Congratulations!

- You have been successfully funded as the PI of a large multi-site study
  - Purpose: effect of high dose Vit B on young adults (16-26) who are HIV positive
  - 50 academic health centers in 35 different states

Your first thoughts…

Your study coordinator
Your first thoughts…

Your study coordinator

For you

Your next thoughts…

• I have to coordinate 50 academic health centers in 35 different states

And on top of it…

• I have to coordinate 50 academic health centers in 35 different states
• That means 50 separate IRBs
  – Protocol submission to multiple local IRBs
  – Each IRB alters the protocol and edits the ICF
  – Only 50% of the sites have IRB approval on the date of trial start
• And that is just the initial review!!
PI of multisite clinical study

If only I had a central IRB!
- Increased efficiency
- Faster turn-around
- Less cost
- Avoid multiple reviews by multiple local IRBS

Life would be grand!
Agenda

• Local IRBs
  – Advantages and disadvantages
    • For whom?
• Central IRBs
  – Perceived advantages and disadvantages
    • For whom?
  – Models of central IRBs
• “Costs” of central IRBs
  • What are they
  • Who pays?

Advantages of local IRBs

• For the institution
  – HRPP (Human Research Protection Program) coordination – local IRB often the ‘hub’
  – Maximizes review of local context
  – Promotes awareness of what research is being conducted and by whom (oversight and control issues)
• For the investigator
  – Provides a local resource – of entire HRPP
  – Comfort with the local system and process
Disadvantages of local IRBs

• For the institution
  – Cost of infrastructure
  – Duplication of effort on some multi-site research

• For the investigator
  – For multi-site research
    • Duplication
    • Additional time

Advantages of Central IRBs

• For the institution
  – Cost savings - maybe

• For the investigator
  – For multi-site research
    • Efficiency
    • No duplication

Disadvantages of Central IRBs

• For the institution
  – Difficulty segregating and fulfilling IRB versus institutional responsibilities
    • Possible shadow systems
  – Possible erosion of cohesive HRPP
  – Distancing of research and researchers
  – Confusion with multiple systems
  – Possible liability issues

• For the investigator
  – Understanding IRB and institutional requirements
  – New system
Agenda

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    • For whom?
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  • What are they
  • Who pays?

Central IRBs come in different models

• Non-share model
  – Central IRB fulfills all IRB-regulatory requirements
• Share model
  – Central IRB and local IRB share various regulatory responsibilities

The taxonomy of Central IRBs
The taxonomy of Central IRBs

Local IRB - Non-share model

- Status quo
- IRBShare
- NCI CIRB
- VA CIRB
- Commercial

IRBshare: Vanderbilt

- Collaborative IRB Review Model
  - Share review documents and review process
- Supported by an Electronic Sharing Resource (eSR)
  - Centralized, secure web portal for sharing
  - Currently operated by Vanderbilt University
How IRBshare works

- Documents available via eSR
  - Redacted minutes/discussion notes
  - Protocol
  - Consent form
  - IRB application
  - Product brochure
  - Any documents relevant to outcome of the review

Site with full IRB review
Sites can consider relying on full IRB review of Site A, or do their own full IRB review

How IRBshare works

- Local IRB sub-committee review by an IRB member to:
  - Verify and accept determination from Full Board Review Site’s IRB
  - Complete review of local context to complete review
- Local IRB can decide to accept the review, or send to their own full committee
- Of note, ICF is stamped by the local IRB
How IRBshare works

• If local IRB relies on full committee review of Institution A – then Institution A is the IRB of record for the initial review
• The local IRB then becomes the IRB of record for all subsequent IRB actions for the life of the protocol

Electronic Sharing Resource

Sites with full IRB review
Sites can consider relying on full IRB review from A, B or C, or do their own full IRB review

NCI Model

• Current model is being reassessed
NCI Model

- CIRB functions
  - Initial and continuing review
  - Amendments
  - Adverse events
- Local “IRB” functions
  - Facilitated review for review of local context
  - Development of ‘site-specific’ ICF
  - Review of locally occurring adverse events and unanticipated problems
  - Oversight of local performance

NCI Model

- Local site must meet eligibility criteria to enroll with cIRB
- Protocol reviewed by cIRB and results posted
- Local IRB conducts a ‘facilitated review’
  - If agree with cIRB, use cIRB as IRB of record
  - If disagree with cIRB, use local IRB as IRB or record

CIRB is not constituted for prisoner research – local IRB retains this responsibility

NeuroNEXT CIRB:
a non-share model
The NeuroNEXT CIRB
-Background-

• NINDS grant to support a network of 25 academic centers to facilitate clinical trials in neurology
• RFA stated preferential funding to those sites that agree to use a central IRB process
  – RFA included three tiers
    • CIRB only
    • Facilitated model
    • Local IRB
• At funding – CIRB only was selected

The NeuroNEXT CIRB

• CIRB had to be situated at the same site as the CCC (clinical coordinating center)
  – Massachusetts General Hospital = CCC
  – Therefore, the Partners* (PHS) IRB becomes CIRB

* MGH and BWH collaborate in a single IRB system under PHS

The NeuroNEXT CIRB

“interesting” nuance

• Presumption that 25 NeuroNEXT sites will be the study sites
• BUT – there may be involvement of additional sites:
  – Investigators from non-NeuroNEXT sites can propose studies to be done by NeuroNEXT
  – Non-NeuroNEXT sites may be invited to join specific studies as needed
Steps

1. Develop the model
2. Develop a Reliance Agreement
   • Protocol agnostic
     • To cover all NeuroNEXT member sites in NeuroNEXT studies
   • Protocol-specific
     • To cover non-NeuroNEXT-sites participating in NeuroNEXT studies
3. Negotiate the Reliance Agreement with all relevant sites
4. Let the fun begin!

NeuroNEXT CIRB

• CIRB responsibility
  – All IRB regulatory tasks
    • Initial review
    • Continuing review
    • Amendments, deviations, AEs
  – HIPAA determination
    • Authorization
    • Waiver

• Local Site responsibility*
  – Site-specific context
    • E.g., Local laws
  – Ancillary review/s
    • E.g., Nursing, Rad’n safety
  – HIPAA implementation
  – Oversight of conduct of research
  – Required reporting

* Institutional NOT IRB responsibility
Communication is KEY

• Single CIRB review
• PI-site submits ‘parent’ protocol for CIRB review
• After approval of ‘parent’ protocol, sites are added as amendments
The Basic Model

- Protocol submitted via CCC
- cIRB
  - Initial assessment to determine 'IRB readiness'
  - 'IRB ready' protocol sent to sites to identify 'substantive' and/or local issues
- Sites
  - IRB ready protocol sent to sites to identify 'substantive' and/or local issues
  - IRB ready protocol sent to sites to identify 'substantive' and/or local issues
- cIRB
  - Reviews 'substantive' and/or local issues from each site
  - AND then reviews protocol
- cIRB
  - CCC sends approved protocol to sites
- Sites
  - Communicate decision to participate
  - Sites participating are added by amendment to the cIRB approved protocol

"Parent-protocol" review

- PI submits protocol to CIRB
- CIRB reviews for 'IRB-readiness'
- IRB-ready protocol is sent to all sites that are interested in participating
  - Sites have 2 weeks to conduct institutional review and submit comments
    - re: the protocol in general as well as local context issues
- CIRB conducts PI protocol review
  - Incorporates feedback from local sites
- PI coordinates ancillary review/s for PI-site and submits to the CIRB
- CIRB can then approve the protocol
ICF:
PI will develop:

– A model ICF that includes:
  • Locked portion, e.g.
    – Study procedures
    – Risks and benefits
  • Customizable portion, e.g.
    – HIPAA
    – COI language
    – Injury language
    – Contact persons

– A PI-site-specific ICF that includes:
  • Locked portion and completed customizable portion

“Child-protocol” review

• CIRB approved protocol is sent to each interested site
• Each site makes final decision re: participation
• Each site will be reviewed as an amendment to the ‘parent-protocol’ and must submit:
  – Evidence of local ancillary review/s
  – A completed ICF that includes:
    • Locked portion
    • Customizable portion that includes local ICF content

After the protocol is CIRB approved
Continuing Review

• Anniversary date for all participating sites is tied to the initial protocol approval
• Each site PI submits site-specific continuing review data to CCC-CIRB liaison who collates and submits to the CIRB
  • Investigators and study teams will not have direct access to PHS electronic IRB submission database at this time
After the protocol is cIRB approved

Adverse events/UAPs, Deviations, Complaints, Changes to Eliminate Immediate Hazards, Non-Compliance, and Suspension or Cessation of Study

- Each site PI submits site-specific reports to CCC-CIRB liaison who will submit to the CIRB
  - If an issue requires notification of all sites, the CIRB will communicate same via the CCC

After the protocol is cIRB approved

Amendments

- Each site PI submits site-specific amendments to CCC-CIRB liaison for submission to the CIRB
  - Site-specific amendments limited to:
    - administrative (e.g., study staff changes) and requests for protocol exceptions;
  - Any amendment that substantively changes the study must be coordinated through the PI-site and CCC
  - Issues identified as a result of CIRB review of amendments requiring notification of all sites will be sent out from the CIRB via the CCC-CIRB liaison

HIPAA

- CIRB will:
  - Make HIPAA determinations
  - Incorporate authorization language into the consent form
- Local sites can use:
  - cIRB developed ICF that includes authorization
  - Insert their own authorization language into the ICF in lieu of authorization language in CIRB ICF*
  - Use their own free-standing authorization in lieu of authorization language in CIRB ICF*

* Final ICF and authorization must be submitted to and approved by the CIRB
COI

- The CIRB will consider COI issues in the approval of the protocol and will include management plan/s.
  - E.g., disclosure in the ICF
- Each local site:
  - Applies local standards and processes
  - Can mandate more stringent management than required by the CIRB.
  - Cannot implement less stringent management
- COI subcommittee of NN-Exec.Com.
  - Resource for the CIRB

Compliance Investigations

- Compliance investigations will be the responsibility of each local institution
- The CIRB will have the right to initiate/conduct its own investigation in addition if necessary
- The expectation is one of collaboration and communication with the CIRB, the CCC, the DCC and the sites

External Reporting

- Logistics of external reporting will be determined on a case-by-case basis
- Site/s and the CIRB agree upon who will report
- Drafts and final reports will be shared between the relevant site/s and the CIRB
  - Allows either the CIRB or individual site/s to submit an additional report as deemed appropriate.
CIRB Goals

• Obtain input from local sites prior to IRB full committee review of parent protocol
• Provide high quality, rapid review for multiple sites
• Work collaboratively with local sites
• Streamline amendments and compliance reporting

Steps

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3. Negotiate the Reliance Agreement with all relevant sites
4. Let the fun begin!

Reliance Agreement

• Delineates
  – The process
  – Assignment of legal, regulatory and contractual responsibilities
• Negotiation:
  – Draft Reliance Agreement sent to all prime sites for comments
  – Two Webinars describing the Reliance Agreement
    • Opportunity for submitted questions
Reliance Agreements

- Prior to any protocol, all network sites must sign a reliance agreement with the CIRB
  - This RA will cover all NeuroNEXT studies
  - All RA’s ‘essentially’ identical
- CIRB required separate RA for all sites and subsites with their own FWA
  - Regardless of relationship or existing reliance arrangements between Primary site and subsites.

Prime sites and Sub-sites

- Scenario 1
  - Prime site A and subsites B and C
  - Each with their own FWA and IRB
Prime sites and Sub-sites

- Scenario 1
  - Prime site A and subsites B and C
    - Each with their own FWA and IRB

Prime sites and Sub-sites

- Scenario 2
  - Prime site A and subsites B and C
    - Each with their own FWA
    - B and C rely on IRB situated at A

Three separate Reliance Agreements

- Scenario 2
  - Prime site A and subsites B and C
    - Each with their own FWA
    - B and C rely on IRB situated at A
Reliance Agreements

- Non-member sites involved in NN-research must also sign the Reliance Agreement
  - Details remain the same, but the agreement is limited to a single protocol
- If non-member sites have sub-sites:
  - All FWA-holding sub-sites must sign their own Reliance Agreement

Steps

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4. Let the fun begin!
NeuroNEXT CIRB

Reliance Agreement

NeuroNEXT
25 Prime sites
BUT...more than 40 sub-sites for a grand total of
more than 60 sites

Non-NeuroNEXT Sites

A
B
C

Steps

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4. Let the fun begin!
Anticipated Challenges

- Differentiating between institutional and IRB tasks
- Obtaining and addressing local context
- Simple logistics of communication
- Different local cultures
- Developing trust
- .....

Agenda

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Costs and Benefits of the NCI CIRB

- Survey study
- CIRB associated with:
  - Faster reviews (28.3 vs 62.3 days)
  - Less research staff time (7.9 vs 14 hrs)
  - Savings of $717 per initial review
    - $321 for research staff
    - $396 for IRB staff
- Note that many sites continue some local review for amendments and continuing review
What are the costs and who pays?

• Completely dependent on the model
• Too early to tell
• All costs are not financial

Pandora’s Box?

Costs of being the CIRB

• Impossible to say….but consider:
  – Developing and negotiating reliance agreements
  – New IRB panel or use an existing one?
  – System of communication – and persons to run said system
  – FTEs that only process CIRB related tasks
    • Will vary with model of CIRB and number of protocols
  – Will you rely on any local site review?
    • If not – will need a central resource for evaluating all relevant local laws, etc.
Costs of relying on a CIRB

- Impossible to say….but consider:
  - Financial
    - Is there a charge for the CIRB?
    - Is there facilitated review and a role for local IRBs?
    - Is local context review required?
      - If yes, by whom?
  - Nonfinancial
    - Loss of comfort with local research portfolio
    - Corrosion of Human Research Protection Program

Final Thoughts

- Variety of CIRBs makes it difficult:
  - To make any generalizations
  - For IRBs, institutions and investigators to know what to expect in different situations
- More guidance is needed re:
  - IRB versus institutional responsibilities
  - What responsibilities come with an FWA
  - Obtaining local context

Final Thoughts

- There are advantages and disadvantages to local and central review
- Advantages and disadvantages are different for:
  - IRBs
  - Researchers
  - Institutions
- Hopefully our NeuroNEXT experience can help to inform the process
Final lesson: No approach is without its snags