COMPLIANCE THROUGH COLLABORATION: PARTNERING WITH INDEPENDENT IRBS TO DEVELOP AND MAINTAIN A STRONG HUMAN RESEARCH PROTECTION PROGRAM (HRPP)

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Overview

- Provide an overview of the current regulatory and business climate for SIRB review, including the NIH Policy on sIRB review and changes to the Common Rule at 46CFR46.
- Discuss models for sIRB review and partnership with academic and commercial IRBs, differentiating and outlining the responsibilities of the institution versus the responsibilities of the reviewing sIRB.
- Demonstrate through case studies how differing business models can both achieve and improve compliance with the new federally mandated requirements for the use of sIRB in multi center clinical research studies.

SETTING THE STAGE

Marketplace
Guidance & Initiatives
Regulation

Setting the stage

- The promise of clinical (human subject) research is to: Generate timely and practical evidence for drug and device development; Support medical treatment decisions; improve the delivery of care; and **Improve health.**
  - **HIV/AIDS:** Since the introduction of highly active antiretroviral treatment (HAART), the HIV/AIDS death rate has dropped **87%**
  - Since peaking in the 1990s, **cancer** death rates have declined **23%**
- The average cost to develop a drug (including the cost of failures): 2000s–early 2010s = $2.6 billion 1990s–early 2000s = $1.0 billion* 1980s = $413 million 1970s = $179 million
- Average time to develop a drug = 10 to 15 years
- Percentage of drugs entering clinical trials resulting in an approved medicine = less than 12%

Source: PhRMA 2016 Profile

SIRB Historical Context

- Need for improved efficiency in multicenter clinical trials.
- FDA and OHRP signaled support for centralized IRB review of multicenter clinical research
  - OHRP template form for IRB Authorization Agreements
  - 2006 National Conference on Alternative IRB Models
  - 2006 FDA Guidance: Using a Centralized IRB Review Process in Multicenter Clinical Trials

Commentary and Guidance

- 2006 Food and Drug Administration Guidance
  - "The Agency hopes that sponsors, institutions, Institutional Review Boards (IRB), and clinical investigators involved in multicenter clinical research will consider the use of a single central IRB (centralized IRB review process), especially if using centralized review could improve the efficiency of IRB review."
- 2010 Menikoff Commentary in NEJM-Scientific Concerns
  - Multiple local IRBs can lead to a diffusion of responsibility and potentially expose trial participants to undue risks
  - Potential "authority vacuum" in which no IRB feels empowered to demand changes in the protocol
- Despite these stated positions, the willingness of institutions to defer to outside IRBs varied

Clinical Trials Transformation Initiative CTTI Project (2010-2013)

- **Goal**
  Identify solutions to address barriers to the adoption of central (single) 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

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PLOS ONE

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.

Flynn KE, Hahn CL, Kramer JM, Check DK, Dombeck CB, et al. (2013) Using Central IRBs for Multicenter Clinical Trials in the United States. PLoS ONE 8(1): e54999. doi:10.1371/journal.pone.0054999

Central IRB, Single IRB?

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
- An institution not using the single IRB-of-record would not participate in that protocol

Perceived Barriers cited barriers

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

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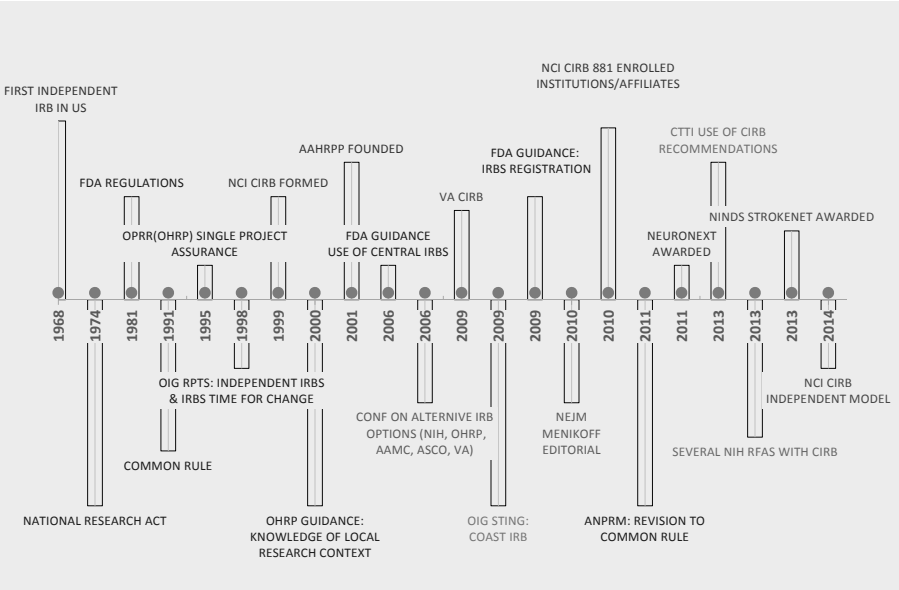
Underlying Concerns

- 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

Timeline Central IRB Use in United States pre-2015



SIRB Regulatory Context

- NIH Policy sIRB Review: Now
- https://grants.nih.gov/policy/humansubjects/single-irb-policy-multi-site-research.htm
  - For applications with due dates on or after January 25, 2018, and contract solicitations published on or after January 25, 2018, NIH expects that all sites participating in multi-site studies, which involve non-exempt human subjects research funded by the NIH, will use a single Institutional Review Board (sIRB) to conduct the ethical review required for the protection of human subjects

- Revised Common Rule sIRB requirement:January 2020
  - 45CFR46.114 (b)(1)Cooperative research. Any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States…(c) For research not subject to paragraph (b) of this section, an institution participating in a cooperative project may enter into a joint review arrangement, rely on the review of another IRB, or make similar arrangements for avoiding duplication of effort.

Perceived Barriers: Resources cited barriers

- Local Context/Policy
  - SMART IRB Agreement: https://smartirb.org/agreement/
  - CTTI Template for IRB Authorization Agreement:
  - https://www.ctti-clinicaltrials.org/briefing-room/tools
- Assurance of review quality by an external IRB
  - Accreditation
  - Comfort Level based on Experience
- Administrative and logistic
  - SACHRP Recommendations https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-a-november-2-2016-letter/index.html
- Local context
  - External Site Questionnaires
  - IRB Reliance Exchange IREx: https://www.irbexchange.org/p/
  - SACHRP Recommendations https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2013-january-10-letter-attachment-a/index.html
- Financial
  - SMART, CTSA, TINS
  - Fee Schedules

MODELS

What is a Human Research Protection Program?

What is an Institutional Review Board?

Scope and Oversight

- A Human Research Protection Program (HRPP) is an institutional program which assures the rights and welfare of research participants are protected and respected for a specific institution or designated group of institutions.
- An Institutional Review Board (IRB) is part of the HRPP and is a committee charged with reviewing research protocols involving human subjects for a specific institution or specific study to ensure the rights and welfare of an individual participants in the research are protected.
- Both are governed by federal (OHRP, FDA, NIH, OCR) and state regulations as well as institutional policies and procedures.
  - Common Rule 45CFR46
  - FDA at 21CFR Parts 50, 56, 312, 812
  - HIPAA 45CFR Parts 160 and 164
  - Promoting Objectivity in Research (COI Rules) 42 CFR 50; 45 CFR 94

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Human Research Protection Program (HRPP)

- The function of a HRPP is to ***coordinate or integrate*** the activities of research support offices (i.e. Research Integrity/Institutional Review Board, Research Compliance, Sponsored Programs/Grants, Finance), investigative sites, applicable review committees and other review units which involve research with human subjects through oversight, education and quality assurance activities, including program administration ***at a specific institution or group of institutions.***

This coordination activity **is often different than what is typically provided inside a single IRB support office. It is an *institutional approval* activity.**

HRPP is IRB agnostic, you can designate more than one IRB.

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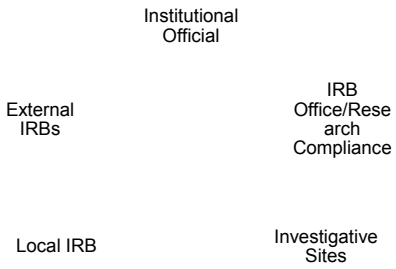
Human Research Protection Program (HRPP)

- The tasks of a HRPP typically include (at a high level):
  - Requiring and ensuring IRB review and approval is in place for all non exempt human subject research conducted at the institution prior to including human participants in any research study.
  - Monitoring, evaluating and continually improving the protection of human research participants.
  - Promoting compliance with relevant laws, regulations, institutional policies and professional and ethical standards.
  - Responding directly to concerns of research participants.
  - Addressing the needs and concerns of researchers in support of their endeavors.
  - Educating investigators and research staff about their ethical responsibility to protect research participants.
  - Conflict of Interest Considerations

Note: The above tasks almost always require coordination amongst multiple "research administrative" or other institutional offices (such as compliance, legal or a medical group)

Example Components of a Human Research Protection Program (HRPP)

- The Institution establishes a system wide Human Research Protection Program (HRPP) to oversee research conducted with human subjects.
- The team is comprised of the Institutional Official, staff in the Office of Research Compliance, staff in the IRB office, investigative sites and the local Institutional Review Board (IRB) with reliance agreements in place to rely on other authorized external IRBs.



Human Research Protection Program

- Distinctions of a Quality Program as per Association for the Accreditation of Human Research Protection Programs (AAHRPP)
  - 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

CONSIDERATIONS

Planning for Success

Institutional Self-Evaluation

- Review your Human Research Protection Program (HRPP) Policies and Procedures
  - Ensure you have institutional policies that apply regardless of IRB utilized
  - Decide what body within the organization will be authorized to provide “institutional approval” once IRB approval is in place
  - Develop training programs for staff
  - Define process for the investigator, institution, institutional HRPP, and central IRB

Institutional Self-Evaluation

- Institutional Approval ≠ Facilitated IRB Review
  - Reviews for Resource Allocation
  - Ensures Compliance Related Reviews
    - IRB
    - IBC
    - Radiation Committee
    - COI
    - HIPAA Security
  - Clinical Trial Agreement Concurrence
  - Ensures Expertise, Credentialing and Training

Institutional Self-Evaluation

- Determine impact on electronic systems used in data collection
- Consider the type of research being conducted
  - Level of risk
  - Funding environment
  - Number of sites involved

Institutional Self-Evaluation

- Conduct a financial analysis
  - Evaluate costs – both of relying on a sIRB and serving as a sIRB
  - Establish fee structure for conducting institutional tasks
  - Assess scalability of the sIRB model

Institution/Sponsor Evaluation of a sIRB

General Considerations when selecting or relying a particular sIRB

- Consider certifications and accreditation
- Investigate compliance history of the IRB
- Review qualifications of board members including therapeutic expertise
- Request references and review organization's history of working with institutions and/or sponsors
- Evaluate IRB's ability to step seamlessly into the process (including state laws and local considerations)

Institution/Sponsor Evaluation of a sIRB

General Considerations when selecting or relying a particular sIRB:

- Determine scope and associated costs of services provided
- Obtain description of support services and communication provided
  - for Institution to manage the relationship with the sIRB
  - for investigator, start up and ongoing

Institution/Sponsor Evaluation of a sIRB

- General Considerations when selecting or relying a particular sIRB

- Specify communication process between institution, investigator, and IRB
  - Assess operational processes (frequency of board meetings, document management, capacity, turn around time, QA processes: internal and external)
  - Inquire about technology used by sIRB and compatibility with existing systems/programs

What might a sIRB want to know about an institution before deciding whether to enter into that relationship?

- Compliance history of the institution
- Goals of the institution – what are the drivers
- Relevant laws, local regulations, institutional norms and values, requirements
- Point of contact
- Level of involvement in unanticipated problems, and other problems

What might a sIRB want to know about an institution before deciding whether to enter into that relationship?

- Lines of communication
- Experience working with outside IRBs
- Institution's expectations regarding performance and metrics
- Scope of agreement and specific studies – one study, all studies, certain subset of studies
- Negotiation of protocol or consent disagreements

Steps to Successful Reliance

- Assess Institutional Culture: scope your reliance and ask questions
- 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?"

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"Considerations" Document

Considerations When Assigning Responsibilities to a SIRB and a Local Institution for a Multicenter Clinical Trial

- Clearly delineate responsibilities and how they might be assigned to each entity (IRB or Institution), or, in some cases, both entities.
- Outline categories of legal and ethical responsibilities of an institution and an institutional review board (IRB) in overseeing the conduct of clinical trials.
- Support communication between institutions and external, central IRBs

CASE STUDY

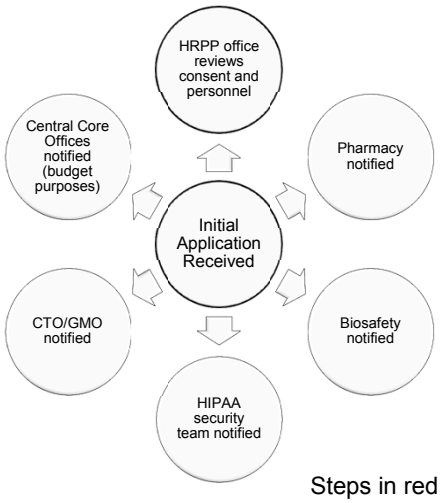
Northwell Health Model

- Institutional approval
- Reportable Event Committee
- Relationship building

Northwell Institutional Approval

- A mechanism to provide Institutional and HRPP oversight to all human subjects research at Northwell Health, regardless of what IRB is performing the review.

What happens upon submission?



Steps in red occur for every application

Next Steps

- HRPP office staff provide study team with “permission email” to use external IRB
- If consent needs modifications due to local requirements, PI of study is informed in the same email as the “permission email”

Institutional Approval Granted

HIPAA Security Approval

Pharmacy Approval

IRB Approval

Radiation Safety Approval

Institutional Approval Granted

Once institutional approval is granted, the study can begin

Ongoing Monitoring

- Compliance teams – routine audits
- Investigators using external IRBs are still required to do the following:
  - Submit personnel mods to HRPP office (In addition to IRB of record, as required)
  - Inform HRPP office of compliance or potential UPIRTSOs
  - Final Reports

Reportable Events Committee

- IO's designated Committee whose purpose includes review potential reportable events for studies under the review by an external IRB
- Has authority to act on behalf of the Institution in collaboration with the reviewing IRB

Relationship Building

- Get to know staff at external IRBs
- Provide them with your local Institution requirements
- Give them feedback when things are not working

Case Study #1

- A study team is relying on external IRB for review of an investigational device study. Local HRPP is notified by local site investigators of a UADE. It is unclear if the external IRB has been informed.

As part of the HRPP office, what would you do?

Case Study #2

- An investigator at your organization is conducting an interventional clinical trial utilizing another academic IRB. As part of that process they complete a site specific/local context questionnaire in which the investigator discloses to the coordinating center and the reviewing IRB a significant financial interest involving the manufacturer of the medication being used in an arm of the trial.
- Your COI policy requires that investigators disclose all external interests annually and at the time of protocol submission to the IRB when the interest is related to the conduct of the study.
- The external interest held by your investigator was obtained 1 month after they were required to complete their annual disclosure and 1 month before they submitted to the external IRB. .
- The HRPP was informed of the interest at the next annual review and realized that while the external IRB was informed, the institution did not know about it and it's been 10 months since the investigator obtained the interest.

Questions

- What do you need to do?
- Whose responsibility was it to notify?
- Who should have been notified?
- Whose responsibility was it to review?
- Should a management plan should have been in place?
- How could this have been dealt with better in the future?

QUESTIONS?