HHS Public Access

Author manuscript

Ethics Hum Res. Author manuscript; available in PMC 2020 May 19.

Published in final edited form as:

Ethics Hum Res. 2019 May ; 41(3): 23–28. doi:10.1002/eahr.500016.

Implementing a Central IRB Model in a Multicenter Research Network

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Abstract

Implementing the National Institutes of Health's (NIH's) new single institutional review board (IRB) policy has caused a paradigm shift in IRB review across the country. IRBs and human research protection programs are looking more closely at their processes for ceding review and developing procedures to handle local review when relying on a single IRB. This article describes an NIH-funded network that proactively instituted a central IRB (CIRB) in 2012, anticipating the NIH future mandate. Lessons learned are described. There was a steep learning curve for IRBs and participating sites. IRB submission workload burden shifted from study teams to the data coordinating center, which created new workflow challenges, especially preparing hundreds of consent documents centrally. Despite difficulties encountered with CIRB review, this network is now fully functioning under a CIRB model. Further review and experience are needed to determine whether this shift in IRB review has eliminated duplicative review or regulatory burden from study teams.

Keywords

institutional review board; single IRB; central IRB; research network; local review; human research protection program; NIH

In the past few decades, multicenter trials have replaced single-center studies as the norm, mainly due to the scientific rigor and external validity required to support widespread changes in clinical practice.[1] Improving clinical trial efficiency has been a common goal among research organizations, and much attention has been specifically focused on multicenter clinical trial start-up periods.

The use of a single or central institutional review board (IRB) has been posited as one method for increasing multicenter trial efficiency during the start-up phase. According to the Office of Scientific Policy at the National Institutes of Health (NIH), a single IRB is the reviewing IRB for a given study, whereas a central IRB (CIRB) is the reviewing IRB designated as the reviewing IRB for a group of studies (e.g., for a research network).[2] For the purposes of this article, CIRB review of "multicenter" research refers to CIRB review of all studies that would be implemented across a network of many sites, as opposed to a single study carried out at more than one site. On June 21, 2016, the NIH released what is, at the time of this writing, their most recent policy on the use of a single IRB for multicenter research.[3] Newly funded investigators of multicenter studies are now expected to rely on a single IRB or CIRB to carry out the functions of IRB review of human subjects research as required by the Common Rule.[4] However, little guidance is available in the peer-reviewed literature on use of CIRBs for multicenter trials.[5]

Centralization of the IRB process requires resources for managing submission to the CIRB while also meeting the remaining human research protection program (HRPP) review requirements at each participating site. This may be achieved through a central administrative group or data coordinating center that acts as a liaison between the CIRB and the participating sites. This article will describe the issues and challenges of creating and implementing a CIRB model for a federally funded research network, discuss the efficiency of the CIRB model compared to the traditional multiple-IRB model, and present the lessons learned through this process. Our experience with these issues and challenges may help other IRBs as they participate in CIRB relationships, as either a CIRB or relying site.

THE CIRB DEVELOPMENT PROCESS

Anticipating the change in NIH policy toward use of a CIRB in multicenter research, the Collaborative Pediatric Critical Care Research Network (CPCCRN) and the University of Utah IRB (UUIRB) partnered in 2012 to develop a CIRB model. The UUIRB was deemed the CIRB for the CPCCRN. Together, the CPCCRN data coordinating center and CIRB developed a standardized CIRB procedure and workflow for use in all research performed within the network.

CPCCRN, which is supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, consists of seven academic clinical sites across the United States and a data coordinating center at the University of Utah. The network seeks to reduce morbidity and mortality in pediatric critical illness and injury and to establish a framework for developing the scientific basis for pediatric critical care practice. These goals cannot be achieved without the support of collaborative clinical trials otherwise impractical in single

institutions.[6] The data coordinating center coordinates all aspects of network studies, including preparing the CIRB submissions on behalf of the network.

The University of Utah HRPP, which includes the UUIRB, is a complex biomedical and social behavioral enterprise with more than 6,000 active studies. The Utah HRPP has maintained full accreditation from the Association for the Accreditation of Human Research Protection Programs since 2007. The Utah HRPP adopted a web-based system for study management in 2006.

Our process for creating and implementing a CIRB model evolved over a four-year period and was standardized into a working guideline for data coordinating center project managers and site personnel. The guideline outlines five major components in the clinical study start-up process using a CIRB model: (1) reliance agreement development and negotiation, (2) local review for site-level HRPP requirements (referred to in this article as “HRP review”), (3) consent and authorization document development, (4) submission and processing of CIRB applications, and (5) tracking lessons learned.

Reliance agreement development and negotiation

A reliance agreement between each CPCCRN institution and the University of Utah was necessary to allow multicenter reliance on the CIRB. The CIRB developed a general reliance agreement that covered key components for ceding IRB review, including all criteria for IRB approval described in the Common Rule (including consent documentation), HIPAA authorization language and documentation, and HIPAA determinations. The reliance agreement allowed CPCCRN sites to incorporate site-specific consent and authorization language into each study’s consent document. The reliance agreement required that each participating site’s HRPP maintain responsibility for the following: verification of investigator and study team qualifications and training; site-specific ancillary reviews, such as a radiation safety review, biosafety review, and financial conflict-of-interest review and management; verification of compliance with state law and institutional policy; and oversight of research compliance at the site.

In the summer of 2012, reliance agreement negotiations were initiated, with the first agreement signed in November 2012. By February 2015, 10 sites had signed the agreement, including 3 sites outside of the network that were participating in network studies. Execution of these agreements required more time than originally anticipated—three years to bring all sites onboard. All sites required review by their institutional legal departments prior to executing the agreement. Some institutions required negotiations to the language, which resulted in time-consuming back-and-forth communications. Participating institutions were slow to sign on because use of a CIRB was not required by the NIH at the time. One CPCCRN site declined participation in the CIRB model, waiting until using a CIRB became mandatory via NIH policy.

Local review for site-level HRPP requirements (HRP review)

HRP review describes the non-IRB components of site-level review that are required under the reliance agreement. Each site was expected to have a policy and process for performing HRP review requirements and communicating the results to data coordinating center staff

members, who then forwarded the information to the CIRB for consideration. The participating study team at each CPCCRN site initiated the HRP review with their institution's HRPP. Depending on site preferences and policies, this began at different times during the CIRB application submission period. Ideally, HRP review was initiated as early as possible and in tandem with the main CIRB application submission. In many instances, however, the CPCCRN sites reported that they were not willing to begin HRP review until initial CIRB approval was completed.

Throughout the implementation process, it was discovered via network meetings and teleconferences that the content of HRP review varied greatly. Generally, sites did not appreciate the differences between the IRB functions and the HRPP functions. Some sites' HRPPs insisted on performing IRB and HRP review, which resulted in duplicative effort. Other sites focused solely on their responsibilities as a relying IRB and performed only the HRP reviews.

Development of consent and authorization documents

Ultimately, uniform consent and authorization templates were developed for all studies conducted through CPCCRN. These templates were approved by the CIRB and the relying IRBs. However, getting to this point required several failed attempts at trying to develop site-specific templates. There were multiple back-and-forth revisions between the data coordinating center and participating sites every time a new study started.

First, the data coordinating center provided a generic editable consent template to the sites and asked them to insert their required local language. This posed a challenge because most sites changed formatting and elements in the main study sections, which resulted in multiple versions of the main study consent document. Thus, reviewers noted inconsistencies in the main study language between each site-specific document. These inconsistencies were consequential, creating problems for the data coordinating center and IRB because the uniform consent study-specific language was no longer consistent between sites.

The next method tried was locking the study-specific parts of the consent document so that only site-specific areas could be edited. Again, the data coordinating center met challenges with the sites' unwillingness to accept language in the locked areas. Study teams were resistant to accepting the locked language because, in their view, the language would not be approvable by their IRB.

The final solution met the least amount of resistance. To alleviate all the back-and-forth review and edits, the data coordinating center decided to create generic consent and authorization templates. Network leadership was approached via teleconference for their input on making consent templates for each site. Once leadership approval was gained, the data coordinating center produced the templates and then asked the principal investigators (PIs) and research coordinators to provide site-specific language. Because of differences in state law and institutional policies, some consent language, such as research-related-injury statements, person-to-contact language, and HIPAA-authorization language, must be site specific. The data coordinating center collected the necessary local language, as well as branding and formatting requirements, from each site and merged the site-specific

formatting and language with the uniform consent and authorization templates. Both the CIRB and the participating site IRB had to approve these templates, which were maintained online. This process took more than a year to accomplish. Thereafter, for all new CPCCRN studies, the data coordinating center used the approved generic templates and inserted the study-specific language prior to submission to the CIRB. This process dramatically reduced consent document preparation time for data coordinating center project managers, as it reduced the back-and-forth review between the data coordinating center and participating sites. Although this solution worked well for this small network in the short term, it is not sustainable as a long-term solution since these templates need to be maintained and kept up to date. New solutions are required for this critical element of developing consent documents for large multicenter studies.

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Submission and processing of CIRB applications

The data coordinating center PI submitted each study application to the CIRB on behalf of the PI and all CPCCRN sites. The study application included information about each of the participating sites as well as applicable site-specific documents and consent forms. Any site that was ready for study start-up at the time of initial CIRB submission was included; remaining sites were added by amendment. The participating sites did not have access to the CIRB's electronic system, so the data coordinating center provided necessary approval documentation to the sites.

The CIRB used its standard operating procedures and reviewer checklists when performing CIRB review. Administrative staff and board members were notified when an application was submitted for CIRB review. They reviewed the online requirements for site-specific consent and authorization documents to ensure that all forms were consistent with site requirements. The study-specific uniform consent and authorization language was reviewed only once, which saved time during the review. The CIRB considered any issues that were identified during HRP review, such as those related to conflict-of-interest management plans and local policies, and ensured that the approved application and associated documents addressed any site-specific issues.

During the five years of this experiment (2012–2017), the CIRB process became more streamlined through continuous process improvement efforts at the data coordinating center and CIRB. Initial CIRB submissions are still complex and time consuming for the data coordinating center because of the number of documents that need to be prepared centrally for this pediatric network, which includes long- and short-version consent, parental permission, child and adolescent assent forms, and translated documents from all participating sites. However, study teams at the sites now report that amendments and continuing reviews submitted centrally by the data coordinating center have saved them time and effort on their end. In the future, we plan to collect the appropriate metrics, which are now being defined nationally, to evaluate effectiveness of the CIRB model.

LESSONS LEARNED

Development and implementation of a CIRB model in a research network was a monumental learning experience that provided the knowledge necessary to move forward with the new NIH policy. Among the many lessons learned are some concerning key problems and recommendations that are beneficial for others to consider when developing and implementing their own model.

The process of negotiating the reliance agreement was a challenge that took a significant amount of time to complete (a little over three years). Development of an agreement that is satisfactory to all parties consumed significant effort by the CIRB and data coordinating center teams, especially with sites that had smaller research portfolios and less IRB review experience. Use of emerging, standardized reliance agreements, such as those provided by SMART IRB (Streamlined, Multisite, Accelerated Resources for Trials IRB Reliance platform)[7] may help to improve efficiency with this process.

Another stumbling block with the reliance agreement was effectively translating its terms into the practice of submitting and reviewing a CIRB application. It can be difficult if there is not a standard mechanism for applying the terms of the agreement to the CIRB review. For example, while the CIRB has an automated electronic process to communicate investigator conflict-of-interest management to its own investigators, no such automated process exists when the investigator is from an external institution that the CIRB is covering. This requires the CIRB and participating site HRPPs to develop additional processes and workflows to ensure that they can meet the demands of the reliance agreement.

According to feedback from study sites and the data coordinating center, local review processes and timelines for site-level HRPP requirements varied extensively across CPCCRN institutions. Although some sites were comfortable with completing and providing the results of their local review to the data coordinating center while the initial CIRB application was being reviewed, other sites would not begin their local review until they received documentation of initial CIRB approval. Additionally, some institutions were able to complete their review in a few days or less, while others took several months. National efforts toward standardization of local review processes would help remedy this problem.

When determining how to incorporate local review into the CIRB model, we debated whether positive confirmation of local review completion was necessary at the data coordinating center level and/or the CIRB level. According to the terms of the reliance agreement, the participating site HRPP had responsibility for ensuring that local review items were completed and that research was compliant with federal regulation as well as state law and institutional policies. Reporting local review completion to the CIRB was not a requirement of the participating site HRPP, although the participating site HRPP was required to report limited information to the CIRB that might affect IRB approval, such as financial conflicts of interest, lack of investigator qualifications, or relevant investigator noncompliance. Ultimately, the CIRB decided that positive confirmation was not required and accountability for reportable information remained with the participating site HRPP. This approach might be pragmatic but risky, so the data coordinating center decided to

require positive confirmation for its records, as part of its role in ensuring compliance across the sites in the network.

During early implementation of the CIRB model, participating sites used the study's uniform consent and authorization template to draft their own consent and authorization documents, which often resulted in inconsistencies between site consent forms, as sites would request changes to the uniform template language. In these cases, the data coordinating center staff was required to have a multistep negotiation process with each site in order to secure approval of local language, and the CIRB was required to review each consent document to determine if the differences were approvable. As a first attempt to minimize this effort, the data coordinating center staff locked certain sections of the uniform consent template, leaving other sections editable for the sites to include local language. However, this presented new issues with formatting and did not reduce the need for lengthy back-and-forth communication, as many sites would still request changes to the locked language. As a final solution, the data coordinating center informed all sites that the majority of the uniform consent template language would not be customizable for each site, although the research-related-injury section, the person-to-contact section, and the HIPAA-authorization language would be. The data coordinating center then collected preapproved, site-specific informed consent language for these sections and merged them with the uniform consent template on a site-specific basis before submission to the CIRB. This effectively eliminated the back-and-forth communication between the sites and the data coordinating center.

The CIRB's electronic application was not originally designed with a CIRB model in mind, and therefore, informal, nonautomated processes were required to accommodate the CIRB model. For example, some application questions were applicable only to University of Utah investigators but were required by the system for CPCCRN studies even when the University of Utah was not considered a participating site. Investigators external to the University of Utah did not have direct access to the electronic system. There was no official mechanism for distinguishing sites ceding to the CIRB versus sites that decided not to cede review. The temporary, nonautomated processes allowed for the data coordinating center and CIRB to use the existing application; however, software changes and additional development were needed to broaden the capacity of the application, making it more suitable for the CIRB model.

The CPCCRN CIRB experiment demonstrated that there is a steep learning curve on the part of both the participating sites and their IRBs to implement this process. Investigators and study teams were not aware that IRB and HRPP functions are separate and distinct. In some cases, a complete duplicative review took place for a participating site IRB to give local approval. Although developing the CIRB process for this research network took years and getting up and running was painful, eventually, CIRB submission preparation and submission became easier. Even though the process has become more streamlined, it is not clear whether there will be any time savings on CIRB submissions reviewed and submitted centrally, especially until the obstacle of duplication of effort is overcome. What is clear is that academic institutions need education and training about the responsibilities of the CIRB and the participating HRPPs. Perhaps there will be savings in time and effort for

amendments and continuing renewals. In our experience, the workload simply shifted from study teams to the data coordinating center, which took over preparation of all CIRB submissions. Central creation of study consent documents is fraught with communication inefficiencies and is an area for improvement down the road. With the implementation of the new NIH single IRB policy, our experience suggests there are areas of inefficiency that are not addressed by our process and will require further study. Once sites and IRBs have overcome the learning curve of CIRB implementation, the question remains whether reliance on a CIRB for multicenter research will improve overall efficiency during a study's start-up process.

ACKNOWLEDGMENTS

We thank Marianne R. Gildea, BSN, MS, CCRC, for providing technical editing and proofreading and Melissa Bolton, MBA, CCRC, Teresa Liu, MPH, CCRP, and Mary Ann DiLiberto, BS, RN, CCRC, for providing project-specific background and data.

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