

CENTRAL INSTITUTIONAL REVIEW BOARDS

INTRODUCTION

Clinical research involving human participants is critical to develop treatments for a broad spectrum of diseases, including many endocrine disorders lacking specialized treatments. To conduct research with human participants, clinical investigators must apply for approval by Institutional Review Boards (IRBs) which ensure that human subjects research is conducted in accordance with applicable ethical and legal guidelines. When a study utilizes facilities spanning multiple institutions, each institution's individual IRB typically reviews and approves the research proposal, unless a single IRB of record, referred to herein as a Federated IRB (FIRB) 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 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 nor higher ethical standards for clinical research¹. To streamline the IRB approval process, improve consistency, and assure accountability, the US National Institutes of Health (NIH) and other federal agencies have proposed policies and guidelines to support the use of FIRBs for multicenter clinical studies.

BACKGROUND

Approval or explicit exemption by the IRB 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 participants and emphasizes full disclosure of information to the potential participant. The IRB considers safety and efficacy of test agents and interventions as well as the scientific merit of the project.

Flagrant human rights abuses in the mid-20th century highlighted the need for IRBs due to the lack of appropriate protections for human participants in research. In several high-profile cases, patients were unethically subjected to serious experimental risks without informed consent. These patients experienced severe harms, and even death, as a result of participating in clinical research². Infamous examples like the Tuskegee Study of Untreated Syphilis prompted the National Research Act of 1974. 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 explicit intent to protect the rights of research participants and to provide full disclosure of medical information related to study participation.

Individual institutions are responsible for maintaining IRBs that uphold national, state, and local laws, along with institutional policies regarding the safety of human research participants. Commercial, for-profit FIRBs independent of specific institutions have recently gained traction to protect study participants with increased efficiency and consistency across institutions. Often called "Central IRBs", these FIRBs typically conduct both the initial and continuing review of applications and in some cases, FIRBs work in conjunction with individual local IRBs to ensure conformity with local requirements. In other cases, the local IRB cedes authority to the FIRB by written agreement.

Recognizing that the use of FIRBs can reduce administrative burdens while maintaining or even enhancing protections for research subjects in multi-center studies, the NIH proposed a draft policy to promote the use of a single IRB of record for domestic sites of multi-center studies funded by the NIH³. In 2015, the US Department of Health and Human Services (DHHS) proposed updates to the Common Rule, a set of ethical rules that apply broadly to Federal Agencies conducting human subjects research⁴. Included in the update is the requirement to use a single IRB of record for most multi-center research studies.

2055 L Street NW
Suite 600
Washington, DC
20036

T. 202.971.3636
F. 202.736.9705

endocrine.org

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

² Kim, WO. Institutional review board (IRB) and ethical issues in clinical research. *Korean J Anesthesiol*. 2012;62:3-12.

³ NOT-OD-15-026: Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research. <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html>. Accessed October 14, 2015.

⁴ <http://www.hhs.gov/news/press/2015pres/09/20150902b.html>. Accessed October 14, 2015.



POSITION STATEMENT

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 interest^v, and increasing institutional demands that distract IRBs from their primary purpose. Instances of non-compliance by individual investigators, along with some high-profile episodes of IRB ineffectiveness^{vi,vii} have led to institutional concerns 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 from 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 delay enrollment by a year or more, as each institution reviews the application and has a separate dialogue with each site's principal investigator. 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 review^{viii}, further delaying the time to approval. Most studies evaluated by IRBs have been previously deemed to be sound by peer review. 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. These variations reduce the scientific value of the study and create unintentional flaws in the study design. This process delays study progress, discourages the investigator(s), and introduces inefficiencies and inconsistencies that reduce the cost effectiveness of research^{ix}.

Previous announcements by federal agencies — including the Food and Drug Administration, Office of Human Research Protections, and the NIH — have strongly supported the use of FIRBs for multi-center studies. Widespread adoption of FIRBs in the US has not yet been achieved due to concerns about regulatory or legal liability and other perceived barriers^x. The Endocrine Society is therefore encouraged by the new NIH and DHHS proposals to require the use of FIRBs for multi-site research. A single Federated (or

central) IRB of record can address major institutional about liability, risk, and conflict-of interest and may better facilitate the progress of multicenter clinical research studies.

It will be critical to ensure that new policies to mandate FIRBs are implemented effectively and with limited disruption to new or ongoing clinical studies. Legal requirements may differ between local, national, and international sites of large clinical trials. Appropriate guidance will therefore be needed to ensure that FIRBs are able to appropriately apply local laws, or effectively and efficiently delegate responsibility to local IRBs when necessary. Several successful FIRBs are already in place, including FIRBs facilitated by the Veterans Administration, National Cancer Institute, and independent committees such as the Western, Independent, and Sterling IRBs. Furthermore, international models exist for centralized review of ethical issues surrounding human subjects research. These and other models for FIRBs could serve as case studies for institutions and agencies as they implement policies to support the use of single IRBs for multi-center studies^{xi}.

POSITIONS

The Endocrine Society views patient safety as a top priority to implement both good research practice and clinical practice.

The Endocrine Society supports NIH and DHHS efforts to promote the utilization of federated IRBs for multi-center clinical studies in order to advance clinical research and improve patient care while maintaining the highest safety standards for research participants. However, additional steps must be taken by institutions, investigators, and federal agencies to facilitate the use of FIRBs. The Endocrine Society supports the following positions:

- The Association for the Accreditation of Human Research Protection Programs (AAHRPP) or a similar entity should enforce a certification process to ensure the quality and compliance of FIRBs.
- Building on the model established by the National Cancer Institute Central IRB^{xii}, NIH and other sponsors of human subject research should establish and fund institute or agency specific FIRBs for all multi-center trials.
- Federal agencies should issue detailed and explicit guidance that recognizes the different models for FIRBs, clarifies institutional liability, and alleviates accountability concerns.

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

^{vi} Stolberg, Sheryl Gay. The biotech death of Jesse Gelsinger. *The New York Times*; November 28, 1999.

^{vii} Bor, Jonathan and Cohn, G. Research volunteer dies in Hopkins asthma study. *The Baltimore Sun*; June 14, 2001.

^{viii} Gunsalus, CK et al. Mission creep in the IRB world. *Science* 2006;312:1441.

^{ix} Kano, M et al. Costs and inconsistencies in US IRB review of low-risk medical education research. *Med Educ* 2015;49:634-637.

^x Flynn KE, et al. Using central IRBs for multicenter clinical trials in the United States. *PLoS ONE* 2013;8:e54999.

^{xi} Check, DK et al. Use of central institutional review boards for multicenter clinical trials in the United States: a review of the literature. *Clinical Trials* 2013;10:560-7.

^{xii} NIH NOT-OD-15-026.



POSITION STATEMENT

- Institutions and agencies should conduct research to compare the effectiveness of different FIRB models for various multi-center studies in the US and worldwide. Revised guidance should disseminate and encourage best practices.
- Researchers, institutions, and professional societies should work to develop effective international practices and models that facilitate the use of FIRBs for international multi-center studies.