

CENTRAL INSTITUTIONAL REVIEW BOARDS

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INTRODUCTION

Clinical research involving human participants is critical for the development of patient treatments for a large spectrum of diseases, including many endocrine disorders for which specialized treatments have yet to be elucidated. To conduct research with human participants, clinical investigators must apply for approval by Institutional Review Boards (IRBs). When a study utilizes facilities spanning multiple institutions, each institution's individual IRB typically reviews and approves the research proposal, unless a central IRB (CIRB) is employed. When multiple, local IRBs are used, the inherent variability in the requirements and review processes among institutions frequently results in a large increase in application processing time and delays in protocol approval, hindering the overall progress of the study. In addition, individual IRBs may request different and sometimes conflicting changes to study design, necessitating re-review by other IRBs.

There is evidence that multiple independent reviews do not promote superior participant safety or higher ethical standards for clinical research¹. In an effort to streamline the IRB approval process for endocrine-related studies and others, improve consistency, and assure accountability, the use of central IRBs has been suggested for multicenter clinical research studies.

BACKGROUND

IRB approval is required of all clinical studies involving human participants. IRB review is meant to evaluate the ethical implications of the proposed research and to promote the welfare of all study participants. A significant portion of IRB guidelines involves oversight of the process of informed consent of prospective research study participants and emphasizes full disclosure of information to the potential participant. In addition, the safety and efficacy of test agents and the scientific merit of the project are considered.

The need for IRBs was highlighted by several high profile instances of flagrant human rights abuses in the mid-1900s. Among them was the Tuskegee Syphilis

Study, conducted in Tuskegee, Alabama, involving the collection and study of blood samples obtained from economically or educationally deprived African-American men who were never informed that they had syphilis and were never offered treatment. Such infamous cases led to the development of the National Research Act of 1974, and in the US, IRBs are now governed by Title 45 of the Code of Federal Regulations (<http://ohsr.od.nih.gov/guidelines/45cfr46.html>) with the intention of protecting the rights of study participants and providing full disclosure of medical information related to participation in the study.

Individual institutions are responsible for maintaining IRBs that uphold national, state, and local laws along with institutional policies regarding the safety of human research subjects. Recently, commercial, for-profit central IRBs (CIRBs), independent of specific institutions, have gained traction in an effort to provide appropriate protection for study participants with increased efficiency and consistency across institutions. CIRBs typically conduct both the initial and continuing review of applications and in some cases, CIRBs work in conjunction with individual local IRBs to ensure conformity with local requirements. In other cases, the local IRB cedes authority to the CIRB by written agreement.

CONSIDERATIONS

The IRB review process, which was initially set up to protect research participants, has in some cases become increasingly sidetracked by local bias, conflict of interest², and increasing institutional demands that distract them from their primary purpose. Instances of non-compliance on the part of individual investigators, along with some high-profile episodes of IRB ineffectiveness^{3,4} have led to institutional concern about liability and decreased focus on the basic elements of IRB review. Many institutions have reacted to these concerns with a proliferation of paperwork required of the IRB to document compliance.

The number of IRB approvals necessary to proceed with a multi-site study that utilizes each site's IRB may

involve waiting periods of a year or more as each institution reviews the application and has a separate dialogue with each site's principal investigator. This process delays the progress of the study, discourages the investigator(s) involved, and is highly cost-ineffective¹. Furthermore, while it is not the purpose of IRBs to review the scientific approach of the proposed research per se, it is not uncommon for IRBs to undertake some level of scientific review⁵, thereby further delaying the time to approval. Most studies evaluated by IRBs have been previously peer-reviewed and deemed to be sound. Though it is appropriate and ethical for an IRB to object to poorly conceived scientific premises, it is unnecessarily cumbersome and duplicative for an IRB to engage in extensive review of the minutiae of a protocol, especially if the proposal has already undergone rigorous peer review. Moreover, different IRBs at different institutions may approve or disapprove portions of the same research project according to their own internal guidelines, completely halting progress and/or introducing inconsistencies into protocol implementation that reduce the scientific value of the study and unwittingly create flaws in the study design.

A central IRB is able to incorporate the major concerns that institutions have about liability risk and conflict-of-interest and may better facilitate the progress of multicenter clinical research studies. Several successful CIRBs are already in place, including CIRBs facilitated by the Veterans Administration, National Cancer Institute, and independent committees such as the Western, Independent, and Sterling IRBs.

The emerging emphasis on interdisciplinary and team research, as evidenced by the nationwide establishment of Clinical and Translational Research Service Awards, promotes multi-institutional collaboration, yet the establishment of efficient and effective collaborative research can only be realized with IRB consensus. Interdisciplinary research is critical to elucidate the mechanisms of a wide spectrum of endocrine disorders and diseases and to identify effective treatments for them. Increased acceptance, accessibility and use of central IRBs could facilitate progress in clinical studies without reducing patient protection.

POSITIONS

The Endocrine Society views patient safety as a top priority in both the implementation of clinical studies and in the practice of patient care. The Society strongly encourages the utilization of CIRBs for multicenter clinical studies in order to advance clinical research and improve patient care while maintaining the highest patient safety standards. Steps must be taken by institutions, investigators and funding agencies to promote the use of CIRBs and to more readily facilitate their use. The Endocrine Society supports the following positions:

- The Association for the Accreditation of Human Research Protection Programs (AAHRPP) or some other such entity should enforce a certification process to ensure the quality and compliance of central IRBs.
- Institutions should establish written agreements with certified central IRBs and facilitate their use for investigators conducting multicenter studies.
- The Office for Human Research Protections should issue guidance on the implications of using CIRBs and should provide assurance that users of CIRBs are protected from additional liability.
- Professional organizations should advocate for the use of CIRBs.
- The National Institutes of Health should encourage investigators to prospectively include the use of CIRBs in investigator-initiated proposals involving multi-site studies. In addition, NIH should require the use of CIRBs for multi-site studies it solicits and should explicitly include this requirement in all future grant solicitations.

¹Menikoff, J. The paradoxical problem with multiple-IRB reviews. *New Engl J Med* 2010; 363:1591-1593.

²McNeil, C. Central IRBs: why are some institutions reluctant to sign on? *J Natl Cancer Inst* 2005; 97: 953-955.

³Stolberg, Sheryl Gay. The biotech death of Jesse Gelsinger. *The New York Times*; November 28, 1999.

⁴Bor, Jonathan and Gary Cohn. Research volunteer dies in Hopkins asthma study. *The Baltimore Sun*; June 14, 2001.

⁵Gunsalus, CK et al. Mission creep in the IRB world. *Science* 2006; 312:1441.