

**Panel 2:  
Oversight of Pragmatic  
Clinical Trials –  
Institutional Review  
Boards and Data & Safety  
Monitoring Boards**



# Oversight of Pragmatic Clinical Trials – IRB and DSMB Considerations

Moderator: Adrian Hernandez

Panel:

Pearl O'Rourke

Susan Ellenberg

Doug Zatzick



# Session Goal

Engage panel and NIH participants in moderated discussion that uses NIH Health Care Systems Research Collaboratory demonstration project example(s) to focus on issues of IRB and DSMB oversight of pragmatic clinical trials

# Session Format

- NIH Collaboratory /*Clinical Trials* 2015 Vol. 12
  - Pearl O'Rourke: IRBs
  - Susan Ellenberg: DSMBs
  - Doug Zatzick: NIH Collaboratory case example
  - Adrian Hernandez: Moderated discussion



# Harmonization and Streamlining of Research Oversight for Pragmatic Clinical Trials

- P. Pearl O'Rourke, Judith Carrithers, Bray Patrick-Lake, Todd Rice, Jeremy Corsmo, Raffaella Hart, Marc Drezner, John Lantos
- Clinical Trials 2015;12:449-456

# Agenda

- Understanding the Human Research Protection Program (HRPP)
  - IRB Responsibilities
  - Non-IRB Institutional Responsibilities
- Central/Single IRBs
  - What are they
  - How they may help
- Other opportunities for harmonization and streamlining

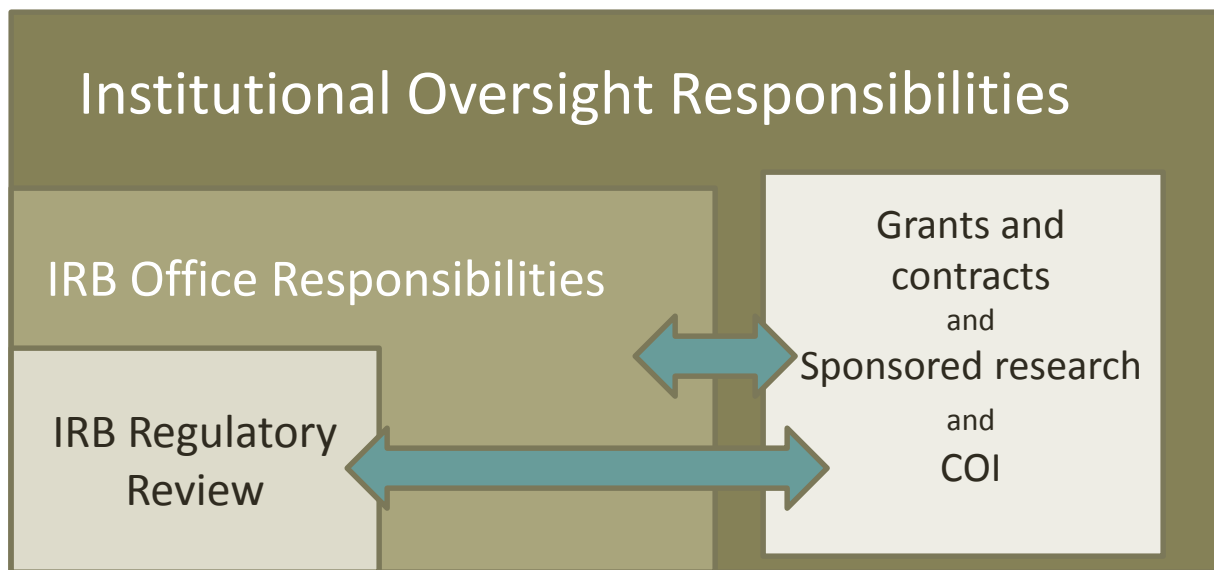
# The HRPP includes:

- Process for IRB review (*can be local or external*)
- Non-IRB institutional responsibilities
  - Ancillary committee review/s (E.g., pharmacy, rad'n safety)
  - HIPAA
    - Although often assumed by the IRB working as Privacy Board
  - Conflict of interest
  - Research billing
  - Investigator training and education
  - Reporting requirements per the FWA (Federal Wide Assurance)

Remember it is the institution that signs the FWA.

# Human Research Protection Program

## IRB vs Institution







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# Helpful Terms

- Reviewing IRB
- Relying institution
  - Remember it is the *institution* that relies
    - Reliance Agreement
    - SOPs



<http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html>

# IRB vs Institution



*The stuff' that can be ceded to an external IRB*

## Note:

- Institution remains responsible for all else
- Need for systems to maintain communication



I thought that I had ceded review!

# CIRB Arrangements to Consider

- Scope of ceded review
- Voluntariness of ceded review
- Who is the reviewing IRB?
- Share versus non-share models

# CIRB Arrangements: Scope

- Single protocol review
- Category of research; e.g.,
  - Cancer
  - Pediatrics
  - Industry sponsored
  - Defined network
- All research
  - If the local institution does not have an IRB.

# CIRB Arrangements: Voluntariness

- Protocol-by-protocol decision
  - When it makes sense
- Mandated – “Thou shalt use a single IRB’
  - By funding agency: e.g., condition of grant award
  - Network ‘business’ rules
  - Perhaps the NPRM → final Rule

# CIRB Arrangements: Who is the IRB?

- Type of IRB
  - Independent/commercial - this is their business
  - Academic Medical Center - this is becoming their business
- Designation of reviewing IRB
  - Reviewing IRB is always the same
    - Commercial/independent IRBs, NCI, NeuroNEXT, StrokeNet
  - Reviewing IRB determined by protocol-by-protocol decision
    - Reciprocal Reliance arrangement:
      - Multiple institutions sign the same reliance agreement
      - Allows any of the signatories to be the reviewing IRB



# Share and non-Share Models

- Based on who does what regulatory review
- Share
  - Regulatory responsibility shared between the CIRB and the local IRBs
- Non-Share
  - Single (reviewing) IRB conducts all regulatory review

# CIRB Models: non-share and share

Task	Non-share Model	Share Model
Initial protocol review	CIRB	CIRB
Continuing review	CIRB	CIRB or local IRB
Significant amendments	CIRB	CIRB or local IRB
Site-specific amendments	CIRB	CIRB or local IRB
Unanticipated problems	CIRB	CIRB or local IRB
Other events	CIRB	CIRB or local IRB

Clinical Trials 2015;12:449-456

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# Challenges and Opportunities for harmonization and/or streamlining

- Comparative effectiveness research
  - Understanding risk which informs oversight
- Social Media
  - Heterogeneity of sites; participant expectations and privacy
- Software applications
  - Accuracy, authenticity, validity, MR-worthiness
- Sponsor requirements
  - One-by-one negotiations
- Patients and patient advocates as research team members
  - Poor definition of role; questions re: required training and oversight

# Challenges and Opportunities for harmonization and/or streamlining

- Privacy
  - Including patients as study team members
- Cluster randomization
  - Questions of informed consent, institutional sign-off
- Local context
  - How best to identify, communicate and consider
- Conflict of interest
  - Heterogeneity of institutions
- Payment
  - Lack of coverage standards – affect the protocol and ICF
- Federal Wide Insurance (FWA)
  - How to handle non-traditional settings

# Summary

- Streamlining and harmonizing oversight of multi-site research is a laudable goal – ***only if human subjects protections are not eroded.***
- Solutions must address the multi-faceted inter-dependent processes of research and research oversight



# Data Monitoring Committees for Pragmatic Clinical Trials

- Susan S. Ellenberg, Richard Culbertson, Daniel L. Gillen, Steven Goodman, Suzanne Schrandt, Maryan Zirkle
- Clinical Trials 2015;12:530-536



# Data Monitoring Committee

A data monitoring committee (DMC) is a group of experts that reviews the ongoing conduct of a clinical trial to ensure continuing patient safety as well as the validity and scientific merit of the trial



# DMCs For Pragmatic Trials

- What are the special issues for DMCs for pragmatic clinical trials?
- (ARE there any special issues for DMCs for pragmatic trials?)

# Do PCTs Need DMCs?

- All clinical trials require some monitoring of interim data
- General guidelines for requiring a DMC apply to pragmatic trials
  - Trials in which participant safety requires regular review of comparative safety and efficacy data
  - Trials intended to have substantial public health impact
- Since pragmatic trials will typically be addressing questions intended to impact health practices, an expert oversight group will be important for most PCTs

# What Gets Monitored?

- Traditional trials: monitor data on safety, efficacy, and quality of study conduct
- These are important in pragmatic trials also
- Possible special issues in pragmatic trials
  - Protocol adherence
  - Cluster randomized trials
  - Issues in data analysis

# What Gets Monitored?

- Protocol adherence
  - A basic tenet of PCTs is to evaluate treatments as they would be given in practice
  - This means no great effort to promote, or even monitor, adherence to protocol
  - However--if adherence is very poor and there is no apparent treatment difference, 2 possibilities:
    - Treatment will be ineffective (or no more effective than control treatment) in general practice
    - Protocol not sufficiently clear to investigators and participants
  - Study results may not be informative

# DMCs and Protocol Adherence

- Should a DMC ignore data on protocol adherence in a PCT? Should these data not even be reported?
- Poor adherence could lead to safety issues in some studies
- Important to distinguish between
  - Lack of adherence as reflecting how a treatment would be used in practice
  - Lack of adherence as reflecting insufficient understanding of trial on part of investigators and/or participants
- DMCs need to pay some attention to this issue
- May be particularly important to review adherence data by site, to assess need for re-training

# Cluster Randomized Trials

- For cluster-randomized trials, design often used in pragmatic trials, also important to monitor the “design factor”
  - Intra-cluster correlation coefficient (ICC)—the extent to which results within a cluster will be more similar than results across clusters—is a component of sample size calculation
  - Typically, hard to estimate ICC from prior data—estimates used to design trial may be way off
  - Interim estimates of ICC important to see whether study will have expected power

# Participant Follow-up

- Pragmatic approaches to follow-up may create challenges for DMCs
- Follow-up information will likely be derived from electronic health records (EHRs) in some trials which may be updated on different schedules if different systems are used
- Follow-up frequency may vary by institution according to local policies
- Interim comparisons will be more difficult without standardized follow-up schedules

# Data Analysis

- Analytical issues
  - Cluster randomization
  - Decentralized analysis
- Philosophical issues
  - Early termination criteria



# Interim Monitoring Strategy

- Early termination for efficacy
  - Since PCTs will be designed to influence practice, could be argued that early termination criteria should be extremely stringent
- Early termination for futility
  - When studies compare two “standard-of-care” regimens, questionable whether early stopping for futility should be considered at all
  - As with efficacy, DMCs and trial leadership must have common understanding of criteria for early termination

# Data Analysis


- Use of cluster designs
  - Many PCTs currently underway with NIH Collaboratory or PCORI funding randomize clusters rather than units
  - Analysis of such trials requires accounting for intra-cluster correlation
  - Differing practices among clusters will have to be accounted for in interim analyses
    - Example: minimally restricting usual practice may mean patients in different clusters are followed on different schedules
    - Complicates interim assessments

# Data Analysis

- De-centralized analysis
  - Privacy concerns may preclude merging data from multiple EHR systems at a central site
  - In such cases, interim analyses may need to be done separately for each site, with summary data only delivered to central statistical group
  - Such arrangements will raise challenges in terms of timeliness of data, quality control and assurance that all analyses have been conducted in identical manner

# Who Serves on a DMC?

- Clinical and statistical expertise needed
- Will probably be more common to include patient representative
  - PCORI-funded studies require patient partners as members of research teams
  - Studies aimed at questions intended to influence clinical practice may particularly benefit from patient insights
- Expertise in medical informatics may be desirable
  - Use of electronic health data
  - Complex database linkages
  - Natural language processing



# NIH Collaboratory Pragmatic Trial: Trauma Survivors Outcomes and Support (TSOS)

## Demonstration Project Case Example

Zatzick, Russo, Darnell, Chambers, Palinkas, Van Eaton, Wang, Ingraham, Guiney, Heagerty, Comstock, Whiteside & Jurkovich: *Implementation Science*, In Press

Funded by Grant UH3 MH106338

# TSOS Pragmatic Trial Study Design

- PTSD and comorbidity targeted
- 24 US trauma centers
- 40 patients per site (960 patients total)
- Baseline electronic health record screen
- Screen positive patient consent
- PTSD Checklist scale completed by patient interview
- 3, 6 and 12 month follow-up assessments
- Cluster randomized - stepped wedge design
- Collaborative care intervention
- Policy summit in final year targets practice change

# TSOS US Level I Trauma Center Sites (N =24)



# TSOS IRB & DSMB Experience

- Prior pragmatic 20 site trial 2007-2012:
  - NIAAA R01 targets national trauma alcohol policy
  - University of Washington (UW) coordinating center
  - UW IRB oversight—single administrative contact
  - 20 individual trauma center site IRB submissions
  - Higher degree of “harmonization”
  - Study team appointed DSMB



# TSOS IRB & DSMB Experience:

- TSOS NIH Collaboratory UH2-UH3 Trial: 2014-2019
  - University of Washington IRB does not have capacity for “Centralization”
  - Western IRB (WIRB) serves as the centralized IRB
  - No single administrative contact
  - Only 4 sites “cede” to centralized WIRB review
  - 20 individual site IRB submissions

# TSOS IRB & DSMB Experience

- Multiple regulatory challenges
  - Example: Variability in rates of regulatory approvals and stepped wedge design considerations
- Consistent interactions with NIMH DSMB provide potential for “harmonization”



# Questions and Answers

**Please submit questions for  
the panelists to:**

**[EthicsofPragmaticTrialsWkshp@mail.nih.gov](mailto:EthicsofPragmaticTrialsWkshp@mail.nih.gov)**