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**An Update on the
CTTI Use of Central
IRBs for Multicenter
Clinical Trials Project**

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Objectives

- ▶ **Review the results and recommendations of the CTTI Use of Central IRBs for Multicenter Clinical Trials project.**
- ▶ **Describe the purpose and utility of the Considerations Document, a CTTI developed guide to support communication and contractual relationships between institutions and a central IRB.**
- ▶ **Share case examples of the successful adoption of the recommendations and use of the Considerations Document.**

Clinical Trials Transformation Initiative (CTTI)

- ▶ **Established by the FDA and Duke University as a public-private partnership in 2007**
- ▶ **All stakeholders involved**
- ▶ **Identifies and promotes practices that will increase the quality and efficiency of clinical trials**

Background

- ▶ 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.^{1,2}
- ▶ Research institutions' willingness to defer to centralized IRB review varies

1. Guidance for Industry - Using a Centralized IRB Review Process in Multicenter Clinical Trials; March 2006
2. Menikoff J. The paradoxical problem with multiple-IRB review. N Engl J Med. 2010; 363:1591-1593.

CTTI Project:

Use of Central IRBs for Multicenter Clinical Trials

▶ Goal

Identify solutions to address barriers to the adoption of central IRBs for multicenter clinical trials

▶ Objectives

- ▶ Solicit current perceptions of barriers
- ▶ Develop a strategy to address the identified barriers
- ▶ Assess reactions to proposed solutions to remove these barriers

Methods

- ▶ **Literature Review**
- ▶ **Expert Advisory Panel**
 - ▶ Institutional, federal, and commercial IRBs, industry, and regulatory agencies
- ▶ **Semi-structured Interviews**
 - ▶ Stakeholders at six research institutions
- ▶ **Expert Meeting**
 - ▶ Federal and industry sponsors, independent IRBs, research institutions, regulatory agencies, and patient advocates

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.

Need to clarify terms

- ▶ **Central IRB = Single IRB-of-record for a given protocol**
 - ▶ To which sites cede all regulatory responsibility for scientific oversight and integrity of the protocol from initial review to termination of the research including informed consent
 - ▶ A range of entities may serve as a central IRB
 - ▶ e.g., independent IRBs, federal IRBs, another institution's IRB
 - ▶ Implies that an institution not choosing to use the single IRB-of-record would not participate in that protocol

Commonly cited barriers

- ▶ **Legal and regulatory**
- ▶ **Assurance of review quality by an external IRB**
- ▶ **Administrative and logistic**
- ▶ **Local context**
- ▶ **Financial**

Common Themes

- ▶ **Concerns seemed to be 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**

Recommendation #1

- ▶ **CTTI recommends using a central IRB (defined as a single IRB of record for all sites) to improve the quality and efficiency of multicenter clinical trials.**

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.**

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.**

“Considerations” Document

- ▶ **Considerations in Assigning Responsibilities to a Central IRB and a Local Institution for a Multicenter Clinical Trial**
 - ▶ Tool created by the project team, which clearly delineates responsibilities and how they might be assigned to each entity (IRB or Institution), or, in some cases, both entities.
 - ▶ The purpose 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.
 - ▶ The document is meant to support communication between institutions and external, central IRBs

Considerations Document: Roles Defined

- ▶ **Central IRB**
- ▶ **Institution**
- ▶ **Either Central IRB or Institution**
- ▶ **Both Central IRB and Institution**

Roles Defined: Central IRB

- ▶ Register with FDA and OHRP
- ▶ Review clinical trials for compliance with regulations
- ▶ Provide investigator with copies of all IRB approvals
- ▶ Collect, review, and take into account site specific information
- ▶ Review and approve informed consent
- ▶ *Provide the institution with information related to any significant financial interests the IRB becomes aware of*
- ▶ Evaluate investigator qualifications to conduct clinical trials.

Roles Defined: Central IRB

- ▶ Provide institution with copies of IRB approvals, rosters, and minutes upon request
- ▶ Notify the institution promptly in writing of serious or continuing non compliance, harm to subjects, or any unanticipated problems involving risks to subjects or others.
- ▶ Notify the institution promptly in writing of a suspension or termination of IRB approval and any remedial actions required.
- ▶ If for an institution that conducts federally sponsored research, the central IRB must commit to adhere to the requirements of the institution's FWA.

Roles Defined: Institution

▶ Not Protocol Specific

- ▶ Maintain program for education and training for human subject research
- ▶ Maintain policies and procedures for the conduct of human subject research
- ▶ Maintain appropriate institution specific credentialing of staff
- ▶ Maintain appropriate approved FWA, ensure that Central IRB arrangements are documented by a written agreement
- ▶ If accredited, maintain all functions relevant to maintenance of accreditation.
- ▶ *Conduct a privacy and security review as required by HIPAA with respect to the use and disclosure of PHI*

Roles Defined: Institution

▶ Protocol Specific

- ▶ Ensure IRB approval is obtained for research protocols involving human subjects
- ▶ For PHS funded research conduct a conflict of interest review pursuant to PHS regulations on promoting objectivity in research
- ▶ Ensure that the investigators are conducting research in accordance with IRB approved protocols, procedures and documents

Roles Defined: Either CIRB or Institution

- ▶ Evaluate the local context
- ▶ If requested, provide a waiver of authorization pursuant to HIPAA

Roles Defined: CIRB and Institution

▶ Execute an IRB Authorization Agreement

- ▶ Develop a SOP detailing roles and timeframes for reporting to sponsors, and applicable agencies serious adverse events, serious and continuing non-compliance, or unanticipated problems involving risks to subjects or others
- ▶ Clearly communicate expectations including requirements, sharing of information, and potential disciplinary actions in the event of non-compliance
- ▶ Develop a communication plan for sharing information about the site, investigators, sponsor, and the clinical trial including communication about any substantive changes

Case Examples

- ▶ **When your institution agrees to rely on an “external” IRB**
- ▶ **When your institution agrees to serve as the “central” IRB.**
- ▶ **In both situations:**
 - ▶ An IRB Authorization or Reliance Agreement must be executed
 - ▶ The IRB Authorization or Reliance Agreement should outline the responsibilities of each party
 - ▶ How you get from agreement to implementation...well that’s another story

Steps to Successful Reliance

- ▶ **Employ Change Management Techniques**
 - ▶ Assess your institutional culture
 - ▶ Establish goals and deliverables (plan!)
 - ▶ Identify potential champions and naysayers
 - ▶ Involve Stakeholders early and often
 - ▶ Provide regular feedback

- ▶ **Develop metrics: “What does success look like?”**

Steps to Successful Reliance

- ▶ **Assess Institutional Culture: scope your reliance and ask questions**
- ▶ **Would you consider:**
 - ▶ All kinds of studies open for reliance?
 - ▶ Any IRB, commercial, federal, academic for reliance?
 - ▶ If commercial: a single commercial IRB that your institution has contracted with or the IRB that “comes” with the study?

Steps to Successful Reliance

- ▶ **Assess Institutional Culture: scope your reliance and ask questions**
 - ▶ If your institution is hesitant consider pilot reliance in certain studies or with certain groups first
 - ▶ Set milestones! As with all “pilot” projects there should be a deliverable (report out) at a set point where a decision should be made:
 - ▶ discontinue the program (why?)
 - ▶ continue the program for X when the next report is due
 - ▶ expand the program

Steps to Successful Reliance

- ▶ **Establish Goals and Deliverables**
 - ▶ What is your desired outcome and timeline?
 - ▶ Stakeholder assessment: Identify your champions and your naysayers and everyone in between!
 - ▶ Develop your project plan: who, what, and when

- ▶ **Identify metrics: “What does success look like?”**

Steps to Successful Reliance

▶ Stakeholder Engagement

- ▶ Start the conversation and continue it formally and informally
- ▶ Hold meetings but also develop an elevator speech for those hallway conversations.
 - ▶ “I just got back from PRIMR and there was a lot of conversation around the best way to conduct ethical review for multicenter studies that involve people. One way would be to use a central IRB for multicenter studies, which would mean a single IRB review for all sites. Have you ever considered this? How do you think we could implement such a program here?”
- ▶ Hold focus groups from across diverse groups of stakeholders to develop workflow, revise forms and inform for necessary policy or procedure changes.
- ▶ Provide regular updates, communicate, communicate, communicate

Steps to Successful Reliance

- ▶ **Plan and Develop a Business Model**
- ▶ **Execute the Model: Just Do it!**
- ▶ **Assess, Reassess and Report Out**

Case: North Shore-LIJ Health System

- ▶ **NSLIJHS is a 16 hospital, 2500+ employed physicians, health system based in the NYC and suburban NY area, geographic reach covers the majority of NYC and Long Island. Currently the 3rd largest secular health system in the US.**
- ▶ **The HRPP manages over 2,000 HRPP projects and our investigators are very collaborative.**

Case: North Shore-LIJ Health System

▶ Selected Internal and External Change

▶ 1998

- ▶ NSLIJHS was created when 2 large local tertiary hospital “systems” merged
- ▶ In 1998 total number of HRPP protocols was less than 1,000
- ▶ In 1998 total number of investigator-sponsor held INDs was 1 a year

▶ 1999

- ▶ April: West LA VA’s MPA is deactivated due to non compliance with OPRR (now OHRP)
- ▶ May: Duke’s MPA is suspended by OPRR for problems with continuing review
- ▶ Sept: Death of Jesse Gelsinger
- ▶ NSLIJHS implements a growth strategy which includes research

Case: North Shore-LIJ Health System

▶ Selected Internal and External Change

▶ 2000

- ▶ DHHS introduces the FWA to soon replace MPAs and SPAs, compliance visits continue
- ▶ NIH requires HRPP training for all NIH funded investigators

▶ 2001

- ▶ June: Death of Ellen Roche at Johns Hopkins
- ▶ July: Suspension of Johns Hopkins' s assurance (# of studies affected 2,500, ~15,000 research subjects)

▶ 2003: HIPAA Privacy Rule

▶ 2005: HIPAA Security Rule

▶ 2007: Clinicaltrials.gov requirements

▶ 2009: HITECH

Case: North Shore-LIJ Health System

- ▶ **Selected Internal and External Change**
 - ▶ 2013 NSLIJHS Research Portfolio
 - ▶ 2000+ active human studies, ~15,000 participants
 - ▶ 6-7 active INDs each year
 - ▶ Growth of 20% each year
 - ▶ Moves scientifically from Phase III studies to earlier phase clinical trials and pre-clinical translational work
 - ▶ Funding moves towards non traditional sources, emphasis on applied discovery and technology transfer

Case: North Shore-LIJ Health System



DINAH SHERIDAN, our "cover girl" this issue, is really pleased with her Hawkins and kindly posed for this picture specially for Silver Lining—stars in their sphere!

A HAWKINS SAVES YOUR WEALTH

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Case: North Shore-LIJ Health System

- ▶ **How do we build efficiencies into the process while still maintaining ethical and compliant systems for our HRPP?**
 - ▶ Since 2003 NSLIHS has been partners with with 4 other academic centers in New York in establishing an IRB to review industry sponsored clinical trials.
 - ▶ However, until recently the institution was reluctant to rely on a central IRB as defined here: as a single IRB of record.

Case: North Shore-LIJ Health System

Accepting Reliance on an External IRB

- ▶ **Initial Scope (our phased approach):** NSLIJ started with minimal risk multicenter projects or studies where we were engaged from a regulatory perspective but minimally involved in the majority of study tasks.
- ▶ **Resource Allocation/Deliverables:** Allows the HRPP to focus on consultation for riskier studies, those involving vulnerable populations, to implement informed consent monitoring, GCP monitoring, investigations etc.

Case: North Shore-LIJ Health System

Accepting Reliance on an External IRB

- ▶ **NSLIJHS now routinely relies on external IRBs: commercial, academic, and federal and those reliance agreements may be based on a program, an institutional alliance or study specific.**
- ▶ **The HRPP workload has not lessened (in some areas it increased) but it has CHANGED**
- ▶ **Resources have been deployed in new ways, focus is more on oversight of study conduct and implementation at our institution, regardless of IRB utilized.**

Case: North Shore-LIJ Health System

Practical Tasks

- ▶ Educate the Institution about Institutional Responsibilities versus IRB Responsibilities!
 - ▶ Widely disseminate the Considerations Document
- ▶ Review and revise all policies and procedures:
 - ▶ “the investigator may not proceed without approval from the NSLIJHS IRB” to “the investigator may not proceed without approval from a NSLIJHS authorized IRB Committee”
 - ▶ “Contact the IRB Office” to “Contact the Human Research Protection Program”
 - ▶ IRB approval versus Institutional approval: who has the final say?

Case: North Shore-LIJ Health System

Practical Tasks

- ▶ Separate HRPP Policies from “IRB” Policies: Ensure you have institutional policies that apply regardless of IRB Utilized
 - ▶ Research with Human Subjects (IRB Approval)
 - ▶ Principal Investigator Responsibility for Human Subject Research
 - ▶ Informed Consent and Recruitment for Human Subject Research
 - ▶ Training in the Conduct of Human Subject Research
 - ▶ Compensation for Research Subjects
 - ▶ Review and Management of Conflict of Interest in Research
 - ▶ Maintenance, Storage, and Archiving of Human Subject Research Data
 - ▶ Access Use and Disclosure of Protected Health Information for Research
 - ▶ Human Subject Research Oversight, Monitoring, and Reporting

Case: North Shore-LIJ Health System

Practical Tasks

- ▶ Review and revise process and forms to facilitate institutional review:
 - ▶ Separate ethical tasks from administrative tasks
 - ▶ Decide what body within the organization will be authorized to provide “institutional approval” once IRB approval is in place
 - ▶ Do not duplicate questions or add in new layers of approval without first assessing why those questions appeared on the IRB forms in the first place.
 - ▶ Consider whether your institution would want to be relied on. What information would you need if you were the IRB of record?

Case: North Shore-LIJ Health System

- ▶ Application for use by collaborative sites which wish to rely on NSLIJHS IRB:

<http://www.feinsteininstitute.org/wp-content/uploads/2013/02/External-Site-Questionnaire-09-10-12.doc>

- ▶ Application for use by NSLIJHS investigators who wish to rely on an external IRB:

http://www.feinsteininstitute.org/wp-content/uploads/2013/02/Application-for-External-IRB-Use_8.29.13.doc

Case: North Shore-LIJ Health System

- ▶ Application for use by collaborative sites which wish to rely on NSLIJHS IRB:

By signing below, I acknowledge that I have reviewed this protocol for scientific validity, and confirm that the investigators have the appropriate credentials to perform the research procedures. I have read the attached protocol submission and the execution of the project has my endorsement. I understand that it is **my responsibility** as to closely supervise research to ensure continued protection of human research subjects at my facility including compliance with 45CFR46, and 21CFRParts 50 and 56.

Facility Approval: Signature: _____ Date _____

Printed Name: _____

Title: _____

Case: North Shore-LIJ Health System

- ▶ **Application for use by collaborative sites which wish to rely on NSLIJHS IRB:**
 - ▶ Confirm that all investigators on this application have the adequate resources to protect human subjects: Yes No
 - ▶ Explain how staff is qualified; include any training and expertise specific to the conduct of this study. Include information about relevant licenses/medical privileges, as applicable:
 - ▶ Detail processes to inform staff of the protocol and their duties and functions for this study:
 - ▶ Have any of these individuals been sighted for noncompliance by a Federal Agency, in the past 3 years? If so, explain:
 - ▶ Have any of these individuals been debarred as a clinical investigator, by the FDA or ORI, in the past 3 years? If so, explain:

Case: North Shore-LIJ Health System

- ▶ **Application for use by NSLIJHS investigators who wish to rely on an external IRB:**
 - ▶ Sections on HIPAA (Privacy and Security), Required Training and COI Disclosure
 - ▶ Institutional Approvals (check and obtain all that apply, note it is the local investigator's responsibility to know and follow all local policies regarding clinical research):
 - ▶ Investigational Drugs Approval: _____
 - ▶ Radioactive Material Approval: _____
 - ▶ Recombinant DNA Approval: _____

Case: North Shore-LIJ Health System

STATEMENT OF COMPLIANCE

If the External Institutional Review Board approves this project, I agree to:

- Execute the research plan as described in protocol, including obtaining informed consent from all subjects as deemed appropriate by the IRB.
- Accept responsibility to comply with the standards and requirements stipulated in the above documents and to protect the rights and welfare of human subjects involved in research conducted under this protocol
- Comply with all other applicable federal, international, state, and local laws, regulations, and policies that may provide additional protection for human subjects participating in research conducted under this application.
- Report immediately to this Institution any unanticipated problems involving risks to subjects or others in research covered under this protocol
- When responsible for enrolling subjects, obtain, document, and maintain records of informed consent for each such subject or each subject's legally authorized representative as required under HHS regulations at 45 CFR part 46 and stipulated by the IRB.
- Report to sponsors and agencies as required.
- Maintain records of research, including consent documents, for a minimum of six (6) years beyond the termination of the study or, if longer, as specified by the funding agency/sponsor of the project.

There will be routine audits of research protocols by Research Compliance. Failure to comply with any of the above regulations may result in CLOSURE OF THE STUDY by this institution.

PRINCIPAL INVESTIGATOR STATEMENT

I hereby assure compliance to the above and assume responsibility for all activities involved in this project.

Printed name of PI

Signature of PI

Date

Case: North Shore-LIJ Health System

- ▶ **Establish the Business Model:**
 - ▶ Define Workflow for the investigator, institution, institutional HRPP, and central IRB: who, what, and when
 - ▶ Evaluate Costs
 - ▶ Establish and publish a HRPP fee structure
 - ▶ Communicate with and educate your grants office and/or your clinical trials office
- ▶ **NSLIJHS builds into budgets study start up and administrative fees.**

Human Research Protection Program

- ▶ Distinctions of a Quality Program as per AAHRP
 - ▶ Strong integrated plan for human research protection
 - ▶ Strong program for scientific review
 - ▶ Strong and highly motivated organizational leader
 - ▶ Program for review of resources for the HRPP
 - ▶ Research specific IRBs
 - ▶ Strong network of communication among units
 - ▶ Policy and procedure to identify and manage organizational conflict of interest
 - ▶ Strong quality improvement programs
 - ▶ Strong education programs for researchers and staff
 - ▶ Highly competent IRB chairs, members, or staff
 - ▶ Impressive educational materials for the community

▶ THANK YOU



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