Use of Central IRBs for Multicenter Clinical Trials

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Background

Maximizing the efficiency of multicenter clinical trials so they can provide high-quality evidence to answer important medical questions is an important public health interest.

To improve the efficiency of conducting multicenter clinical trials in the United States, the Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), and the Department of Health and Human Services (DHHS) support the use of central IRBs.

Despite this support, research institutions differ in their willingness to defer to centralized IRB review.

Objective

To facilitate the ethical and efficient conduct of multicenter trials, the Clinical Trials Transformation Initiative (CTTI) supported this project to:

- Determine the barriers to using central IRBs for multicenter clinical trials in the United States,
- Formulate solutions to overcome these barriers,
- Obtain feedback on the proposed solutions from stakeholders at diverse US research institutions, and
- Develop recommendations for implementing these solutions.

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Methods

1. Identify current perceptions of the barriers to central IRB review and formulate potential solutions to overcome these barriers (see Table).

   Literature Review

   We noted barriers from the 33 peer-reviewed journal articles that we found on the use of central IRBs for multicenter trials in the U.S.

   Expert Discussions

   We held a series of group and individual discussions with 43 experts, including representatives from institutional, federal, and commercial IRBs, industry, and regulatory agencies to refine the list of barriers and to generate solutions to remove them.

2. Obtain feedback on proposed solutions

   Stakeholder Interviews

   We interviewed 25 stakeholders at 6 diverse research institutions that have their own IRB and do not routinely use central IRBs. Stakeholders included:

   - ✓ IRB chair,
   - ✓ IRB administrator or manager,
   - ✓ Institutional general counsel,
   - ✓ Vice dean for research,
   - ✓ Director of clinical trials, or
   - ✓ Others responsible for making decisions regarding the use of outside IRBs.

3. Refine the solutions & develop policy recommendations

   Expert Meeting

   This 2-day working meeting in April, 2012 included 47 representatives from government and industry sponsors of clinical research, FDA, OHRP, academic and non-academic research institutions, commercial IRBs, and patient advocacy groups.

Barrier	Potential Solutions
Feasibility of working with multiple outside IRBs, each requiring different forms and/or electronic systems to submit a protocol	Identify standard data elements to facilitate review and reporting across disparate systems.
Loss of revenue generated from fees for institutional IRB review of studies with commercial sponsors	Charge an administrative fee for institutional responsibilities. (Institutions may need to find a new way to cover fixed costs for the IRB for non-sponsored activities.)
Concern about regulatory liability in the event of noncompliance	OHRP policy is to take action against the IRB of record as opposed to participating sites for noncompliance with regulations.
Concern about legal liability in the event of litigation secondary to errors, omissions, or negligence of an IRB not directly affiliated with the institution conducting research	Establish liability protections through a well-defined communication plan and standard contracts with the outside IRB**. CTTI has developed a guide to support communication and contractual relationships between institutions and central IRBs.**
Quality of review, such as missing important human subject protections issues without redundant review, caliber/expertise of reviewers, and insufficient time spent on protocols	Conduct standardized tests of IRBs to demonstrate quality (eg, send a standardized protocol to an outside IRB and the local IRB to compare results). Note: Evaluating review quality is hampered without an agreed way to measure it.
Potential loss of local context	In a well-defined relationship, the local institution retains authority to decide whether to participate in a study or to limit an investigator's involvement. Consent forms can have a core that is the same for all sites, and a section customizable to the institution that addresses relevant state laws or institutional concerns regarding (e.g., compensation for research-related injury, institutional contact information, surrogate consent, and costs of participation).

Abbreviations: IRB, institutional review board; OHRP, Office of Human Research Protections

Results & Discussion

Need to clarify terms

Confusion abounds about the term "central IRB." We defined a central IRB as a properly constituted IRB to which sites cede all regulatory responsibility for scientific oversight and integrity of the protocol from initial review to termination of the research, including review of informed consent. Or, briefly, **a single IRB of record for a multicenter clinical trial.**

Decoupling institutional and ethical review responsibilities

Many of the perceived barriers to using central IRBs arise from the fact that most (or all) of the tasks related to protecting the institution from risk are often coordinated through the institution's IRB office, which seems to have altered perceptions of what is entailed in the ethical review of research.

This conflating of institutional responsibilities with the ethical review responsibilities of the IRB leads to confusion about how institutional responsibilities would be handled in the context of a central IRB review. There is a need for concrete tools to help research institutions separate institutional responsibilities from ethical responsibilities required of the IRB. We developed one such tool, a document that delineates these responsibilities and how they might be assigned to each entity or both entities.

Level of comfort and trust with central IRB review

Many institutional stakeholders expressed discomfort with an external entity handling the ethical review and oversight of a multicenter protocol, which seemed to be related to previous experiences with outside IRBs. What is still needed is experience with, not just knowledge about, using the central IRB model.

Addressing concerns about local context

Institutions and central IRBs need a detailed communication plan that includes a way to share information about local issues (site, investigators, etc.).

The regulatory positions of OHRP and FDA specify their position, that an outside, central IRB could reflect local context issues satisfactorily.

Recommendations

The Clinical Trials Transformation Initiative (CTTI) recommends using a central IRB (defined as a single IRB of record for all sites) to improve the quality and efficiency of multicenter clinical trials.

To address blurred distinctions between responsibilities for ethics review and other institutional obligations, CTTI recommends that sites and IRBs use a CTTI-developed guide to support communication and contractual relationships between institutions and a central IRB.

CTTI recommends that sponsors in a position to require the use of central IRB review for multisite trial networks should do so in order for relevant stakeholders to gain experience with central IRB review. The resulting experiences may foster greater comfort and trust with the central IRB model.

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