



CLINICAL  
TRIALS  
**TRANSFORMATION**  
INITIATIVE

*November 14, 2017*

# 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

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# **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:

- 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.
    - 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.

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## 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 conflating responsibilities of the institution with the ethical review responsibilities of the IRB. We identified the need for concrete tools to help research institutions separate institutional responsibilities from ethical responsibilities required of the IRB. One such tool is a document we created that delineates these responsibilities and how they might be assigned to each entity, or, in some cases, both entities. This tool and project 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.

**Citation:** Flynn KE, Hahn CL, Kramer JM, Check DK, Dombeck CB, et al. (2013) Using Central IRBs for Multicenter Clinical Trials in the United States. PLoS ONE 8(1): e54999. doi:10.1371/journal.pone.0054999

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**Competing Interests:** SB is an employee of Celgene Corporation. FK is an employee of Chesapeake IRB, and JP is an employee of the Gemini Group. There are no patents, products in development or marketed products to declare. This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials, as detailed online in the guide for authors.

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### Introduction

Maximizing the efficiency of multicenter clinical trials so they can provide high-quality evidence to answer important medical questions is an important public health interest. As multicenter clinical trials have become more common, researchers have begun to question whether the goal of protecting research participants is enhanced by having each site's local institutional review board (IRB) conduct a full review of multicenter protocols, which can add significant delays to study start-up [1,2]. In addition, multiple reviews may result in differences in the way patients are treated at different sites (eg, because of differences in informed consent forms) for which there is no ethical justification but may cause confusion among participants.

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

Despite this support, research institutions differ in their willingness to defer to centralized IRB review [6,7].

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 at diverse 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 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. We identified 33 published reports (unpublished data). Identified barriers included apprehension about regulatory and legal liability, issues regarding the local context of research, and logistic barriers such as loss of income

## Use of central institutional review boards for multicenter clinical trials in the United States: A review of the literature

Devon K Check, Kevin P Weinfurt, Carrie B Dombeck, Judith M Kramer and Kathryn E Flynn

**Background** To improve the efficiency of conducting multicenter clinical trials, the Food and Drug Administration, the Office of Human Research Protections, and the Department of Health and Human Services have expressed support for using a centralized institutional review board (IRB) process. However, research institutions differ in their willingness to defer to central IRBs.

**Purpose** We aimed to review and describe peer-reviewed journal articles on the use of central IRBs for multicenter clinical trials in the United States in an effort to inform the policy discussion about central IRBs.

**Methods** We used a PubMed search and consulted IRB experts and the bibliographies of other reviews to identify relevant commentaries and empirical studies.

**Results** Our search identified 33 articles related to the use of central IRBs for multicenter trials in the United States. Of these, 22 were commentary pieces and 11 were empirical studies.

**Limitations** Our review was restricted to journal articles about the use of central IRBs for multicenter clinical trials in the United States.

**Conclusions** There is limited empirical work on the use of central IRBs for multicenter trials in the United States. Most published studies focused on problems in efficiency associated with redundant local reviews of multicenter studies and the potential benefits of a centralized system. Because the absence of studies on the use of central IRBs may be due to their infrequent use, additional work is needed to generate data on the use of central IRBs and to elucidate and address the concerns that research institutions have about deferring ethical review to a central IRB. *Clinical Trials* 2013; 0: 1–8. <http://ctj.sagepub.com>

### Introduction

Maximizing the efficiency of conducting multicenter clinical trials would serve the public health interest by allowing more trials to be performed to provide unbiased answers to important medical questions. Procedural requirements at research sites before participant enrollment are often a source of significant delay. Review and approval of the trial protocol by multiple institutional review boards

(IRBs) can delay start-up in multicenter trials [1]. To improve trial efficiency, the Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), and the Department of Health and Human Services (DHHS) expressed support for a centralized IRB review process [2–4]. In July 2011, DHHS proposed to change the Common Rule to require centralized review for multicenter trials, and in October 2012, the Secretary's Advisory Committee on Human Research Protections

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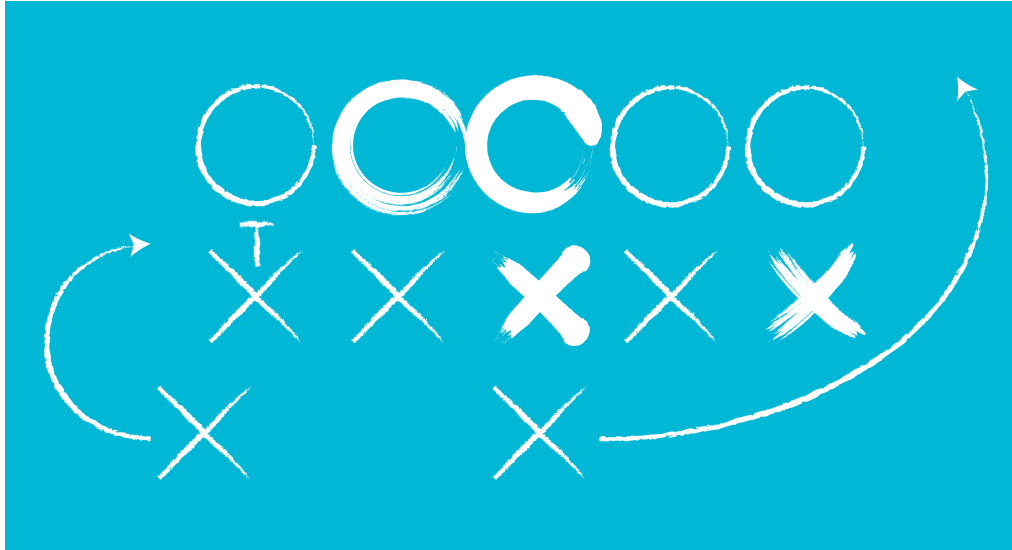
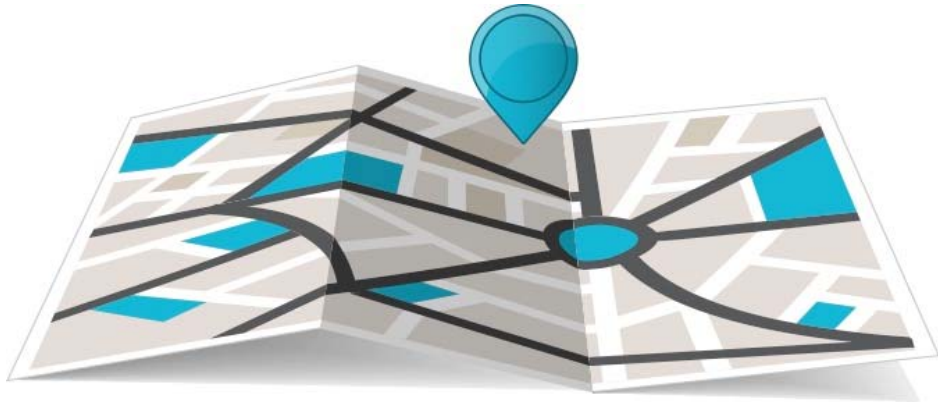
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# What do we need?



## 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](#)

\*<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html>

# CTTI Central IRB Advancement – Follow-on Project (2013-2015)

- ▶ 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?

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# **CTTI Recommendations: Central IRB Advancement Project (2015)**

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# 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.

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## Recommendation #3

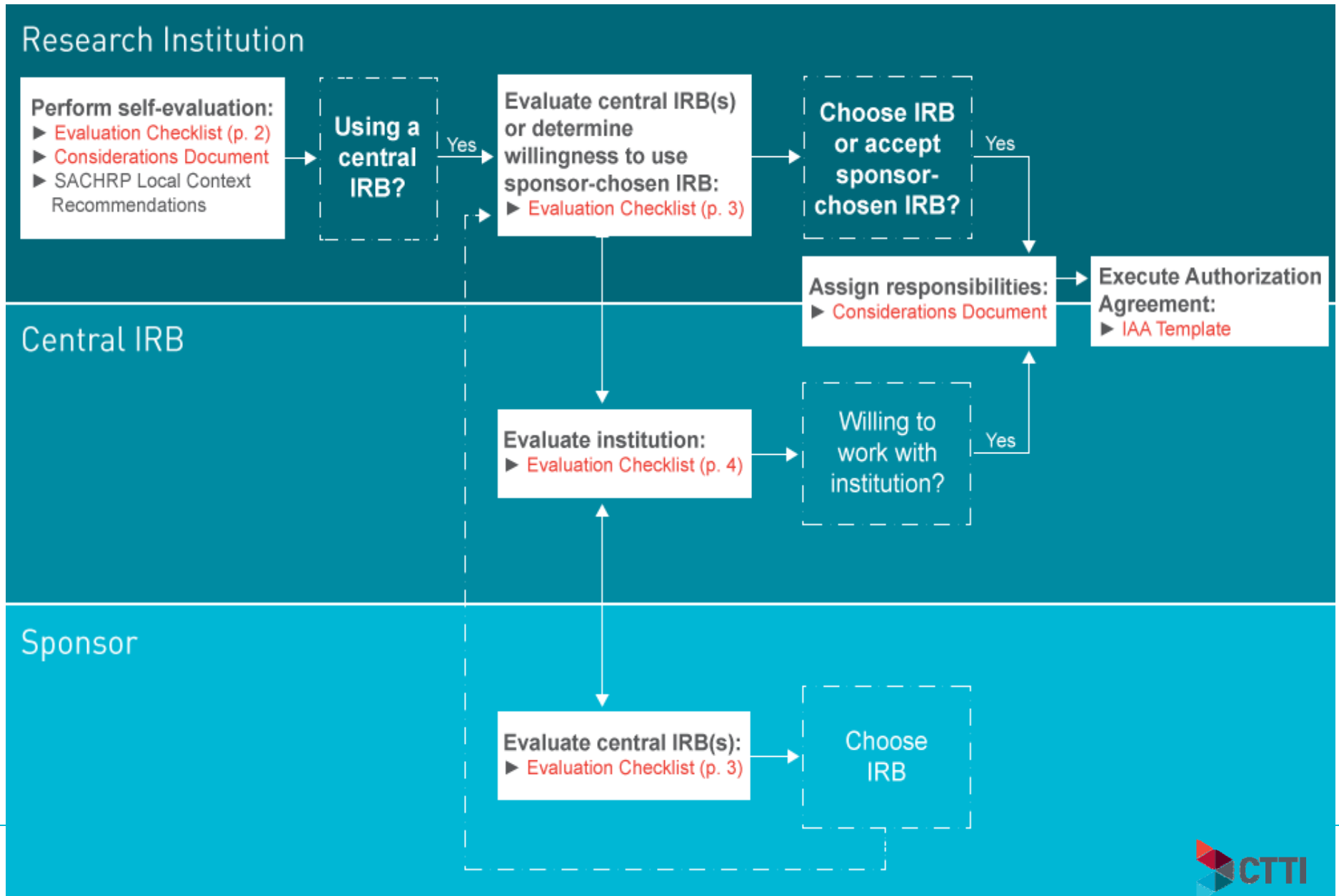
- ▶ To address local context concerns, CTTI recommends that IRBs and institutions follow the [Secretary's Advisory Committee on Human Research Protections \(SACHRP\) Recommendations on Consideration of Local Context with Respect to Increasing Use of Single IRB Review \(January 2013\)](#).



## 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



# All project information available at:

 <https://www.ctti-clinicaltrials.org/projects/central-irb>

## QUICK LINKS TO TOP DELIVERABLES

### Project Summary

April 27, 2015

Summary of CTTI's Central IRB Projects

### Recommendations

April 27, 2015

Advancing the Use of Central IRBs for  
Multi-center Clinical Trials

### Recommendations

January 30, 2013

Use of Central IRBs for Multi-center  
Clinical Trials

### Tool

January 30, 2013

Considerations Document: To address blurred distinctions between responsibilities for ethics review and other institutional obligations, sites and IRBs can use this tool to support communication and contractual relationships between institutions and a central IRB.

### Tool

April 27, 2015

Evaluation Checklist: To assist organizations with adoption of a central IRB model for multi-center clinical trials

### Tool

April 27, 2015

Template IRB Authorization Agreement (IAA): Intended to address an administrative concern about using a single central IRB

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# THANK YOU.



[www.ctti-clinicaltrials.org](http://www.ctti-clinicaltrials.org)

