CTTI Advancing the Use of Central IRBs Project: Academic Institution and Government Sponsor Perspectives

NIH Collaboratory Grand Rounds: Rethinking Clinical Research

25 April 2014

CLINICAL TRIALS TRANSFORMATION INITIATIVE

CTTI Advancing the Use of Central IRBs Project: Academic Institution Perspective

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CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

CTTI Project: Use of Central IRBs for Multicenter Clinical Trials

- **Issue:**
  - FDA, OHRP, and DHHS support the use of central IRBs to meet the requirements of existing IRB regulations
  - Research institutions' willingness to defer to centralized IRB review varies
- **Goal: Identify solutions to address barriers to the adoption of central IRBs for multicenter clinical trials**
- **For more info: ctti-clinicaltrials.org/what-we-do/study-start/central-irb**

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Results: 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

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Results: 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 ("Considerations Document") to support communication and contractual relationships between institutions and a central IRB.

“Considerations” Document

- **Considerations in Assigning Responsibilities to a Central IRB and a Local Institution for a Multicenter Clinical Trial**
- **Roles defined:**
  - Central IRB
  - Institution
  - Either Central IRB or Institution
  - Both Central IRB and Institution

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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.**

IRB Authorization Agreements (IAA)

- **Whether your institution agrees to rely on an "external" IRB or agrees to serve as the "central" IRB.**
  - 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!)
  - Develop a business plan
  - Identify potential champions and naysayers
  - Involve Stakeholders early and often
  - Provide regular feedback

- **Develop metrics: "What does success look like?"**

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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?

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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

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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 participated in a webinar around alternative 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

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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

- **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.

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Case: North Shore-LIJ Health System

Accepting Reliance on an External IRB

- **Initial Scope (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.**

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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.

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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?

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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

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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?

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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.**

Advancing the Use of Central IRBs

- **To assess and propose solutions for remaining areas of concern for using a single central IRBs for multicenter clinical trials**
  - Collected Tools and Templates
  - Developing “Best Practice” IRB Authorization Agreement
  - Expert Meeting: June 2014

- **To advance the use of central IRBs for multicenter clinical trials**

CTTI Advancing the Use of Central IRBs Project: Government Sponsor Perspective

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National Institute of Neurological Disorders and Stroke (NIH/NINDS)

25 April 2014

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Background and Rationale for cIRB use

- **Patients are frustrated with the slow pace of translational clinical research**
- **Research teams spend too much time on bureaucratic tasks**
- **Typical start-up time for NINDS funded trials is about 1 year**
- **Separate local IRB review at each site adds delays and cost (Ravina et al, 2010)**
- **Uncertain value-added**
  - Inconsistencies in IRB assessment between sites (Hirshon et al, 2002)
  - Local context, but also different levels of scrutiny and differences in interpretation of federal regulations (Silverman et al, 2001)
  - Distributed accountability; no IRB takes charge? (Menikoff 2010)

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Aims for streamlining IRB and subcontracting

- **Promote the use of a fully central IRB in NINDS-funded multi-center research**
- **Track effect on trial start-up**
- **Use NeuroNEXT trial network as demonstration project to gain experience with**
  - Developing master trial agreement templates
  - Establishing reliance agreements between institutions
  - Defining the scope of work at central IRB site and relying sites

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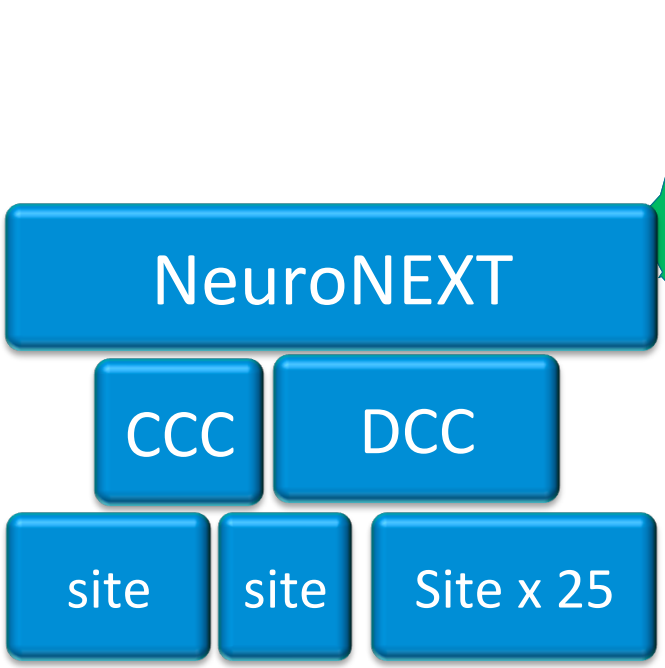
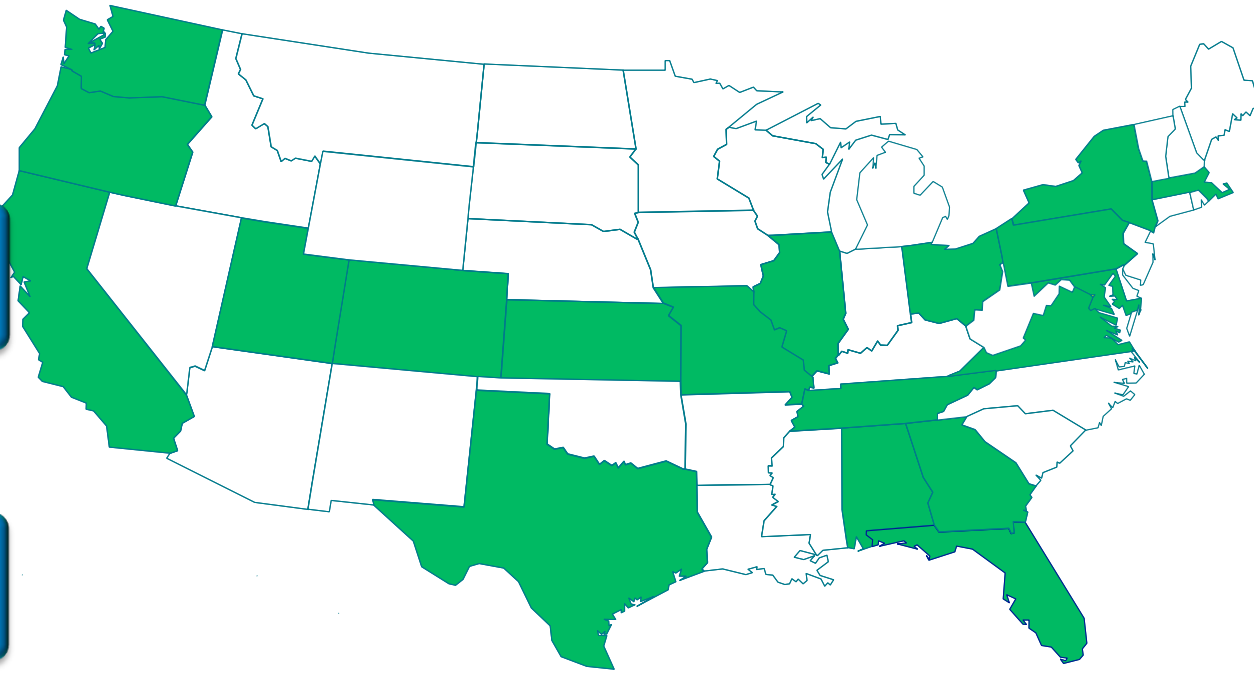
What is NeuroNEXT

- **Phase 2 clinical trials network with goals to**
  - Conduct high quality phase 2 trials, using biomarkers when available
  - Accelerate drug development through established infrastructure
  - Coordinate between private and public sector through partnerships
- **Additional process goal to**
  - Streamline trial process through central IRB and master trial agreements





Clinical sites

- Albert Einstein College of Medicine- Yeshiva
- Children's of Boston
- Children's National
- Columbia/Cornell
- Emory, Atlanta
- Harvard Partners (MGH/BWH)
- Northwestern University
- Ohio State University
- Oregon Health and Science University
- Swedish Health Services (Seattle)
- SUNY (Buffalo, Downstate, Upstate, and Stony Brook)
- University of Alabama, Birmingham
- University of California, Davis
- UCLA
- University of Cincinnati
- University of Colorado, Denver
- University of Kansas
- University of Miami
- University of Pittsburgh
- University of Rochester
- University of Utah
- University of Virginia
- University of Texas, Dallas
- Vanderbilt
- Washington University in St. Louis

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Interview phase

- **Stakeholder interviews to understand barriers and opportunities**
  - FDA
  - NIH
  - OHRP
  - Patient groups
  - Industry
  - Academic investigators
  - Institutional officials

Outcomes

- **Most stakeholders support streamlined IRB models**
- **Institutional officials voiced concerns**
  - Local context (knowledge of PI's and participants)
  - Protecting "our" participants
  - Autonomy
  - State law
  - Institutional research oversight other than IRB review is linked to IRB operations

Three models

1. Entirely local
2. Collaboration/coordination/information exchange
3. Central/shared: Full reliance (legal agreements)

- NINDS RFAs encouraged Option 3 (central IRB)
- All 25 NeuroNEXT sites accepted a central IRB

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Communication

- IRB representatives invited to investigator meeting
- IRB session at investigator meeting
- Follow-up webinar with focus on IRB
- Transparency for ad hoc sites

Results

- NeuroNEXT investigators were quickly able to implement a central IRB
- Minor barriers could be overcome
- Early experience suggests that the start-up time for NeuroNEXT is shorter than for other NINDS-funded research

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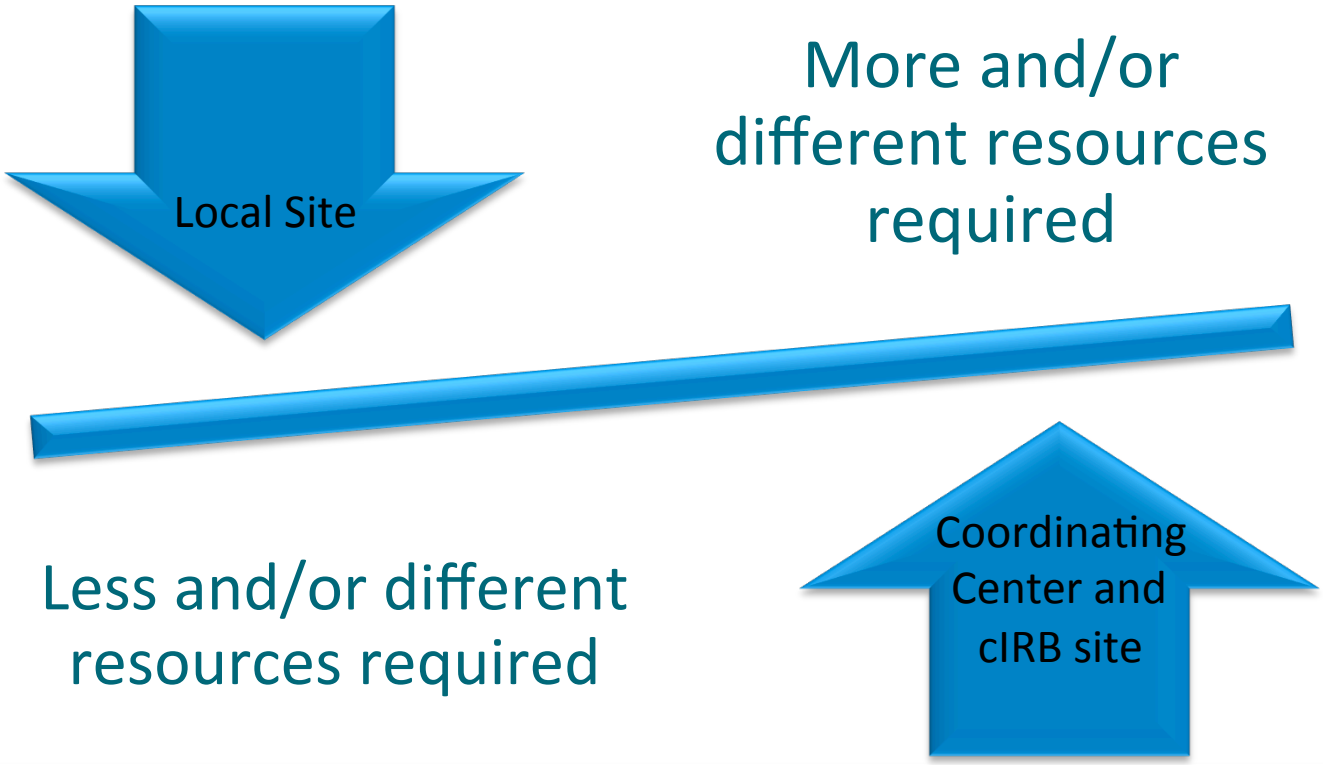
Decreased redundancy expected to be efficient



Administration at the local clinical research site

- **IRB often serves as central operations unit beyond IRB approval**
- **Other functions may be organizationally linked to IRB, such as for example:**
  - Radiation safety, nursing review, COI
- **Electronic systems often designed to address more than IRB issues**
- **Plethora of models, procedures and systems in the US**

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Using cIRB in network of US academic institutions

- **Many models how academic medical centers or larger hospital collaborate with regional partners such as hospitals and clinics.**
- **NeuroNEXT cIRB required reliance agreements with each performance site enrolling patients**
  - Unanticipated delays in obtaining contact and administrative information from some academic institutions that are made up of multiple components

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Change from local to more central IRB models

- **Stakeholders supportive of cIRB use**
- **cIRBs represent disruptive change from status quo**
  - Uncertainty on how to plan and budget
  - IT systems and SOPs need to be modified
  - Multiple models and limited experience
  - Need clear goals and evaluation criteria

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IRB Conference on NINDS experience June 2013

- **cIRB use is a reality at US clinical sites**
- **Institutions often simultaneously work under a spectrum of IRB centralization**
  - Local
  - Shared/fully centralized
  - Mixed local/shared models
- **Institutions work with multiple types of IRBs**
  - Commercial
  - Academic
- **Institutions work under multiple cIRB models**
  - Multiple SOPs
  - Multiple templates
- **Conference participants discussed the potential value of some standardization of the cIRB process**

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NINDS Strategy

- Establish future networks with central IRB and standing master trial agreements
- Next: Stroke network to use central IRB
- Harmonize agreements and procedures

Summary

- Most stakeholders support central IRBs
- Institutional officials in NeuroNEXT agreed to a central IRB
- NeuroNEXT central IRB: early evidence suggests shorter start-up time
- Economies of scale
- NINDS encourages central IRBs for its networks and multi-center trials

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Acknowledgments

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THANK YOU

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