Approaches to Facilitate Institutional Review Board Approval of Multicenter Research Studies

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Background and Objectives: Gaining Institutional Review Board (IRB) approval for a multicenter research study can be a lengthy and time-consuming process. It can increase the complexity of consent forms, decreasing patient understanding and lowering recruitment numbers. It also leads to increased costs through the duplication of effort. This paper examines some of the strategies used to streamline the IRB review process for multicenter studies and provides examples used by 2 existing multicenter comparative effectiveness research networks.

Methods: A literature search was conducted to identify sources that described the challenges and potential strategies to facilitate multicenter IRB approval. The most promising avenues were identified and included in this review. Phone interviews were conducted with the Principal Investigators and Project Managers of 2 successful multicenter research networks to learn their "keys to success" and their lessons learned.

Results: Three strategies were identified that held the most promise: working with IRBs before submission, the use of central and/or federated IRBs, and the establishment of an umbrella protocol. Each of these strategies was used to some degree by the case study projects.

Conclusions: Although the approaches documented here can help streamline the IRB approval process, they are not a "silver bullet." Because some of these approaches are still relatively new, empirical data are sparse. However, it is believed that they will significantly reduce the administrative burden of the project as a whole and lead to a decrease in the overall time to protocol approval.

Key Words: Institutional Review Board, multicenter research, ethics, protocol

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Institutional Review Boards (IRBs) serve to protect patients and review the ethics of all proposed research studies. When research is conducted at multiple centers, this review is typically repeated for each institution in the study. Although it could reasonably be expected that the increased scrutiny of the protocol would provide increased benefit to patients, studies have not found that to be the case.[1,2] Investigators involved in multicenter studies have documented that the numerous reviews have often resulted in changes to the consent form that have introduced errors and increased complexity while reducing readability and potentially affecting the study response rate.[3,4] Other studies have found that for a single protocol, different IRBs will require a range of review levels, from exempt to review by the full board. For most investigators, the single largest frustration stems from the time, cost, and workload on local centers that result from the multiple reviews.[5]

The original United States regulations regarding the protection of research subjects were designed at a time when research typically occurred at a single center (also referred to interchangeably as a "site").[1] Most comparative effectiveness research (CER) or research on rare diseases, which includes most pediatric diseases, requires collaboration across multiple sites in order to obtain a large enough population to conduct a proper study. Although it is necessary for each institution participating in the study to have the protocol approved by an IRB, any qualified IRB can provide the review.[6] According to the regulations that govern cooperative human subjects research (research involving >1 site, 45CFR46.114), "With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort."[7] This allowance creates the opportunity for alternative strategies of approval.

There have been many calls for reforms to the IRB review process for multicenter studies in America.[3–5,8,9] These calls range from those that require change in regulations, like reforming the Heath Insurance Portability and Accountability Act to exempt research,[3] to those that can be accomplished within today's regulatory framework, like the use of central IRBs (CIRBs)[4,5,8] or upfront work with IRBs before submission.[10] This paper focuses on the avenues that are available to investigators conducting research in the United States today. In addition to the 2 approaches mentioned above, working with IRBs before submission and CIRBs, this paper also explores the use of federated IRBs and the establishment of an umbrella protocol. Also included are case studies on 2 multicenter CER networks: the Distributed Ambulatory Research in Therapeutics Network (DARTNet) and the Scalable PArtnering Network for CER (SPAN). None of these approaches are a "silver bullet" to

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streamlining approval. IRBs serve a purpose and play a vital role in protecting patients, and the goal is not to work around them. It is possible, however, to avoid some of the redundancies and duplication of effort that can occur in the approval of multicenter research studies.

METHODS

Working With IRBs

Engaging IRBs early in the planning process of the study is 1 simple way to streamline approval.[10] There are a number of ways that this engagement can occur. The creation of model protocols and consent forms as templates for the local sites is 1 method. These can be submitted to the local (site) IRBs for approval without modification. However, local IRBs have expressed concern with this tactic, as it requires overburdened IRB staff members to deal with unfamiliar protocol formats.[11] As a result, it can have the opposite effect of slowing down the approval process, as staff spends more time hunting for required information. One slight alternative is to break the protocol down into components or sections, allowing local site Principal Investigators to plug the information into their standard templates. Because there is no standardized way of presenting protocols and consent forms, this may prove to be a more practical approach. In addition, with the move to electronic submission of IRB protocols,[9] these sections provide the answers to questions that are often captured as discrete, required elements.

Another strategy that greatly increases the buy-in and ownership from local sites is frequent communication, particularly through the use of conference calls or webinars with the IRB chairs from each site.[10] These can be recorded and provided to chairs that may not have been able to make the original discussion. Sites with very specific concerns can be contacted for 1-on-1 conversations, although this is obviously a more time-consuming process. By talking with sites upfront and explaining the proposed study, it provides an opportunity for sites to ask questions or express their concerns with the research. It is even more beneficial to provide the protocol and consent forms to the IRBs as part of this discussion. Letting the sites review the protocols for any showstoppers before submission occurs can again minimize the time to approval. Investigators should not allow for endless feedback or review, but by asking for local IRB chairs to identify any big problems and by discussing them in conference calls, once the protocol is actually submitted to the local IRB, there should be few, if any, surprises. This helps address problems before the protocol is actually submitted and reduces need of the investigators having to deal with multiple changes requested by the various local IRBs.[10]

CIRBs

The literature has numerous examples of calls for the establishment and wider use of CIRBs.[3,4] CIRBs are not tied to an institution and may focus on a particular type of research, like cancer or drug trials, or a single geographic region or city. CIRBs can serve as the IRB of Record on a study, removing the need for individual sites to have the protocol approved by their local IRB. The CIRBs (pediatric and adult) of the National Cancer Institute[12] are among the most cited, but there are a number of other examples, including those established by networks, such as the IRBs of the Children's Oncology Group or the American Academy of Family Physicians (AAFP)[13,14]; regional IRBs like the Ontario Cancer Research Ethics Board or the Biomedical Research Alliance of New York[15,16]; and commercial IRBs like Western IRB.[17] There is evidence that the use of CIRBs can result in faster reviews and approvals, as well as lower administrative staff burden.[18] The National Cancer Institute CIRB has had a track record of success,[19] and although some of this may be due in part to the fact that its review is required for all phase 3 adult trials and certain phase 2 pediatric studies, it also allows for facilitated review, giving local IRBs a chance to provide local context.[12,20] However, other CIRB initiatives have had a harder time gaining acceptance. For instance, the Ontario Cancer Research Ethics Board found that other institutions would not use it unless it could demonstrate efficiency, but without studies, it could not demonstrate efficiency.[21] Thus, without a compelling need, or a mandate, it is difficult to convince local IRBs to adopt CIRBs. Once they are familiar with the concept, however, they are more open to their future use.[22,23]

Some of this hesitation reflects the concerns of local IRB chairs as they relate to CIRBs. For many local IRBs, there are serious concerns about research integrity, particularly related to coercion in drug trials.[1,22,24] With CIRBs, specifically commercial IRBs, there is a fear that investigators may "IRB shop" in order to find a board willing to sign off on the research.[24,25] Along the same lines, local IRBs have concerns about the review quality of CIRBs, particularly if they do not allow for input on local context. If a CIRB is far removed geographically or demographically, there may be a failure to understand the local culture and community values. In addition to understanding local culture, local IRBs have a local knowledge of subjects and Principal Investigators, and they are available for face-to-face chats that can quickly resolve issues that might require several rounds of back and forth with a remote CIRB.[22] On the flip side, there are often cases where a local IRB may lack the expertise to provide adequate scientific review of a protocol. In such instances, the review of an IRB that strictly focuses on a particular type of protocol may be beneficial.[8,22]

Federated IRBs

An avenue for streamlining IRB review that incorporates many of the benefits of CIRBs while avoiding some of the potential pitfalls is to use a federated IRB. The concept of a federated IRB emerged out of needs identified by the Clinical and Translational Science Awards Child Health Oversight Committee.[23] It was developed in consultation with the Office for Human Research Protections and first deployed during the pilot phase of the National Children's Study. The goal of the federated IRB is to maintain high ethical standards of review while reducing duplicative efforts among IRBs across multiple study sites.[26] It provides a formalized framework for many of the approaches that are discussed in this review.

The federation concept is flexible, allowing local institutions to select from multiple levels of participation.

There are 3 tiers from which an institution can choose. Tier 1 allows the local institution to rely on the lead site as the IRB of Record, with a mechanism for providing input on local context. This effort is facilitated by an IRB Operations Center, which is located at the lead site. If all sites in a study chose to participate at tier 1, the lead IRB would essentially serve as a CIRB. The only difference is that in most cases, the lead IRB would actually be tied to an institution and not freestanding. However, that is not required. With the National Children's Study, the IRB of the National Institute of Child Health and Human Development, a CIRB, is serving as the IRB of Record.[23]

Under tier 2 of the federated model, the lead IRB and an IRB designated by the local institution participate in a joint IRB review. The lead IRB or the designated IRB may serve as the IRB of Record, which allows for facilitated review by the local IRB. Alternatively, the local IRB may choose to serve as the IRB of Record. Under tier 3, institutions endorse the Federation Compact (the guiding principles and policies that allow the Federation to function) but rely on local IRB for review.

Under all tiers, local IRBs may require the development of addenda to core consent material in order to comply with local institutional and state requirements. All institutions also agree to follow the framework outlined in the Federation Compact and adhere to the roles and responsibilities described in the Memorandum of Understanding.[26] A summary of Responsibilities by Tier of Participation, taken from the Federation of IRBs FAQ,[26] is provided in Table 1.

The federated approach has many advantages including allowing sites to choose their own desired level of participation. Although the federated approach is still being evaluated, it is expected that sites choosing to participate in tier 1 will face a lower administrative burden, as the review occurs at the lead site. With a reduction in the time spent on review, local IRBs can focus on local context.[23] There is a greater burden on the lead site, which needs to maintain the IRB Operations Center, but the remote sites should save time and effort. Another advantage is that within a federation, a single IRB can serve as the IRB of Record or the IRB can rotate study-by-study to take advantage of certain expertise that may exist at different institutions.[23]

One of the goals of the federated IRB is to establish trust between institutions.[23] Indeed, the use of the federated IRB, with "local" IRBs serving as the IRB of Record, may alleviate some of the concerns that IRBs have in regard to seemingly remote CIRBs. Sites with a common interest can pull together and agree on a compact. The approach is similar in spirit to the IRB reciprocity agreement used by the Multicenter Academic Clinical Research Organization[27] and very much along the same lines as the facilitated IRB approach adopted by the HMO Research Network (HMORN) for low-risk data-only studies (broadly defined as observational studies that rely on

TABLE 1. Federation of IRBs Responsibilities by Tier of Participation[26]

Tier	Review Responsibilities of Local IRB	Review Responsibilities of Lead IRB	IRB of Record
Reliance on lead IRB as IRB of Record	Communication of local context issues to lead IRB through IRBs Operations Center	Initial reviews Continuing reviews Protocol amendments applicable to all sites Protocol amendments applicable to local site(s) initiated by local Principal Investigator Serious adverse events DSMB reports Consider local context issues in review of all submissions Unanticipated event reporting to OHRP	Lead IRB
Facilitated or full review by local IRB of materials reviewed and approved by the lead IRB	Communication of local context issues to lead IRB through IRBs Operations Center Full or facilitated review of all materials submitted to and approved by the lead IRB Local implementation, review and oversight Protocol amendments initiated by local Principal Investigator Serious adverse events DSMB reports Unanticipated event reporting to OHRP		Local IRB or the lead IRB
Reliance on local review	Communication of local context issues to lead IRB through IRBs Operations Center Full review of all materials submitted to and approved by the lead IRB Local implementation review and oversight Protocol amendments initiated by local Principal Investigator Serious adverse events DSMB reports Unanticipated event reporting to OHRP		Local IRB

DSMB indicates Data and Safety Monitoring Board; IRB, Institutional Review Board; OHRP, Office for Human Research Protections.

data generated through health care operations).[11] It is also similar to the approach taken in South Carolina with their collaborative, state-wide IRB.[28] Studies can originate at any of the participating institutions and all institutions agree to accept the decision of the originating IRB.

One potential drawback to the federated approach is that institutions that wish to serve as the lead IRB on studies are taking on increased liability. As a result, it may end up that only institutions that wish to specialize in multicenter research studies choose to purse this approach. The other drawback, at least from the view of the participating centers, is that even if they choose to rely on another IRB for review, some kind of document will need to be submitted to allow for institutions to track the study against other ancillary processes (conflict of interest, contracting, reimbursement). Thus, although the protocol review may occur elsewhere, a protocol must still be submitted.

Umbrella Protocols

For investigators who are part of a larger network or a collaborative that wishes to conduct multiple studies, 1 strategy that is often used is to create an "umbrella" protocol that covers the establishment of the research database, including information on items like data processing and governance (see case studies below). Research studies are added later, either as amendments to the umbrella or as separate protocols that cite the original submission.[29,30] The first submission deals with data issues and the subsequent submissions can be focused solely on the research questions. Because the use of an umbrella protocol includes multiple submissions, it would not streamline the process for a single study. But if multiple studies are envisioned, the use of an umbrella protocol, although possibly increasing the time to approve the first study, may ultimately save time in the long run.

RESULTS

Case Study: DARTNet

The DARTNet is a federated network of care centers that was established in 2008. It has an administrative home at the University of Colorado, Denver. The main aims of the network are to facilitate quality improvement in a primary health care setting and to compile clinical data that can be used for CER.[31] In this type of federated network, a single query is submitted to a set of geographically and organizationally distinct databases. A set of governance rules dictate whether a database will "respond" to the query, allowing the database owners to maintain privacy and confidentiality.[30]

When an organization joins DARTNet, each center assembles a database of patient-level information (such as vital signs, social history, family history, and physical examination findings) from electronic health records, pharmacy utilization databases, and billing systems. This aggregated clinical information is then standardized, deidentified, and linked securely through the Web to databases that have been similarly prepared and standardized by other DARTNet members. Once linked, a database query can be sent to all federated databases at once. For many of the DARTNet centers, the standardization and deidentification of the clinical data is performed by software and services provided by the Clinical Integration Networks of America Inc.,[32] a private vendor, although this is not required. For centers that do use Clinical Integration Networks of America Inc., a Business Associates Agreement is signed to cover this work.[33]

DARTNet is governed by an umbrella IRB protocol that describes all of the processes, procedures, and technology used to pull, standardize, and deidentify the data housed in the various clinical sources. The umbrella protocol allows the centers to use the data for quality improvement and to share aggregate, practice-level counts that are used for ongoing benchmark reports. Each center signs a letter of agreement upon joining DARTNet that states they agree to share such data.[30,33]

Every new research study requires a new protocol, and for each protocol, centers choose whether they wish to participate in the study. Local IRBs approve these protocols, unless the center lacks an IRB, at which point, they typically complete an investigator-level agreement with a CIRB.[30,33] In the case of DARTNet, many of the participating centers are family practices; thus, the IRB of the AAFP typically serves as the CIRB. Each study also requires the completion of a data use agreement (DUA), which typically takes about 4 to 6 weeks to complete. To avoid the back and forth between lawyers of the various centers, the language is kept standard, unless there is specific verbiage required by a particular state's laws or regulations.[33]

Although IRB protocols are typically required for new DARTNet research studies (they often require the collection of prospective data), the use of a federated IRB, along with established processes and umbrella protocols, makes the approval of follow-up studies easier. Although DARTNet does not officially use a federated IRB (it was established before the federated IRB guidelines were adopted), it uses a mixed IRB model that is allowable within the federated IRB framework. Although some centers have their own IRB, the IRB of the AAFP serves as a CIRB for many of the research studies.

Case Study: SPAN

The SPAN is another federated, distributed query network. Funded by the Agency for Healthcare Research and Quality, SPAN aims to conduct CER across several HMORN sites and other community partners. SPAN takes advantage of many of the policies and procedures that were established by the HMORN for their data-only studies, particularly documentation that allows participating sites to cede IRB oversight to the lead site IRB and a template DUA. The IRB ceding documentation is similar to documents used in the federated IRB model, in that it provides a mechanism to allow the IRB of the lead site to serve as the IRB of Record to the rest of the sites in the study. The DUA used by SPAN is somewhat unique in that it is a reciprocal DUA, allowing limited datasets to flow in multiple directions. Rather than have all data flow to a central coordinating center, data can flow to other sites within the network. This allows investigators at other sites to lead the data analysis on different projects.[34]

According to the SPAN study staff, the process of obtaining IRB approval was facilitated by several factors: (1)

meeting with local IRBs before the protocol was submitted; (2) familiarity with the HMORN model, which made IRBs comfortable with ceding oversight; (3) frequent meetings of the HMORN IRB administrators, which led to the collective development of what policies they would and would not accept (for HMORN, not just SPAN); (4) an IRB protocol that covered the development and governance of the federated database, decoupling any research from the establishment of the database. Unlike DARTNet, which created separate protocols for each research study, SPAN added them as amendments to the database protocol.[34] Whether to create a separate protocol versus an amendment depends on a number of factors, including the type of research, data used, number of participating sites, etc.

DISCUSSION

One of the keys in all of the approaches discussed here is to build trust with the IRB. Engaging IRB chairs in the process increases buy-in, allows them to voice their concerns, and minimizes the chances of any surprises when the protocol is actually submitted. Simple steps such as these can go a long way toward minimizing delays in approval, no matter whether a study elects to use a CIRB, a federated IRB, or the traditional approach of multiple reviews. Although all of the techniques listed in this paper are expected to speed the IRB approval process, there are no real studies into whether one is faster than the others. They are all likely to require a fair amount of preparation and a large number of meetings.

At the time of this writing, the Department of Health and Human Services has announced a proposal to improve the rules protecting human research subjects.[35] Among the proposed changes is a mandate that all domestic sites in a multicenter research study use a single IRB as the IRB of Record.[25] This would imply that future multicenter research would require the use of a federated or CIRB. Given the hesitations and concerns voiced by local IRB chairs about CIRBs, the proposed mandate to use centralized review may be toned down to a recommendation. In either case, for multicenter studies, that would require a change in the now traditional process of multiple-IRB review. As a result, some of the approaches described here may end up becoming the norm.

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