Implementing the Single Institutional Review Board Model: Lessons from the Undiagnosed Diseases Network

Kimberly Splinter1,4, Sara Chandros Hull2,3, Ingrid A. Holm4,5, Tara L. McDonough3, Anastasia L. Wise3, Rachel B. Ramoni6 and Members of the Undiagnosed Diseases Network

INTRODUCTION

In 2008, the National Institutes of Health (NIH) Undiagnosed Diseases Program (UDP)1,2 was established to provide answers for patients with conditions that had long eluded diagnosis. Based on the success of the UDP, the NIH elected to support the program’s expansion into a network of medical research centers in 2013, the Undiagnosed Diseases Network (UDN). Here we outline the steps required for implementing a single Institutional Review Board (IRB), highlighting our experience in the UDN.

ESTABLISHING A SINGLE IRB

At the time of the initial UDN funding announcements, use of a single IRB for NIH-funded multisite research projects was not a requirement. However, the announcement for the UDN clinical sites (CS FOA (RM-13-004)) cited a preference for support of a single IRB model: “the network will use a central IRB to accelerate IRB approval of network-wide protocols. Applicants and their institutions should indicate their willingness to participate in a network that uses a central IRB.” Of note, documents related to the UDN have used the terms single and central IRB interchangeably; we will use the term single IRB from this point forward, defined as “the single IRB of record for a multisite study.”

In June 2016, the NIH issued its Policy on the Use of a Single Institutional Review Board for Multi-Site Research,3 “to establish the expectation that a single IRB (siIRB) of record will be used in the ethical review of non-exempt human subjects research protocols funded by the NIH that are carried out at more than one site in the United States.” This policy was intended to address inefficiencies that have been identified with having multiple IRBs review multisite research.4 For a multisite project, IRBs at multiple institutions may request minor institution-specific changes to study documents, vary in review times, require different levels of review, and have different interpretations of the risks associated with the project. These issues can substantially increase the review time and delay study implementation. Having a single IRB means there is one process and set of procedures that all sites agree to, creating a substantially more efficient process. The notice announcing the NIH policy called for public comments on the evaluation of costs and benefits of single IRB review. In this spirit, we are sharing our experience with a single IRB model.

Work to establish a single IRB began upon award of the UDN clinical site grants in July 2014. Based on its experience overseeing the protocol for the UDP within the NIH intramural research program, the National Human Genome Research Institute (NHGRI) IRB agreed to serve as the single IRB of record for the UDN, while NHGRI continued to be an enrollment site for the protocol. Additionally, the intramural NIH oversight office was willing to modify its standard reliance agreement template to be suitable for this kind of multisite protocol.

Considerable effort was required to draft a reliance agreement and standard operating procedures (SOPs) acceptable to the ceding institutions. Institutions initially varied in how much detail they wished to include in the reliance agreement about regulatory requirements vs. policy and implementation decisions. Ultimately, the reliance agreement was written as a more streamlined document focused on responsibilities of the institutions as defined by regulations, while the SOPs detailed how various tasks associated with the oversight of human subjects research would be handled between the clinical sites, core laboratories, coordinating center (CC), and single IRB. The CC engaged an expert in reliance agreements to coordinate this process in cooperation with representatives from the single IRB and the NIH Office for Human Subjects Research Protections. This group held weekly meetings with CC representatives and NHGRI program officials to chart progress and discuss obstacles.

The institutions retained several oversight responsibilities, including review of investigator conflicts of interest and human subjects research training completion, investigation of noncompliance allegations, and Privacy Board review. HIPAA-covered entities, like many of the institutions relying on the single IRB, are required to follow HIPAA
regulations. Local IRBs can serve as Privacy Boards to review and address reports of HIPAA-related problems, such as the use of protected health information (PHI) without appropriate authorization. The decision to have institutional Privacy Boards provide oversight, rather than joining the functions of the single IRB and Privacy Board, was bolstered by the fact that the NIH intramural research program is not a HIPAA-covered entity.

During this time, the Principal Investigator (PI) at the NIH began to draft the protocol and consent forms with members of the CC. Throughout this process, stakeholders from the institutions were engaged and a number of decisions were made in response to institution-specific preferences. For instance, the network opted to have age-specific assent forms, as well as separate consent and assent forms for full participants and family member participants. Model informed consent and assent forms were created with limited sections that could be customized by the institutions. These sections included letterhead, privacy language, signature block, and institutionally required boilerplate, like language regarding compensation for research-related injury.

Once the protocol and accompanying documents were drafted, the single IRB conducted two prereviews prior to a full board meeting. At the full board meeting, the study was determined to involve minimal risk to participants. In total, the process took 9 months, which was longer and more resource-intensive than planned. A timeline with events related to the single IRB submission, review, and implementation is presented in Figure 1. Although the initial participating institutions scrutinized the reliance agreement and UDN SOPs very carefully and requested revisions, institutions added at later dates accepted the reliance agreement and SOPs without revisions. This was fortunate, as any changes would have meant re-executing the agreements with all institutions.

**SINGLE IRB MODEL IN PRACTICE**

Eighteen UDN institutions currently rely upon the single IRB at the NHGRI. A CC-based liaison supports UDN IRB-related efforts and has weekly telephone calls with representatives of the single IRB to ensure that the process runs smoothly. During the biweekly UDN Steering Committee meetings, the CC IRB liaison provides a summary of the IRB-approved amendments with the full UDN membership. A diagram of the UDN single IRB communication network is presented in Figure 2.

Over the course of 2 years, 60 amendments were submitted and approved by the single IRB. UDN amendments are submitted on a schedule to reduce the number of total submissions; study-wide amendments are submitted on a monthly basis and site-specific amendments are submitted on a biweekly basis. Study-wide amendments, like consent form modifications, impact the protocol at all sites, while site-specific amendments, like personnel changes, only impact one site. Multiple site-specific and study-wide amendments can be included in a single IRB submission in the NHGRI IRB electronic Protocol Tracking and Management System (PTMS). The CC IRB liaison adds amendments PTMS, which are formally submitted to the single IRB by the PI at the NIH. To obtain access to PTMS, the CC IRB liaison had to obtain NIH Guest Researcher status. The single IRB communicates the results of amendment review to the PI at the NIH, the CC IRB liaison, the clinical site and core PIs, and the Institutional Designees. The CC IRB liaison then communicates the results of the review to the clinical site and core site coordinators and makes the approved amendment documents available in a centralized document storage system.

Unanticipated problems, including adverse events, protocol violations, and noncompliance, are reported by clinical site and core PIs to the CC IRB liaison and PI at the NIH. The standard problem report form used by the NIH human research protection program is submitted, with all supporting documentation, to the NHGRI IRB PTMS. Following review, the single IRB communicates the results of the review to the PI at the NIH, the CC IRB liaison, the clinical site or core PI, the Institutional Designee, and in some cases, the Institutional Official.

In addition to improving operational efficiency, we have found that having a single protocol reduces confusion about what is covered or “allowed” under the protocol at each institution, although there have been circumstances in which the single and local IRB policies differ. For example, performing skin biopsies for research on unaffected family members is considered to involve a minor increase over minimal risk according to the policies of some, but not all, of the relying institutions.

**LESSONS LEARNED**

Our early experience with a single IRB model has provided insights generalizable to other research projects. For instance, the UDN research study took 9 months to establish a single IRB model, which shortened the time available to meet study milestones. Funding agencies need to account for the upfront investment and continuing costs of a single IRB model when preparing timelines and budgets. Longer funding periods with an initial, lower budget phase to establish a single IRB model could be implemented.

Early in the process, we recognized that having relying institutions separately communicate with the single IRB would be untenable. Having a CC-based liaison between the single IRB and institutions has been invaluable, as has the designation of staff at the single IRB. Establishing the role and responsibilities of the CC in its support of the IRB was critical. We also centralized document storage where all UDN members can access the protocol, consents, SOPs, approval letters, and necessary forms. This system has helped to ensure that institutions are using up-to-date documents. Studies considering a single IRB should plan to support these resources.

Much of the single IRB startup time was devoted to negotiating among the 11 original institutions to develop the reliance agreement and SOPs. As mentioned previously, later additions to the network accepted the reliance agreement without modification. This gives us hope that efforts to create vetted master reliance agreements and SOPs, such as SMART IRB, will gain traction and substantially reduce the lead-time needed to establish a single IRB. It is also possible that if the use of a single IRB had been presented as mandatory rather than voluntary, the institutions involved...
would have signed on more readily without extended negotiations.

The most common ongoing activity related to the single IRB is the submission and review of amendments. With 146 institution-specific consent and assent forms and eight template documents, amendments that involve modification and review of these forms are the most time-intensive. Because of this, we learned that institution-based customization had to be minimized wherever possible. A large number of amendments have also been submitted to add UDN investigators and noninvestigator research staff. In the future, electronic systems should evolve to better support single IRB models by allowing individuals at multiple institutions with roles-based access to download documents and submit site-specific amendments, such as the addition of study personnel.

The UDN experience demonstrates both the envisioned efficiencies and investments required to make a single IRB model successful. Notably, a single IRB does not mean simply reducing the IRB process to a single institution; it requires that the processes and infrastructure be reengineered to support the new paradigm. There are some shifts that can be made on an individual level, including dedicating personnel to IRB coordination activities and involving coordinating centers to help navigate changing requirements. Other changes, such as the creation of broadly accepted master reliance agreements, will need to be implemented at a systems-level for the full benefits of single IRBs to be realized.

Acknowledgments. We thank Sabune J. Winkler for her substantial contribution to the conception and design of the single IRB for the UDN. Research reported in this article was supported by the NIH Common Fund through the Office of Strategic Coordination/Office of the NIH Director under Award Number U01HG007530 and by the intramural research program of the NHGRI, NIH. The content is solely the responsibility of the authors and does not necessarily represent the official policies of the DHHS, NIH, or NHGRI.
Conflict of Interest/Disclosure. Kimberly Splinter, Sara Chandros Hull, Ingrid A. Holm, Tara L. McDonough, Anastasia L. Wise, and Rachel B. Ramoni declare that they have no conflicts of interest.

Author Contributions. Kimberly Splinter, Sara Chandros Hull, Ingrid A. Holm, Tara L. McDonough, Anastasia L. Wise, and Rachel B. Ramoni wrote this article. These authors also provided substantial contribution to the conception and design of the single IRB for the UDN. All authors read and approved the final article.

1. Gahl, W.A. & Tifft, C.J. The NIH Undiagnosed Diseases Program: Lessons learned. JAMA. 305, 1904–1905 (2011).
2. Tifft, C.J. & Adams, D.R. The National Institutes of Health Undiagnosed Diseases Program. Curr. Opin. Pediatr. 26, 626–633 (2014).
3. Department of Health and Human Services, National Institutes of Health. Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research [Internet]. 2016 [cited 2017 May 25]. Notice Number: NOT-OD-16-094. Available from: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html
4. Menikoff, J. The paradoxical problem with multiple IRB review. N. Engl. J. Med. 363, 1591–1593 (2010).
5. The President and Fellows of Harvard College, Trustees of Dartmouth College, UW Institute for Clinical and Translational Research. About Us [Internet]. 2017 [cited 2017 April 6]. Available from: https://smartirb.org/about-us/

© 2017 The Authors. Clinical and Translational Science published by Wiley Periodicals, Inc. on behalf of American Society for Clinical Pharmacology and Therapeutics. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Supplementary information accompanies this paper on the Clinical and Translational Science website.

cts-journal.com