



Sponsors' Perspectives on Advancing the Use of Central IRBs for Multicenter Clinical Trials in the United States

14th November, 2013

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Clinical Trials Transformation Initiative (CTTI)

- ▶ Established by Duke University and the FDA as a public-private partnership in 2007
 - ▶ All stakeholders working together to improve the clinical trials enterprise
 - ▶ Identify and promote practices that will increase the quality and efficiency of clinical trials
-

Thank you!

- ▶ **Advancing the Use of Central IRBs for Multicenter Clinical Trials Project Team**
 - ▶ **Team Leaders/Today's Presenters:**
 - ▶ Cynthia Hahn, VP, Clinical Research and Regulatory Affairs, North Shore-LIJ Health System
 - ▶ Soo Bang, Sr. Director, Business Development & Global Alliances, Celgene Corporation
 - ▶ Petra Kaufmann, M.D., M.Sc., Director, Office of Clinical Research, National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)
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**Cynthia Hahn, VP, Clinical Research and
Regulatory Affairs, North Shore-LIJ Health System**

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Background

- ▶ **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 to meet the requirements of existing IRB regulations.^{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 were to:**

- ▶ 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 that did not typically use central IRBs

- ▶ **Expert Meeting**

- ▶ FDA, OHRP, federal and industry sponsors, independent IRBs, research institutions, and patient advocates
-

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
-

Results: Commonly cited barriers

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

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 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.**

Recommendation #3: Sponsor role

- ▶ **When project results were published (Jan 2013) there was no known examples of industry sponsors requiring the use of a central IRB for MCTs**
- ▶ **NeuroNext was the only known example of NIH sponsored research requiring central IRB use**
- ▶ **National Cancer Institute has transitioned their facilitated review model to an independent model (NCI CIRB is the sole IRB of Record)**
- ▶ **Following are two sponsor examples of utilizing a centralized IRB model**



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**Advancing the Use of Central IRBs
Sponsors' Perspective**

November 14, 2013



Speaker Disclosure & Disclaimer

- ▶ **Presenter is employed by Celgene Corporation**
 - ▶ receives stock options as part compensation
 - ▶ does not hold private stocks in any single pharmaceutical/biotechnology company
- ▶ **The views and opinions are those of the presenter and do not represent those of the speaker's employer or industry**
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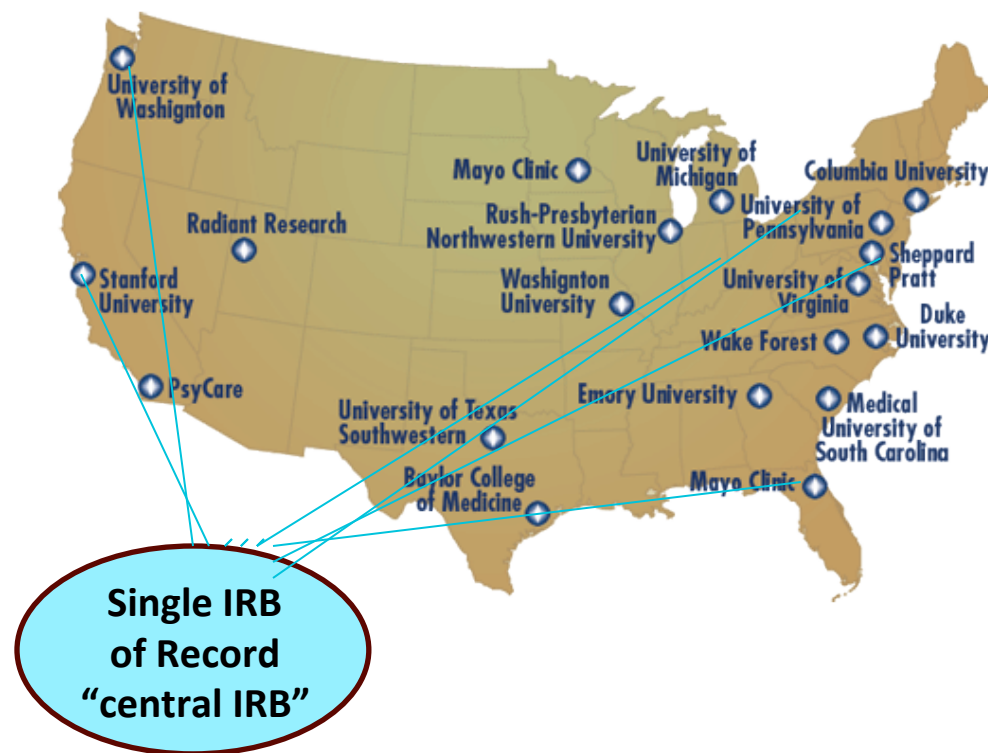
Common Misunderstanding of central IRB Concept

Barriers in realizing efficiencies of central IRB model – Concept Misunderstanding



Institutional
IRB

Commercial
IRB



A "central IRB" can be a non commercial IRB, but used as a single IRB of record to which sites cede all regulatory responsibilities / scientific oversight and integrity of the protocol from initial review to termination , including ICF.

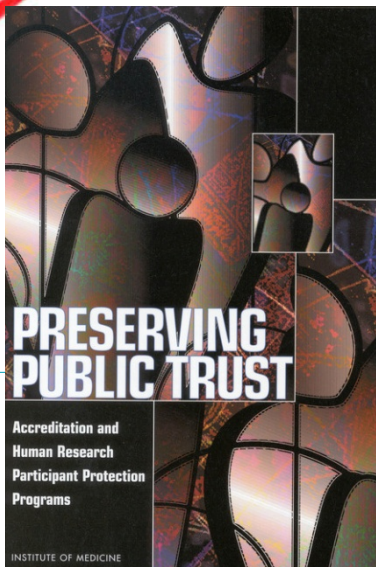
Changing the Paradigm

- ▶ *“Our biggest obstacle in medical research is inertia. We must feel free to abandon failing projects, even if we’ve convinced someone to give us money to work on them.”*
 - ▶ *Adam Ruben, Scientist, Sanaria Inc.*

Journey to Change



Ensuring Human Research Protection



SAFEGUARDS

Human Nature



"YOU ARE NOW LEAVING
THE COMFORT
ZONE"

first step"

Sponsor - central IRB - 2009

- ▶ **Supported large pharmaceutical commitment to Human Research Subject Protection and commitment to AAHRPP accreditation**
 - ▶ Address concerns with commercial IRBs “Coast IRB” OIG Sting Operation
 - ▶ Aligns with (New SOP) – states commitment to Human Research Protection and IRB that will review sponsored research will be AAHRPP accredited
- ▶ **Formalized Sponsor’s relationship with Master Agreements (7 Masters with 5 Preferred IRBs)**
 - ▶ Better legal protection moving forward
 - ▶ Measure performance with quality metrics
 - ▶ Utilize based on more precise expertise in certain Therapeutic Areas
- ▶ **Process of selecting of high quality central IRBs through a transparent, audit-ready sourcing process based upon:**
 - ▶ Quality: Evaluation with AAHRPP accreditation standards
 - ▶ Speed: Cycle times
 - ▶ *Costs (low on evaluation scoring)*

Contractual Performance Metrics

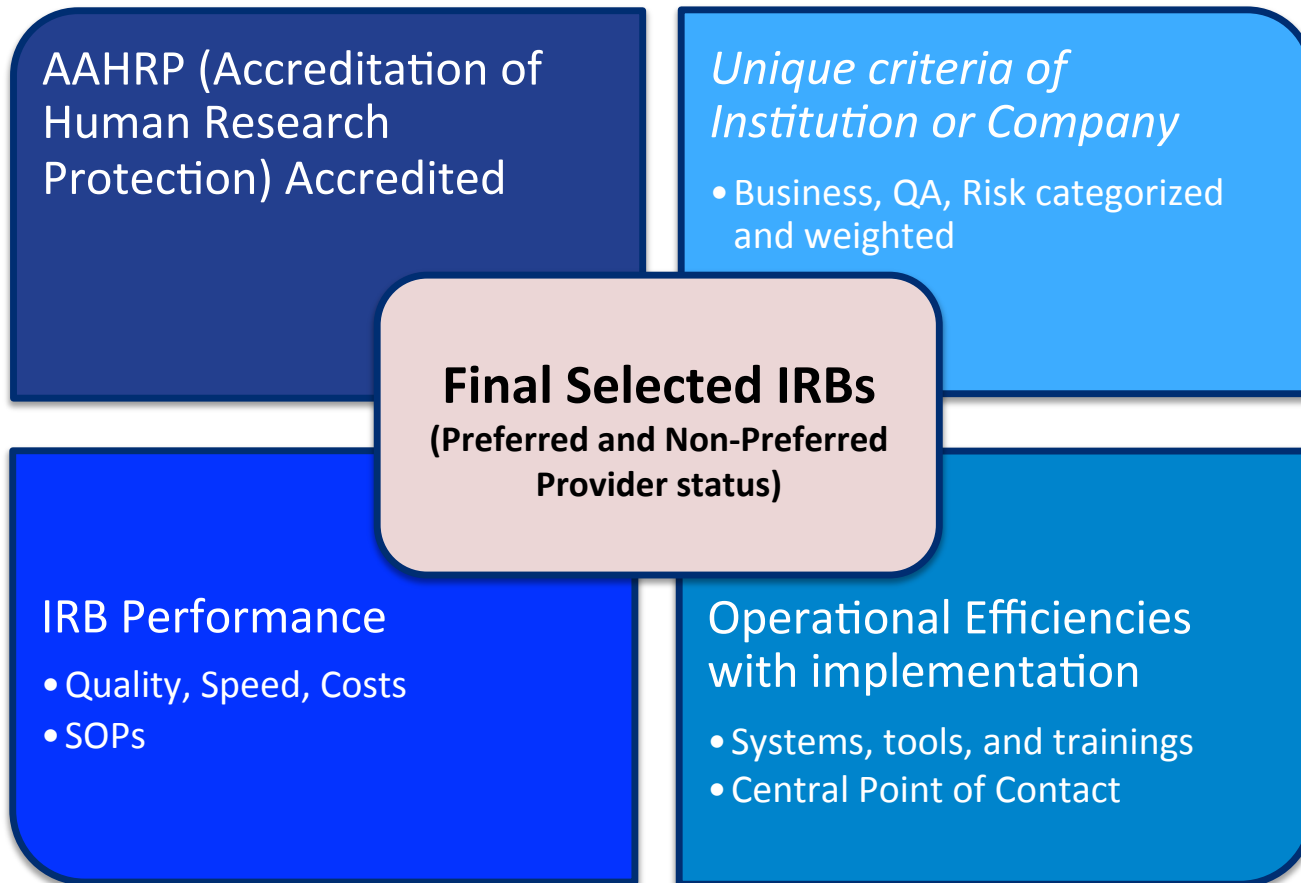
Quality

- ▶ Electronic Transmission/IRB submission portal
- ▶ Communication Follow-up
- ▶ Accuracy of Approval Documents
- ▶ AAHRPP Accreditation Standing
- ▶ Staff Attrition/Retention

Speed

- ▶ Sponsor Submission Receipt to Review issued
- ▶ Investigator Site Submission to Review issued
- ▶ Protocol review Cycle Time
- ▶ Informed Consent Review Cycle time/ Revisions

Industry Sponsor's Development of Criteria for Selection



2012 Central IRB Initiative - Celgene

- ▶ **Sponsor's selection process of adapting to new paradigm in the US for IRB review**
 - ▶ Overcoming perceptions, challenges with communication on model
 - ▶ Cross functional, multi-faceted selection process (Clinical Research & Development Operations, Legal, and Quality Assurance)
 - ▶ Project Managed by Global Site Contracts
- ▶ **Adoption of CTTI recommendations: Selection process for central IRB; implemented through upcoming multi-centered studies**
 - ▶ Implementation Plan
 - ▶ Master Contract & ICF Negotiations
 - ▶ Communication with Our sites

Implementation - Key Take Aways

- ▶ **Communication, Communication, Communication**
 - ▶ Internal Stakeholders (complete list)
 - ▶ Sites & Institutional Officials (Informational letter to sites)
 - ▶ How to work with selected IRB
 - ▶ CROs and vendor partners
- ▶ **Training & Awareness**
 - ▶ Train the Trainer, Line function champions, Clinical / TA leadership
 - ▶ Wide spread communication plan (including RMLs/CRAs)
- ▶ **IRB – Sponsor Dialogue / Collaboration**
 - ▶ On going Training, Feedback and Guidance

Key Take Aways

- ▶ **Establish and Maintain Key IRB relationships**
 - ▶ Expert consultation / counsel / advisor
 - ▶ FDA Final Guidance on IRB Responsibilities
 - ▶ Sounding Board: Subject Reimbursement, Pediatric Studies, ICFs
- ▶ **Feedback on Sponsor Protocols & Other related documents & IRBs**
 - ▶ Lines of communication
 - ▶ Routine Performance Evaluation Review
 - ▶ Distribution of work among selected cIRBs
 - ▶ Feedback from CRO Partners & Sites
- ▶ **Sponsor adoption - May foster Comfort and Trust**
 - ▶ *Change the paradigm of our current system*

Additional Information & Resources

- ▶ [PLOS ONE Peer Reviewed Article](#)
- ▶ [CTTI Recommendations](#)
- ▶ [Dr. Weinfurt Central IRB Recommendations](#)
- ▶ [Dr. Weinfurt Duke Medicine Interview](#)
- ▶ [CTTI Central IRB Expert Panel Mtg April 2012](#)

Thank you

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November 14, 2013

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The NEXT Generation of Neurologic Treatments
NIH-Network for Excellence in Neuroscience Clinical Trials

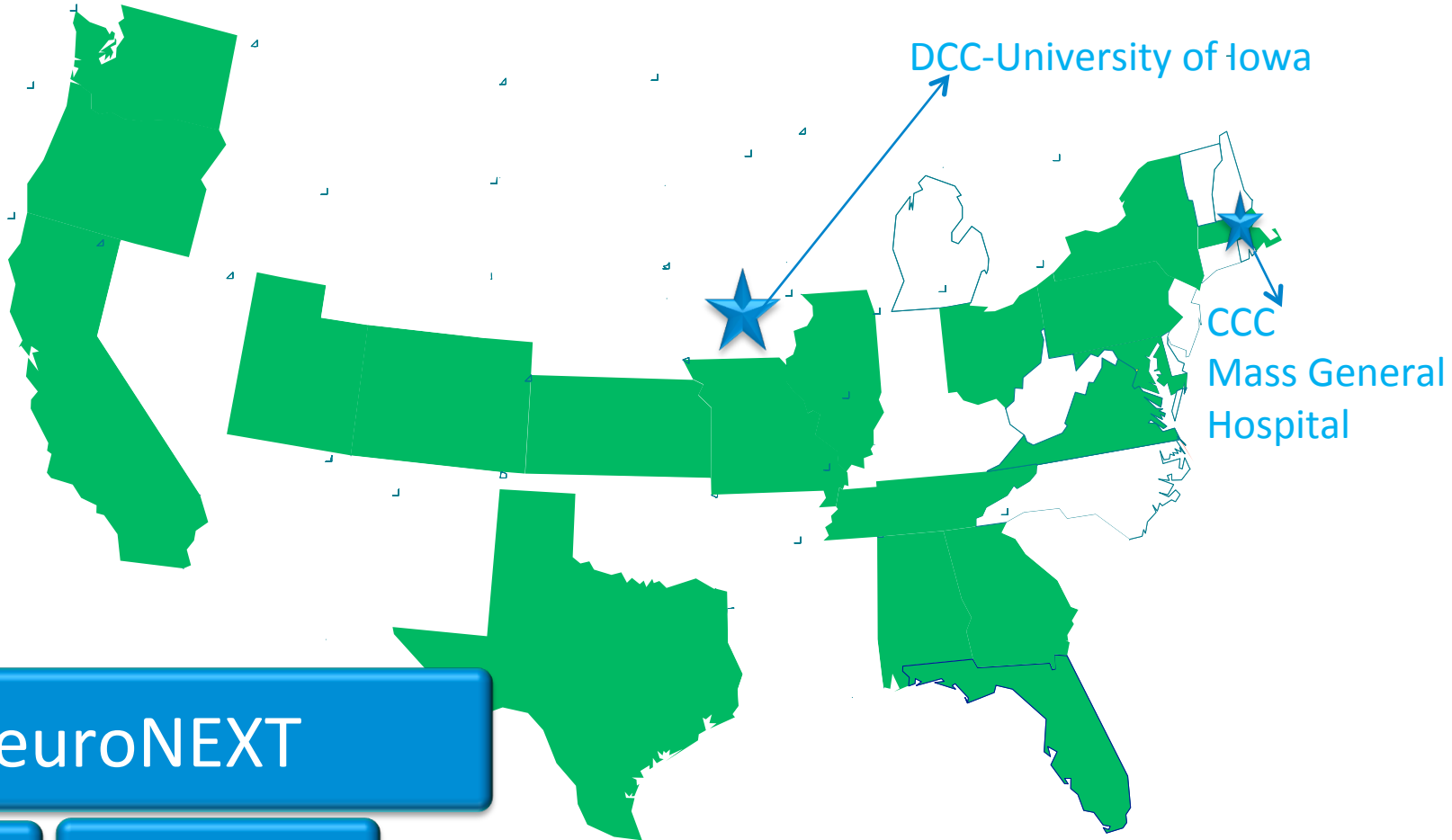


NINDS-funded Network for Exploratory Clinical Trials

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NeuroNEXT



NeuroNEXT

CCC

DCC

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

NeuroNEXT goals

- ▶ **Test promising therapeutics in Phase 2 clinical trials**
 - ▶ Using biomarkers when available
 - ▶ Providing results that allow for Go/No go decisions
- ▶ **Accelerate drug development through an established clinical trials infrastructure**
 - ▶ Responding flexibly to opportunities as they arise
 - ▶ Sharing expertise between disease areas
- ▶ **Coordinate public/private sector**
 - ▶ Test rigorously chosen therapeutics, whether from academic or industry investigators
 - ▶ Leveraging NINDS' existing relationships with academic investigators and patient advocacy groups
 - ▶ All NeuroNEXT Protocol Working Groups include a patient representative to provide input on the protocol as well as the informed consent from the very beginning.
- ▶ **Decrease the time between trial design and trial completion**
 - ▶ Using a central IRB, and standing master trial agreements

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? (Meninkoff 2010)

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**

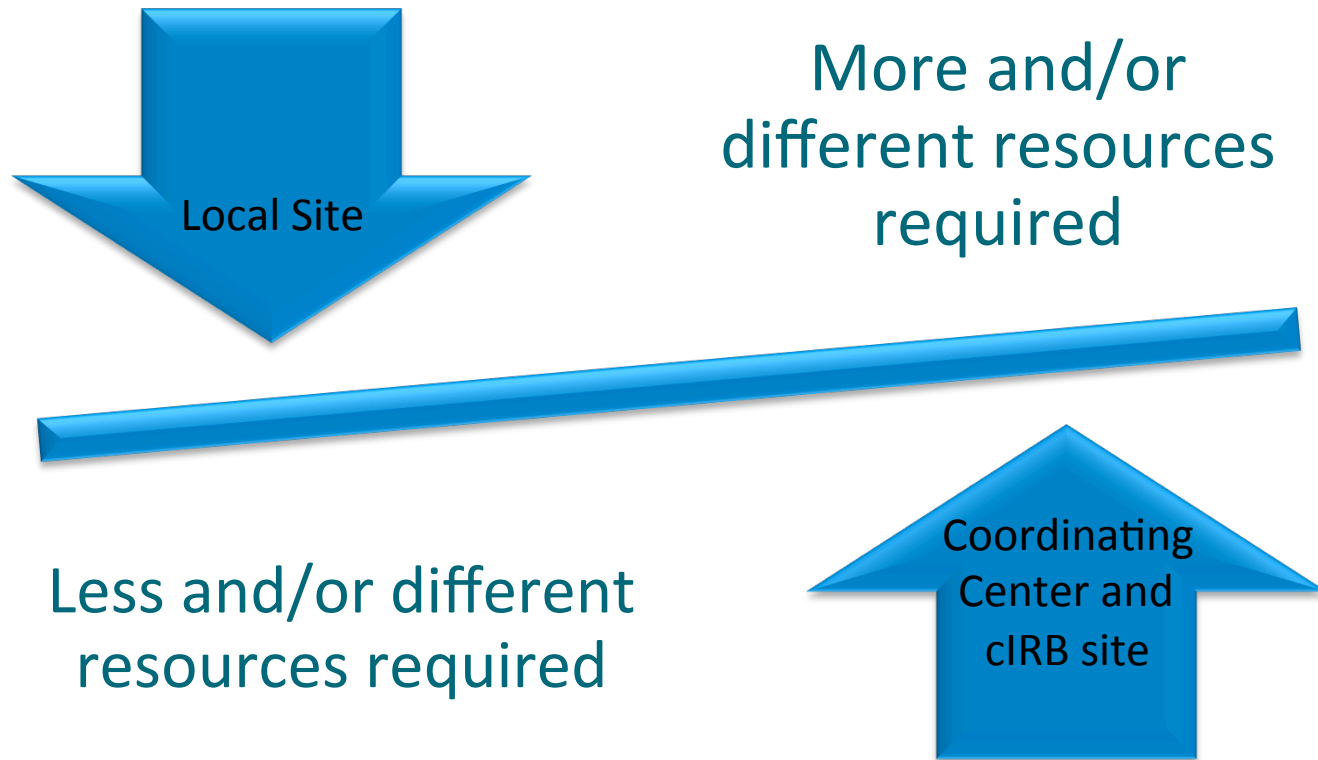
Communication

- ▶ **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**

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**

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

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
 - ▶ Multiple models and limited experience
 - ▶ Need clear goals and evaluation criteria

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**

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**

Acknowledgments

Thanks to:

The NeuroNEXT investigators and institutional officials


The Partners Central IRB team

The NINDS Office of Clinical Research team

Webinar Summary

- ▶ **Central IRBs are attractive to sponsors because they can enhance quality, efficiency and decrease start-up time for multi-centered trials**
- ▶ **Institutions may have to adapt their research infrastructure to increase central IRB use**
- ▶ **Investigators and institutions need to plan and budget for working with central IRBs**
- ▶ **Sponsor harmonization of procedures and templates could facilitate central IRB use; increases collaborative partnerships**
- ▶ **Future webinar – research institution perspective**

▶ THANK YOU

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