procedures describing how it implements its responsibilities under the agreement.

VII. USING A CENTRAL IRB AT UNAFFILIATED SITES

At clinical sites in a multicenter trial that are not already affiliated with an IRB, investigators and sponsors rely on the review and oversight of a central IRB. This is the common practice in studies with some or all sites in physician office settings that are not affiliated with an institution that has an IRB. If the central IRB is not located near the study site, we recommend that the central IRB document in its review how it considered relevant local factors for the various communities from which research subjects are to be drawn. The central IRB should document its agreement with each site to conduct IRB review for the site, and it should have procedures describing how it will perform its initial and continuing review responsibilities at remote sites (as discussed in Sections IV, V, and VI).

VIII. EXAMPLES OF COOPERATIVE IRB REVIEW MODELS

There are a variety of mechanisms that have been used to distribute IRB review responsibilities between an institution's IRB and a central IRB. This guidance is not intended to endorse any particular mechanism. These examples are provided only to illustrate possible mechanisms.

A. Multicenter Trial in Which Multiple Sites Rely on a Central IRB

The primary model contemplated by this guidance is a centralized IRB review process developed for a single multicenter trial performed by a commercial or publicly funded sponsor. Under 21 CFR 56.114, IRBs affiliated with the study sites could enter into agreements with a central IRB to accept all or some of the findings of the central IRB, or could decline to participate in centralized IRB review (i.e., do their own complete review). Sites not already affiliated with an IRB would rely on a central IRB for all IRB review responsibilities.

B. Central IRBs Formed to Review Multicenter Trials in a Therapeutic Category

The National Cancer Institute (NCI) has created a freestanding central IRB (NCI central IRB) to provide the option for centralized IRB review for the many multicenter cancer trials conducted by NCI. This NCI central IRB is a standing body with subject matter expertise that reviews all NCI-sponsored phase 3 trials in adults with cancer. The IRBs affiliated with the study sites have the option of accepting the review of the NCI central IRB, or doing their own complete review of the protocol and informed consent. (See http://www.ncicirb.org/DivResponsibilities1.pdf)

C. Regional and Nonregional Cooperatives

IRBs at some academic medical centers have entered into ongoing cooperative agreements in which their IRBs have the option of accepting reviews by IRBs at other centers when both centers are participating in a multicenter trial.