Guidance for Industry

Using a Centralized IRB Review Process in Multicenter Clinical Trials

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U.S. Department of Health and Human Services
Food and Drug Administration
Good Clinical Practice Program, Office of the Commissioner (OC)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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Contains Nonbinding Recommendations

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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 (use of a single central IRB), especially in situations where centralized review could improve efficiency of IRB review.

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 respective responsibilities of the central IRB and each institution's IRB, (4) recommends that IRBs have procedures for implementing a centralized review process, and (5) makes recommendations for a central IRB's documentation of its reviews of studies at 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).

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[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 amount of clinical research generally, the number 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] For example, sometimes the IRB at each center of a multicenter trial conducts a complete review of the protocol and informed consent. Such 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, could reduce IRB burdens and delays in the conduct of multicenter trials.

Use of a centralized IRB review process is consistent with the requirements of existing IRB regulations. Section 56.114 (21 CFR 56.114, Cooperative Research) provides that, "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] An IRB that is at a different location from the research site can review the research, 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 and the ability to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice (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 consortium, *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] *Federal Register*, Vol. 40, pp. 47688, 47700, August 14, 1979.

[8] *Federal Register*, Vol. 46, pp. 8958, 8970, January 27, 1981.

A centralized IRB review process involves an agreement under which multiple study sites in a multicenter trial rely in whole or in part on the review of an IRB ***other*** than the IRB affiliated with the research site. Because the goal of the centralized process is to increase efficiency and decrease duplicative efforts that do not contribute to meaningful human subject protection, it will usually be preferable that a central IRB take responsibility for all aspects of IRB review at each site participating in the centralized review process. Other approaches may be appropriate as well. For example, an institution may permit a central IRB to be entirely responsible for initial and continuing review of a study, or apportion IRB review responsibilities between the central IRB and its own IRB.

III. ROLES IN ENSURING IRB REVIEW

The following sections describe the roles and responsibilities of the principal parties as they relate to a centralized IRB review process.

A. Institution

Under 21 CFR 56.114, institutions that participate in multicenter studies can use joint review, rely on the review of another qualified IRB, or establish other arrangements aimed at reducing duplicative efforts. For example, the decision could be made in a multicenter trial to rely primarily on the review of a central IRB while establishing an agreement that all site-specific IRBs will review their informed consent documents for local concerns. Institutions should develop policies for determining when and which studies conducted in the institution would be appropriate for centralized review and how a centralized review would be conducted for such studies.

B. Institution's IRB

An *institution's IRB* is the IRB designated or formed by an institution for the purpose of reviewing research conducted at the institution or with institutional support. For multicenter studies, an institution's IRB can serve as a central IRB; an institution's IRB can rely on the review of a centralized IRB (in whole or in part) in place of its own IRB review of the study; or it can conduct its own review of the study. The institution's policies will dictate under what circumstances the institution's IRB can participate in a centralized review process and the role of the institution's IRB in that process.

C. Sponsor

For studies conducted under an IND, 21 CFR part 312 provides that a *sponsor* is responsible for obtaining a commitment from each investigator that he or she will ensure that requirements in part 56 relating to IRB review and approval are met with respect to the research conducted by the 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.

D. 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 (21 CFR 312.53(c)(1)(vi)(d); 312.66). If the investigator is conducting clinical research as part of a multicenter study at an institution with its own IRB and is subject to the policies of that institution, those policies would dictate how the investigator will ensure IRB review. Those policies may provide that the investigator's responsibility can be met by ensuring review through a centralized IRB review, through the institution's IRB, or through apportionment of IRB review responsibilities between a centralized IRB and the institution's IRB.

E. Central IRB

For multicenter studies, the *central IRB* is the IRB that conducts reviews on behalf of all study sites that agree to participate in the centralized review process. For sites at institutions that have an IRB that would ordinarily review research conducted at the site, the central IRB should reach agreement with the individual institutions participating in centralized review and those institutions' IRBs about how to apportion the review responsibilities between local IRBs and the central IRB (21 CFR 56.114).

IV. ADDRESSING LOCAL ASPECTS OF IRB REVIEW

The implementation of a centralized IRB review process involves addressing a number of issues related to the communities where the research will take place. 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 was 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 members 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 its 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

[9] *Federal Register,* Vol. 44, p. 47699, August 14, 1979, and *Federal Register,* Vol. 43, p. 56174, November 30, 1978.

[10] *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 other 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 communities from which research subjects will be drawn.

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:

- Provision of relevant local information to the central IRB in writing by individuals or organizations familiar with the local community, institution, and/or 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.[12] IRB meeting minutes or other records should document how relevant community issues were considered in the review (21 CFR 56.115(a)) (see section V).

V. IRB RECORDS — DOCUMENTING AGREEMENTS AND PROCEDURES

IRBs and institutions are required to prepare and maintain adequate documentation of IRB activities (21 CFR 56.115(a)). IRBs are also required to follow written procedures for the conduct of initial and continuing review of clinical research and for reporting their findings and actions to the investigator and the institution (21 CFR section 56.108(a), 56.115(a)(6)). The following recommendations should help IRBs fulfill these requirements.

A. Documenting Agreements

If an institution, its IRB, and a central IRB agree (under 21 CFR 56.114) to participate in a centralized IRB review process, they should document that action in an agreement signed by the parties. IRBs should report this action to the investigator and the institution, for example, by providing copies of the agreement to the investigator, and the institution.[13] If the agreement

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[11] *Federal Register*, Vol. 46, p. 8966, January 27, 1981

[12] Guidance issued by the Department of Health and Human Services, Office of Human Research Protections (OHRP) (*IRB Knowledge of Local Research Context*) discusses mechanisms for ensuring adequate consideration of local factors by IRBs in review of clinical research that is supported by DHHS funding. Although the guidance applies only to DHHS funded research, it may be also helpful to off-site IRBs seeking to provide meaningful consideration of relevant local factors for non-DHHS funded clinical research.

[13] When research covered by a Federal wide 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

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.

B. Written Procedures

When an institution and an institution's IRB rely on review by a central IRB, both IRBs must have written procedures in place to implement the centralized IRB review process (21 CFR 56.108, 56.114). For example, procedures should address the following:

- How the institution's IRB determines that the central IRB is qualified to review research conducted at the institution
- How the central IRB intends to communicate with relevant institutions, the institutions' IRBs, and investigators regarding its review
- How the central IRB ensures that it provides meaningful consideration of relevant local factors for communities from which research subjects will be drawn (see Section IV)
- How the central IRB assesses the ability 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)

When an institution, an institution's IRB, and a central IRB agree to apportion IRB review responsibilities between the two IRBs, each IRB must have written procedures describing how it implements its responsibilities under the agreement (21 CFR 56.108, 56.115(a)(6)).

VI. USING A CENTRAL IRB AT UNAFFILIATED SITES

At clinical sites that are not already affiliated with an IRB, investigators and sponsors typically rely on the review and oversight of a central IRB. In this situation, the central IRB should document in meeting minutes or other records how it considered relevant local factors for the various communities from which research subjects are to be drawn (see Section IV). The central IRB must also document its action in agreeing to conduct IRB review for the site (21 CFR 56.115) and must have written procedures in place that describe how it will perform its initial and continuing review responsibilities at remote sites (21 CFR 56.108, 56.115(a)(6)) (see Section V).

46.103(b)(2)). Procedures for respective responsibilities for IRB review activities must be documented (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 useful to allocate responsibilities between IRBs, or the institutions may develop their own agreement.

VII. 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. Trial in Which Multiple Sites Rely on a Central IRB

The primary model contemplated by this guidance is a centralized IRB review process used 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 rely on all or some of the review findings of the central IRB, or could decline to participate in a centralized IRB review (i.e., do their own complete review). Study sites not already affiliated with an IRB would rely on a central IRB for all IRB review responsibilities.

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

A central IRB can be formed to review multicenter trials in a therapeutic category. For example, 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.[14]

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.

VIII. CONCLUSION

The Agency hopes that sponsors, institutions, institutional review boards (IRBs), and clinical investigators involved in multicenter clinical research will consider the use of a single central IRB (centralized IRB review process), especially if using centralized review could improve the efficiency of IRB review.

[14] See http://www.ncicirb.org/Div_Responsibilities1.pdf.