Review of Resources from CTTI Central IRB Projects

Cynthia Hahn, Integrated Research Strategy
First CTTI Central IRB Project Findings

- Need to define “central IRB”
- Concerns associated with conflation of the responsibilities of the institution with the ethical review responsibilities of the IRB
- Remaining discomfort due to lack of experience using centralized review
CTTI Recommendations: Use of Central IRBs for Multicenter Clinical Trials (2013)
Recommendation #1

CTTI recommends using a central IRB* to improve the quality and efficiency of multicenter clinical trials.

*CTTI's Definition of Central IRB: A single IRB of record for all sites involved in a multi-center protocol. A range of entities may serve as a central IRB (e.g. another institution’s IRB, a federal IRB, an independent IRB).
Recommendation #2

To address blurred distinctions between responsibilities for ethics review and other institutional obligations, CTTI recommends that sites and IRBs use a CTTI-developed guide* to support communication and contractual relationships between institutions and a central IRB.

*Considerations Document
Considerations Document

Designates the responsibilities of:
- the Institution
- the IRB
- Either Central IRB or Institution
- Both Central IRB and Institution

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.

Responsibilities that both the central IRB and the institution should assume:

   1. Identify and define roles and timetables 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/ameliorative 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.
      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.
Recommendation #3

CTTI recommends that sponsors in a position to require the use of central IRB review for multisite trial networks should do so in order for relevant stakeholders to gain experience with central IRB review. The resulting experiences may foster greater comfort and trust with the central IRB model.
Using Central IRBs for Multicenter Clinical Trials in the United States

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Abstract

Research institutions differ in their willingness to defer to a single, central institutional review board (IRB) for multicenter clinical trials, despite statements from the FDA, OHRP, and NIH in support of using central IRBs to improve the efficiency of conducting trials. The Clinical Trials Transformation Initiative (CTTI) supported this project to solicit current perceptions of barriers to the use of central IRBs and to formulate potential solutions. We held discussions with IRB experts, interviewed representatives of research institutions, and held an expert meeting with diverse stakeholder groups and thought leaders. We found that many perceived barriers relate to conferring responsibilities of the institution with the ethical review responsibilities of the IRB. We identified the need for concrete tools to help research institutions acquire institutional responsibilities from ethical responsibilities required of the IRB. One such tool is a document that creates a structure to divide responsibility and how they might be assigned to each entity, so that in some circumstances, the trial and research recommendations will be broadly disseminated to facilitate the use of central IRBs in multicenter trials. The ultimate goal is to increase the nation’s capacity to efficiently conduct the large number of high-quality trials.

Introduction

Maximizing the efficiency of multicenter clinical trials is an important public health interest. As multicenter clinical trials become ever more common, researchers have begun to question whether the goal of protecting research participants is accomplished by having each site’s local institutional review board (IRB) conduct a full review of multicenter protocols, which can add significant delay to study startup [1-3]. In addition, multiple IRB reviews may result in different ethical or regulatory standards at different sites, which may frustrate trial recruitment and make it difficult to compare across sites [4]. To improve efficiency, the Food and Drug Administration (FDA) has developed guidelines for the use of central IRBs [5-7]. However, despite the growth in the number of central IRBs, they still face many challenges. The longer time between submission of a protocol to an IRB and the time it takes to receive review and approval can be a major constraint in the conduct of clinical research, especially in situations where speed is critical. The use of central IRBs in multicenter trials can also lead to logistical challenges, such as the need to coordinate the activities of multiple sites and to ensure that all sites are compliant with the same ethical and regulatory standards. In addition, the use of central IRBs can lead to increased costs, as well as potential legal and regulatory issues.

Despite this support, research institutions differ in their willingness to defer to a central IRB review [8]. To facilitate the ethical and efficient conduct of multicenter trials, we sought to determine the barriers to using central IRBs for multicenter clinical trials in the United States, formulate solutions to overcome these barriers, obtain feedback on the proposed solutions from stakeholders to discuss US research institutions and develop recommendations for implementing these solutions.

Methods

The Clinical Trials Transformation Initiative (CTTI) supported this project to solicit current perceptions of barriers to the use of central IRBs and to formulate potential solutions. We conducted a review of the literature and held a series of discussions with 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 IRB review and to generate solutions. We identified 33 published reports (unpublished data). Identified barriers included differences in the way regulating and regulatory bodies interpret and apply regulations, and differences in the way IRBs interpret regulations, which can lead to inconsistencies in the way trials are conducted across sites. In addition, the lack of clear guidance from regulatory bodies on how to handle central IRB review can also be a barrier.

Results

Our findings indicate that central IRBs can be effective and efficient for conducting multicenter clinical trials. However, there are several challenges that need to be addressed. These include differences in the way regulatory bodies interpret and apply regulations, differences in the way IRBs interpret regulations, and the lack of clear guidance from regulatory bodies on how to handle central IRB review. These challenges can be addressed through the development of clear, consistent guidance from regulatory bodies on how to handle central IRB review, as well as the development of tools that can help research institutions to overcome these barriers and to improve the efficiency of conducting clinical trials.
What do we need?
Comments to Dec 2014 NIH Draft Policy* – Tools, Please!

“Develop tools, guidance, and best practices to help facilitate the use of single IRB review mechanisms (e.g., model reliance agreements, standard operating procedures, etc.)” - PRIM&R

“Roles and responsibilities of all sites must be clearly and explicitly defined before institutions will be confident in the ability to cede or take on IRB review for all NIH-funded multi-site studies.” - AAMC

“Institutions will need more guidance on how to choose a single IRB, and when this decision needs to be made.” - AAMC

Guidance should clearly define the role and responsibilities of “a single IRB of record” and that of the institution, with concrete suggestions for implementation. - SCRS


To assess and propose solutions for remaining areas of concern for using single IRBs of record for multicenter clinical trials

Address the “How-To”

- What about local context?
- Is there an example IRB Authorization Agreement?
- What do I need to do at my institution?
- How do I select a central IRB?
- I’m a sponsor, can I really require my sites to do this?
CTTI Recommendations:
Central IRB Advancement Project (2015)
Recommendation #1

CTTI recommends use of the CTTI-developed *Evaluation Checklists*:

- for institutions to determine their readiness to use a Central IRB (federal, academic, or independent IRB) for multicenter clinical trials,
- for institutions/sponsors when selecting a particular IRB to serve as the single IRB of record, and
- for Central IRBs when deciding whether to work with a specific institution during a multicenter clinical trial.
Three Evaluation Checklists

Are you CONSIDERING adopting a Central IRB model for multicenter clinical trial protocols?

▶ Institutional Self-Evaluation

General considerations for institutions deciding whether to adopt the Central IRB model

Have you DECIDED to use a central IRB for a multicenter clinical trial?

▶ Institution / Sponsor Evaluation of a Central IRB

General considerations for institutions and sponsors when selecting a particular Central IRB

Are you SERVING as the Central IRB for a multicenter clinical trial?

▶ Central IRB Evaluation of an Institution

General considerations for Central IRBs when deciding whether to work with a specific institution
Recommendation #2

To address administrative and legal concerns and to reduce time when first executing a reliance (authorization) agreement, CTTI recommends that institutions and IRBs adopt or begin negotiations with the CTTI-developed IRB authorization agreement template.
Recommendation #3

To address local context concerns, CTTI recommends that IRBs and institutions follow the Secretary's Advisory Committee on Human Research Protections (SACHRP) Recommendations on Consideration of Local Context with Respect to Increasing Use of Single IRB Review (January 2013).
Recommendations #4 & #5

CTTI recommends additional research be conducted to further define quality in IRB review.

CTTI recommends research be conducted to develop data and technology standards across electronic IRB application systems to facilitate communication and efficacious and transparent review.
CTTI Tools in Process of Adopting Central IRB Model

Research Institution

Perform self-evaluation:
- Evaluation Checklist (p. 2)
- Considerations Document
- SACHRP Local Context Recommendations

Using a central IRB?

Yes

Evaluate central IRB(s) or determine willingness to use sponsor-chosen IRB:
- Evaluation Checklist (p. 3)

Choose IRB or accept sponsor-chosen IRB?

Yes

Assign responsibilities:
- Considerations Document

Willing to work with institution?

Yes

Evaluate institution:
- Evaluation Checklist (p. 4)

Central IRB

Execute Authorization Agreement:
- IAA Template

Sponsor

Evaluate central IRB(s):
- Evaluation Checklist (p. 3)

Choose IRB
All project information available at:
https://www.ctti-clinicaltrials.org/projects/central-irb

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THANK YOU.

www.ctti-clinicaltrials.org