Use of Central IRBs for Multicenter Clinical Trials

Final Report

Project: Use of Central IRBs for Multicenter Clinical Trials

Clinical Trials Transformation Initiative

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Table of Contents

Background

The regulatory requirement of institutional review board (IRB) oversight of clinical trials was established to protect research participants. However, as the clinical research enterprise has evolved and multicenter trials have become more common, IRBs also concern themselves with assessing the risk of a given trial to the institution participating in the trial. The goal of protecting research participants may not be enhanced by having each site's local IRB conduct a full review of multicenter protocols (including review of the protocol and consent form). The most intuitive objection to full review by multiple local IRBs is the additional time and expense involved.[1] However, Dr. Jerry Menikoff's editorial in the *New England Journal of Medicine* suggested that this may be an ethical issue as well as an efficiency issue, as multiple local IRBs reviewing the same multi-site study may lead to a diffusion of responsibility and potentially expose trial participants to undue risks.[2] All sites in a multi-site trial need to use the same protocol for scientific reasons, so any local IRB that has major concerns about a protocol may simply prevent their institution from participating. This, then, does not result in meaningful changes to the flawed protocol, and "therefore no reduction in the number of subjects exposed to whatever risks the IRB identified." Dr. Menikoff describes an "authority vacuum" in which no IRB feels empowered to demand changes in the protocol. More commonly the local IRB may require changes in the informed consent form. To the extent that some of the required changes identify serious problems with the consent form, and these concerns are not communicated to other IRBs, the ethical integrity of the study can be compromised.

The Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) support the use of central IRBs for multicenter trials.[3,4] In July 2011, the Department of Health and Human Services (DHHS) invited commentary on their proposal to change the Common Rule to include mandated centralized review for multicenter trials.[5]

Despite this support, local IRBs vary in their willingness to defer to centralized IRB review.[6,7] In 2005, a workshop sponsored by several organizations (the NIH, OHRP, Department of Veterans' Affairs, Association of American Medical Colleges, and American Society of Clinical Oncology) explored alternative models to local IRB review. The 2005 workshop was followed by a national conference in 2006. Results of the workshop and conference revealed the following concerns about deferring to a central IRB review:

- Review quality, including loss of safety net of redundant review, lack of attention to local concerns, and inappropriate consent forms
- Regulatory liability, because the OHRP in the past has held the "institution" responsible for non-compliance
- Legal liability, should there be any litigation secondary to errors, omissions, or negligence of an IRB not directly affiliated with the institution conducting research
- Potential negative "public relations," should an IRB not directly affiliated with the institution be found to be non-compliant (e.g., Coast IRB)
- Loss of income generated from fees for IRB review of studies with commercial sponsors, which is often used to cover institutional costs of IRB infrastructure

In a March 2006 FDA guidance document,[3] the US FDA states: "The Agency hopes that sponsors, institutions, Institutional Review Boards (IRB), and clinical investigators involved in multicenter clinical research will consider the use of a single central IRB (centralized IRB review process), especially if using centralized review could improve the efficiency of IRB review." The National Cancer Institute (NCI) at the NIH has created a central IRB (NCI CIRB) for oversight of multicenter, phase 3 cancer trials sponsored by NCI. However, adoption of the NCI CIRB by institutions participating in large multicenter, NCI-sponsored trials has been inconsistent. In a public letter dated April 30, 2010,[4] the OHRP articulated its agreement with the FDA's position supporting the use of central IRBs for multicenter protocols, which Dr. Menikoff reiterated in his editorial in the *New England Journal of Medicine*.

Because the willingness of institutions to defer to a central IRB in multicenter trials continues to vary and because of uncertainty about how the more recent OHRP endorsement would affect IRB behavior, in 2010 the Clinical Trials Transformation Initiative (CTTI) launched its project "Use of Central IRBs for Multicenter Clinical Trials." This project was intended to explore current perceptions of barriers to relinquishing full local IRB review to a designated central IRB, to solicit stakeholder reactions to proposed solutions developed with input from an advisory panel, and to develop recommendations for implementing these solutions.

This project team included participants from CTTI member organizations representing academia, government, patient advocates, and industry. An organizational chart showing the project team is provided as **Appendix A**. The research was led by Kathryn Flynn and Kevin Weinfurt at the Duke Clinical Research Institute (DCRI).

Methods

The following approach was used to gather data for this project:

- Identify current perceptions of the barriers to central IRB review and formulate potential solutions to overcome these barriers through
  - Review of the literature
  - Discussions with experts in the field, from a variety of agencies
- Obtain feedback on proposed solutions through
  - Interviews with stakeholders at research institutions that do not routinely use central IRBs
- Refine the solutions and develop policy recommendations through
  - Expert meeting with representatives from a broad cross-section of the clinical research enterprise

A. Literature Review

Overview

In an effort to inform the policy discussion about central IRBs, the scientific literature was reviewed to describe peer-reviewed journal articles on the use of central IRBs for multicenter clinical trials in the U.S.

Methods

A PubMed search was used to identify relevant articles. The search strategy used a combination of terms, including: “regional IRB,” “multicenter IRB,” “multi-site IRB,” “central IRB,” and “multiple IRB,” as well as a search for “clinical trial” and “monitoring” combined with “IRB.” We used the bibliographies of other systematic reviews and consulted with experts in the field to identify articles not captured in our main search strategy. Articles were selected for consideration by screening titles and abstracts.

Results

We identified 33 published reports related to the use of central IRBs for multicenter trials in the United States. There is limited empirical work on this topic, as only 11 of these articles were empirical studies; the remainder were commentaries. The literature that exists is focused primarily on problems in efficiency associated with redundant local reviews of multicenter studies and the potential benefits of a centralized system. Additional work is needed, both to generate data on the use of central IRBs and to elucidate and address the quality concerns that research institutions have about deferring ethical review to a central IRB.

B. Discussions with Experts

Overview

We held a series of group and individual discussions with 43 experts in the field—including representatives from institutional IRBs, federal IRBs, commercial IRBs, industry, and regulatory agencies—to arrive at an understanding of the barriers to central review and to generate solutions.

Methods

Participants were identified by the project team, drawing on CTTI members as well as other known experts in the field.

Results

Table 1 summarizes the barriers and proposed solutions identified during these discussions. Of note, an early finding from the expert discussions was the need to clarify the term “central IRB.” Although many people refer to an independent or commercial IRB as a central IRB, an independent or commercial IRB can also be contracted by an institution to serve as the institution’s “local” IRB. In addition, the term “central IRB” is commonly used to describe other alternative models, such as facilitated, federated, and consortium models.

Table 1. Perceived Barriers to Using Centralized IRB Review in Multicenter Clinical Trials in the United States and Proposed Solutions

Barrier	**Potential Solutions**
Feasibility of working with multiple outside IRBs, each requiring different forms and/or electronic systems to submit a protocol.	Identify standard data elements to facilitate review and reporting across disparate systems.

Loss of revenue generated from fees for institutional IRB review of studies with commercial sponsors.	Charge an administrative fee for institutional responsibilities (Institutions may need to find a new way to cover fixed costs for the IRB for non-sponsored activities).
Concern about regulatory liability in the event of noncompliance.	Clarify OHRP policy to take action against the IRB of record as opposed to participating sites for noncompliance with regulations.
Concern about legal liability in the event of litigation secondary to errors, omissions, or negligence of an IRB not directly affiliated with the institution conducting research.	Establish liability protections through a well-defined communication plan and standard contracts with the outside IRB.
Quality of review, such as missing important human subject protections issues without redundant review, caliber/expertise of reviewers, and insufficient time spent on protocols.	Conduct standardized tests of IRBs to demonstrate quality (e.g., send a standardized protocol to an outside IRB and the local IRB to compare results). Note: Evaluating review quality is hampered without an agreed way to measure it.
Potential loss of local context.	In a well-defined relationship, the local institution retains authority to decide whether to participate in a study or to limit an investigator's involvement. Consent forms can have a core that is the same for all sites, and a section customizable to the institution that addresses relevant state laws or institutional concerns regarding (e.g., compensation for research-related injury, institutional contact information, surrogate consent, and costs of participation).

C. Stakeholder Interviews

Overview

We conducted interviews with 25 stakeholders at 6 research institutions that do not routinely use central IRBs to obtain feedback on the proposed solutions. Our goal was to identify the range of perceptions and beliefs among diverse participants, and not to establish the prevalence of different views.

Methods

Each research institution had its own IRB, and institutions were purposely selected to be diverse with respect to their volume of federally and industry-funded clinical research, the type of institution (e.g., academic medical center or independent hospital), and geographic location. The stakeholders at each institution included an IRB chair, IRB administrator or manager, institutional general counsel, vice dean for research, director of clinical trials, or other individuals responsible for making decisions regarding the use of outside IRBs.

Results

A major finding was that many of the perceived barriers to using central IRBs arise from the fact that most or all of the tasks related to protecting the institution (e.g., conflict of interest review) are often coordinated through the institution's IRB office and incorporated into their review process. What evolved as bureaucratic convenience in most institutions—locating certain institutional review processes in the IRB office—seems to have altered perceptions of what is entailed in the ethical review of research. This conflating of institutional responsibilities with the ethical review responsibilities of the IRB leads to confusion about how institutional responsibilities would be handled in the context of a central IRB review, creating resistance to using central IRBs.

The second major theme to emerge from our interviews was a feeling of discomfort with an external entity handling the ethical review and oversight of a multicenter protocol. Institutional stakeholders frequently made reference to issues of "comfort" and "trust" in the review by a central IRB. These issues appeared to be influenced by the institution's previous experiences with outside IRBs. When an institution had no prior experience, there was less comfort and trust. Moreover, although IRB accreditation from the Association for the Accreditation of Human Research Protection Programs was important, it was not sufficient to alleviate these concerns. The data suggest that experience, not simply increased knowledge, is necessary to allow institutional stakeholders to feel more comfortable with central IRB review.

Additionally, one of the most frequently cited barriers to using a central IRB was the idea that some aspects important to IRB review could not be adequately addressed by a central IRB, since an outside group may not have necessary knowledge about the site's unique local context. Some specific examples we heard included local knowledge about investigators, the research setting, capacity to conduct the trial (resources), or unique patient populations. In some of these situations, institutional stakeholders were concerned about not wanting local knowledge to become public (e.g., in the case of investigator conflicts of interest), while in other situations it was an issue of not having an opportunity to share the local information about unique populations. Many interviewees described a desire to protect their research subjects, whom they regarded as unique.

D. Expert Meeting

A meeting was convened on April 25-26, 2012, in Rockville MD, to further refine the solutions, analyze stakeholder reactions to the solutions, and develop policy recommendations. This meeting brought together 47 representatives from a broad cross-section of the clinical research enterprise, including government and industry sponsors of clinical research, FDA, OHRP, academic and non-academic research institutions, commercial IRBs, and patient advocacy groups.

A summary of this meeting is included as **Appendix B.**

Conclusions and Recommendations

Need to Clarify Terms

In our discussions with experts, we learned that we needed to clarify and define the term "central IRB." Consequently, in the interviews with institutional stakeholders, we provided interviewees with both a brief definition of central IRB, "a single IRB of record for a multicenter clinical trial," and a

longer definition, “a properly constituted IRB to which sites cede all regulatory responsibility for scientific oversight and integrity of the protocol from initial review to termination of the research, including review of informed consent.” These definitions were effective in clarifying the model of ethical review under consideration, suggesting that they might be useful in future policy discussions.

Decoupling Institutional and Ethical Review Responsibilities

To address the conflation of institutional responsibilities with the ethical review responsibilities of the IRB, we developed a guide for institutions that can help to decouple institutional and IRB responsibilities to assist in the acceptance of centralized ethical review, which has the potential to result in more consistent and efficient reviews. The guide outlines categories of legal and ethical responsibilities of an institution and an IRB in overseeing the conduct of clinical trials. (**Appendix C)** This document is meant to support communication between institutions and central IRBs when assigning responsibilities for multicenter clinical trial protocols that are using a central IRB. Thus, it is most relevant for institutions that have their own local IRB. We solicited feedback on the guide during our interviews with institutional stakeholders and further refined it in the context of our expert meeting.

Level of Comfort and Trust With Central IRB Review

Stakeholder interview data suggests that experience using central IRBs, not simply increased knowledge about how they operate, is necessary to allow institutional stakeholders to feel more comfortable with central IRB review. However, the majority of institutions have little motivation to participate in protocols with central IRB review, so gaining this experience may be difficult. Although industry sponsors would have an incentive to use a central IRB (believing it to be more efficient and less expensive), we could find no examples of industry sponsors who mandate use of a central IRB for all participating sites. In contrast, the National Institutes of Health (NIH) is in a unique position to make this happen, and there is now at least one example of a government sponsor, the National Institute of Neurological Disorders and Stroke NeuroNEXT Network,[8] that has required the use of a central IRB. Research institutions that want to participate in prestigious research networks like NeuroNEXT will likely accept review by a central IRB despite discomfort with the model because the use of the central IRB is a prerequisite to membership.

Thus, we encourage the NIH and other government sponsors to consider requiring the use of central IRB review for some multisite trial networks so that relevant stakeholders can gain experience that will inform their levels of comfort and trust. Without such initiatives, there is little incentive for research sites to overcome their feelings of discomfort with central IRB review. Another advantage of providing more opportunities to participate in research networks with mandated central IRB review is that institutional stakeholders can observe how concerns about local context can be addressed.

Addressing Concerns about Local Context

To address the concerns about local context, we considered feedback from our stakeholder interviews and the expert meeting. We recommend the following:

(1) Clarify how and where local issues are reflected. In the detailed guide provided in Appendix C, we outline the need for the institution and the central IRB to develop a detailed communication plan to share information about the site, the investigators, and other details of the trial. The guide also specifies that the central IRB should specify where local institutions should insert informed consent language specific to their state, for example, or the special populations they serve.

(2) Reiterate the regulatory positions of OHRP and FDA. Both OHRP and FDA have published their support for using central IRBs for multicenter protocols.[3-5] Moreover, in the Advanced Notice of Proposed Rule Making (ANPRM), the DHHS position on local context reads, "Relevant local contextual issues (e.g., investigator competence, site suitability) pertinent to most clinical studies can be addressed through mechanism other than local IRB review. For research where local perspectives might be distinctly important (e.g., in relation to certain kinds of vulnerable populations targeted for recruitment) local IRB review could be limited to such consideration(s) but again, IRB review is not the only mechanism for addressing such issues. The evaluation of a study's social value, scientific validity, and risks and benefits, and the adequacy of the informed consent document and process generally do not require the unique perspective of a local IRB."[5]

Conclusions

This CTTI project identified specific steps likely to facilitate adoption of central IRB review for multicenter clinical trials. The clinical trials community has an opportunity to significantly improve the quality and efficiency of one essential aspect of the clinical research enterprise, as there is good reason to believe that central IRB review in multicenter trials would be beneficial to clinical research. The FDA, OHRP, and DHHS have already demonstrated their support for central IRB review. What is still needed is experience using the model under circumstances where there are potential solutions to anticipated barriers. We hope that the solutions proposed herein can maximize successful institutional collaboration with central IRBs to facilitate ethical and efficient conduct of multicenter trials.

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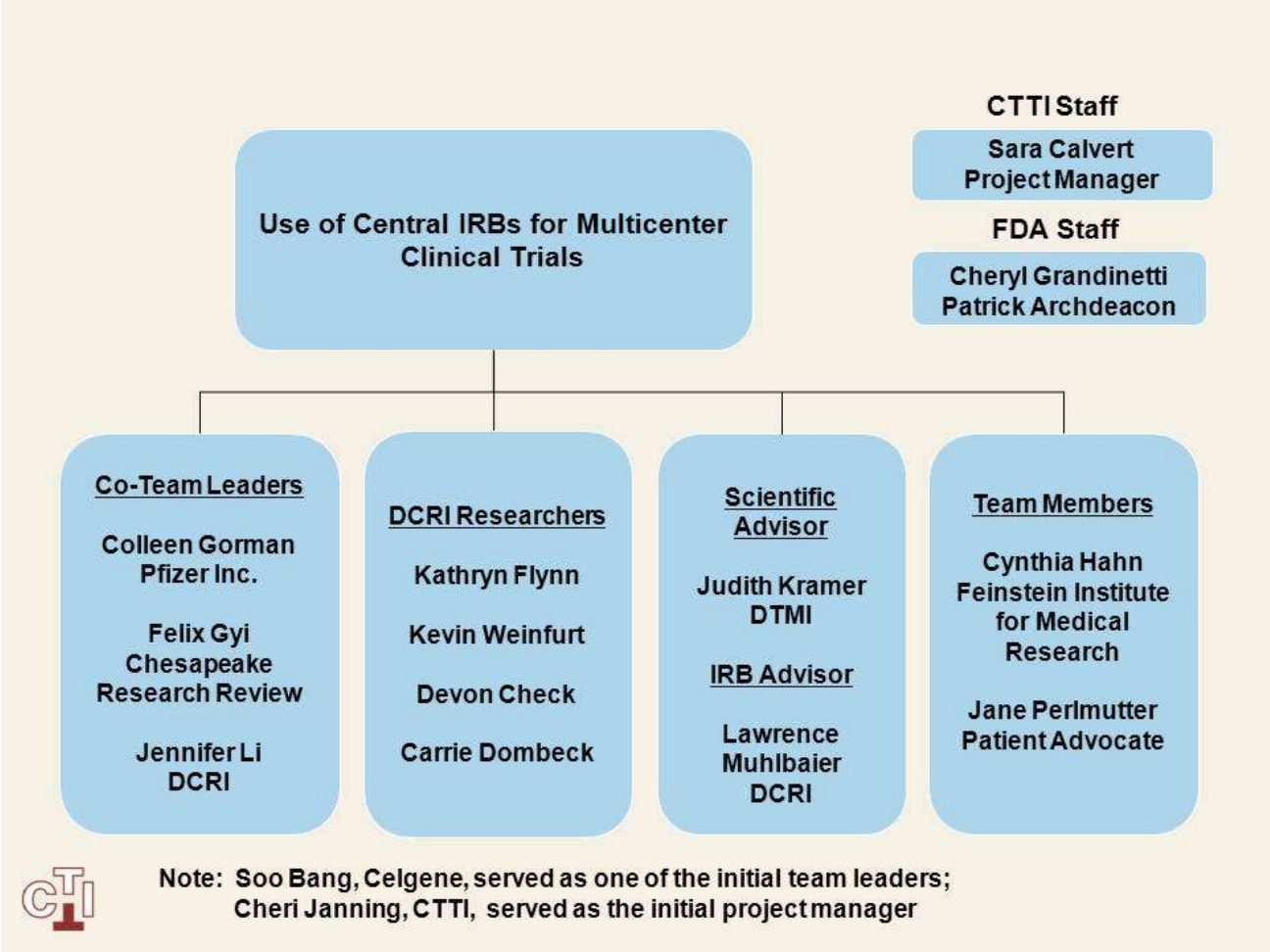
Appendix A. Project Team Organization



Appendix B. Summary of an Expert Meeting held April 25-26, 2012

Meeting objectives

The Clinical Trials Transformation Initiative (CTTI) has been conducting a project to summarize known barriers to using central IRBs for multicenter clinical trials and to propose solutions to obviate these barriers. To further explore these solutions, the CTTI working group invited representatives from a broad cross-section of the clinical trial enterprise, including government and industry sponsors of clinical research, academic and non-academic research institutions, commercial IRBs, and patient advocates, to an expert meeting held in Rockville, MD, on April 25-26, 2012. The key objectives of this meeting were to:

- Present research findings from the CTTI project entitled, *Use of Central IRBs for Multicenter Clinical Trials*
- Discuss research findings among experts present at the meeting
- Solicit additional feedback to refine proposed solutions

Overview of CTTI Central IRB project

As multicenter clinical trials have become more common, many have begun to question whether the goal of protecting research participants is enhanced by having each site's local IRB conduct a full review of multicenter protocols. Both the FDA and OHRP have issued statements in support of central IRBs as a means of improving the efficiency of clinical trials. However, local IRBs differ in their willingness to defer to central review. The present research was conducted by the Clinical Trials Transformation Initiative (CTTI) in an effort to solicit current perceptions of barriers to the use of central IRBs and to articulate solutions to obviate these barriers.

The study team began by conducting a review of the literature and holding a series of discussions with experts in the field (n=43) to arrive at an understanding of the barriers to central review. As a result of these activities, an early research finding was the need for clarity in defining what is meant by "central IRB." For purposes of this research, the following definition was adopted: "A properly constituted investigational review board to which sites cede all regulatory responsibility for scientific oversight and integrity of the protocol from initial review to termination of the research, including review of informed consent." This is distinct from other alternative models of review, such as the facilitated, federated, and consortium models.

We also conducted interviews with stakeholders (n=25) at six different research institutions to obtain feedback on proposed solutions to the identified barriers to central review. The research institutions had various concerns about using an external central IRB. Many of these concerns seemed to be associated with the conflation of the responsibilities of the institution with the ethical review responsibilities of the IRB. Thus, we concluded that there would be value in decoupling these distinct sets of responsibilities to help elucidate how an institution might operate when using an external central IRB.

Expert meeting

At the meeting, we discussed detailed strategies and tools for helping research institutions separate institutional responsibilities from those required of the IRB. One such tool was a document created by the project team, which clearly delineates these responsibilities and how they might be assigned to each entity, or, in some cases, both entities. A number of other strategies were also discussed that would allow institutions to gauge their comfort with using centralized review for a particular protocol, including strategies for evaluating the central IRB's policies and procedures. Recommendations and strategies from this meeting are being compiled for publication and dissemination.

Appendix C. Considerations to Support Communication Between Institutions and Outside IRBs When Responsibilities are Being Assigned for Multicenter Clinical Trial Protocols

The purpose of this document is to outline categories of legal and ethical responsibilities of an institution and an institutional review board (IRB) in overseeing the conduct of clinical trials. This document is meant to support communication between institutions and external central IRBs when responsibilities are being assigned for multicenter clinical trial protocols that are using a central IRB. This document is most relevant for institutions that have the option to use their own local IRB and should be used as a starting point for decoupling institutional and IRB responsibilities.

The **central IRB for a multicenter protocol** is the single IRB of record for the protocol. It has regulatory responsibility for assuring the protection of the rights and welfare of research participants from initial review to termination of the research, including review and approval of informed consent.

The **institution** is the local entity setting standards to determine whether a research investigator can conduct research under its auspices (e.g., allowing admitting privileges to a hospital, authorizing an investigator to use facilities to conduct research, or determining faculty status). Clinical sites participating in a multicenter protocol may, in some instances, not be associated with an institution. In these cases, the clinical investigator or the study sponsor would assume some of the institutional responsibilities.

1. Responsibilities that **both** the central IRB and the institution should assume:

   A. Execute an IRB Authorization Agreement.
      1. Identify and define roles and timeframes for reporting to sponsors and federal and applicable state agencies serious adverse events, serious and continuing non-compliance, unanticipated problems involving risks to subjects or others, or suspension or termination of central IRB approval.
      2. Clearly communicate expectations, including regulatory requirements, sharing of information between the institution and the IRB, and a process for determining potential corrective/remedial actions in the event of non-compliance.
      3. Develop a communication plan for sharing information about the site, the investigators, the sponsor, and the clinical trial between the institution and the IRB.
         i. Identify the plan to evaluate investigator qualifications.[1]
         ii. Communicate any substantive changes to the institution, its human research program, or the local research context in connection with the clinical trial to the reviewing IRB and vice versa.
      4. Identify a process for responding to participant concerns and grievances, including coordination of communication to subjects.

2. Responsibilities of the central IRB for a multicenter protocol:

Responsibilities (non protocol-specific):

[1] This is the responsibility of the IDE/IND holder and the IRB for FDA-related clinical trials.

A. Maintain program for education and training in human subjects research for IRB personnel.
B. Register with FDA and OHRP.
C. Notify institution if accreditation status changes.

Responsibilities (protocol-specific):

A. Ensure clinical trial meets generally accepted ethical standards of human subjects protections and complies with applicable regulations, for example, the Common Rule (45CFR 46), 21 CFR Parts 50, 56, 312, and 812, as well as state and applicable international regulations, such as the European Clinical Trial Directive.
B. Collect, review, and take into account site-specific information provided by the individual sites. This information could include special considerations regarding local populations, or state laws and any restrictions placed on the clinical trial by the institution, such as the need for radiation safety or pharmacy and therapeutic committee review, as well as feasibility of the research or special training requirements.
C. Review and approve the informed consent form and any other research-related documents or media. The process for review and decision could include the following steps:
    1. Provide the investigator/researcher with the sponsor-approved informed consent form. This form should indicate where the institution may add or modify language specific to their site, for example, to the sections on compensation for research-related injury, compensation to subjects, institutional contact information, and costs of participation.
    2. If applicable, review and approve any site-specific modifications.
D. Provide the investigator/researcher with copies of all IRB decisions.
E. Provide the institution with copies of IRB approval documents, IRB rosters, and meeting minutes upon request or in accord with the IRB authorization agreement.
F. Notify the institution promptly in writing of serious or continuing non-compliance or unanticipated problems involving risks to subjects or others.
    1. As appropriate, notify the institution about information from internal and external reports and complaints determined, discovered, or learned by the central IRB in connection with the conduct of a clinical trial by the institution, or in connection with the conduct of the clinical trial by another site if such discovery or determination regarding the other site affects the conduct of the clinical trial at other sites.
G. Notify the institution promptly in writing of any suspension or termination of central IRB approval and of remedial actions required of the institution or its agents by the central IRB.
H. If review is for an institution that conducts federally-funded research, the central IRB must commit to adhere to the requirements of the institution's federal-wide assurances (FWA(s)).

3. Responsibilities of the **institution** where research is being coordinated or conducted:

Responsibilities (non protocol-specific):

A. Maintain program for education of investigators and research staff and training in human subjects research.
B. Maintain policies and procedures for the conduct of human subjects research as appropriate for the particular institution.
C. Maintain appropriate institution-specific required credentialing of staff.

D. If institution conducts federally-funded research, maintain approved federal-wide assurances FWA(s), including ensuring that the arrangement with the central IRB is documented by a written agreement.
E. Conduct a privacy and security review as required by the Health Insurance Portability and Accountability Act (HIPAA) of 1996 with respect to the mechanisms for permitting the use and disclosure of Protected Health Information (PHI) for clinical trials:
    A. The covered entity (typically the institution) is responsible for the authorization.
    B. The covered entity is responsible for receiving the notice of decedent research.
    C. The covered entity is responsible for the Limited Data Set with Data Use Agreement.
F. Ensure that the investigator/researcher is conducting research and recruiting potential research participants in accordance with IRB-approved protocol, procedures, and documents.

Responsibilities (protocol-specific):

A. Designate the IRB of record for the protocol.
B. Obtain IRB approval of research protocols involving human subjects.[2]
C. For PHS-funded research, conduct a conflict of interest (COI) review pursuant to the Public Health Service regulations on Promoting Objectivity in Research, 42 CFR Part 50, Subpart F.
D. Notify the IRB promptly in writing of serious or continuing non-compliance or unanticipated problems involving risks to subjects or others.

4. Responsibilities that **either** the central IRB or the institution could assume, depending on the specific protocol:

A. Evaluate the local context in which the research will be conducted, including consideration of any specific requirements of state or local laws, regulations, policies, or standards. If this responsibility is assumed by the institution, they should inform the central IRB of any relevant requirements or findings from the analysis that would affect conduct of the clinical trial at that institution.
B. If one is requested, provide a waiver of authorization as described under the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

[2] This is the responsibility of the Clinical Investigator under FDA-related clinical trials.