About Schulman Associates IRB

- Established in 1983
- Superior audit history with FDA—five consecutive audits with no findings
- 21 CFR Part 11 compliant electronic systems
- Compliant with FDA, OHRP and Health Canada requirements
- Full board meetings **five days a week**
- Dedicated **daily expedited review** of qualifying minimal risk protocols
About Schulman Associates IRB

- Review outcome provided within **one business day** of new study review
- **One business day** turnaround for complete new site submissions
- **Phase I Board** with streamlined processes tailored to Phase I timelines
- **Oncology Review Board** for all phases of oncology research
- Customized services for **institutions**
- Experienced **primary points of contact** for sponsors, CROs, institutions and sites
About Schulman Associates IRB

- Clinical Quality Assurance (CQA) and Human Research Protection (HRP) consulting services provided by Provision Research Compliance Services

Provision is a joint venture between Schulman Associates IRB and Falcon Consulting Group
About Today’s Presenter

Fred Hamilton, Esq.
Vice President, Ethics and Compliance at Mount Sinai Medical Center of Florida

- Associate General Counsel, Office of Research Compliance and Regulatory Affairs (ORCRA), University of Cincinnati, 2003-2008
- Has represented hospitals in regulatory affairs in healthcare
- Attorney and graduate of the Salmon P. Chace College of Law of Northern Kentucky University
Objectives

- Describe the evolution of the central IRB in the protection of human subjects
- Discuss the establishment of the central IRB – institutional relationship
- Define delegated and shared responsibilities of the local IRB and the central IRB (FDA, OHRP, AAHRPP)
- Explain special circumstances
“In the 1980s, IRBs were mostly at institutions with NIH funding; few had more than one IRB, and the number of active studies seldom exceeded 200. These IRBs rarely reviewed external studies. The IRB Chair was part-time and IRB staff was largely viewed as secretaries. There were no training requirements to serve on the IRB. The rule of the day was ‘trust, but don’t verify.’”

Ernie Prentice (PRIM&R, 2013)

Cooperative Research Regulation – 1979

21 CFR 56.114 ("Cooperative Research") (1979)

[Code of Federal Regulations]
[Title 21, Volume 1]
[Revised as of April 1, 2014]
[CITE: 21CFR56.114]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A--GENERAL

PART 56 -- INSTITUTIONAL REVIEW BOARDS
Subpart C--IRB Functions and Operations

Sec. 56.114 Cooperative research.

In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.
"The guidance (1) describes the roles of the participants in a centralized IRB review process, (2) offers guidance on how a centralized IRB review process might consider the concerns and attitudes of the various communities participating in a multicenter clinical trial, (3) makes recommendations about documenting agreements between a central IRB and the IRBs at institutions involved in the centralized IRB review process concerning the respective responsibilities of the central IRB and each institution's IRB, (4) recommends that IRBs have procedures for implementing a centralized review process, and (5) makes recommendations for a central IRB's documentation of its reviews of studies at clinical trial sites not affiliated with an IRB."

**FDA Guidance for Industry – Using a Centralized IRB Review Process in Multicenter Clinical Trials**

(March 2006)

[http://www.fda.gov/RegulatoryInformation/Guidances/ucm127004.htm](http://www.fda.gov/RegulatoryInformation/Guidances/ucm127004.htm)
“The Office for Human Research Protections (OHRP), Office of Public Health and Science, is seeking information and comments on whether OHRP should pursue a Notice of Proposed Rulemaking to enable OHRP to hold institutional review boards (IRB) and the institutions or organizations operating the IRBs … directly accountable for meeting certain regulatory requirements[.] Historically, OHRP has only enforced compliance with 45 CFR part 46 through the institutions that were engaged in human subjects research… OHRP believes that such a regulatory change in its enforcement authority may address one of the main disincentives institutions have cited as inhibiting them from … rely[ing] on the review of an IRB operated by another institution or organization.”
“Public comment is requested on the feasibility, advantages, and disadvantages of mandating that all domestic sites in a multi-site study rely upon a single IRB as their IRB of record for that study. (This would apply regardless of whether the study underwent convened review or expedited review.) This proposal would only affect which IRB would be designated as the IRB of record for institutional compliance with the IRB review requirements of the Common Rule. It would not relieve any site of its other obligations under the regulations to protect human subjects. Nor would it prohibit institutions from choosing, for their own purposes, to conduct additional internal ethics reviews, though such reviews would no longer have any regulatory status in terms of compliance with the Common Rule (and could be discouraged).”
“NIH generally expects all domestic sites of multi-site NIH-funded studies to use a single IRB of record…. The single IRB will be accountable for compliance with regulatory requirements for IRBs specified under the HHS regulations at 45 CFR part 46…. All participating sites will be responsible for meeting other regulatory obligations such as obtaining informed consent, overseeing the implementation of approved protocols, and reporting unanticipated problems and adverse events to the single IRB of record.”


- When research covered by a federalwide assurance approved by the Office for Human Research Protections (OHRP) is to be reviewed by a central IRB, the central IRB must be designated under the FWA (45 CFR 46.103(b)(2)).

- Procedures for respective responsibilities for IRB review activities must be documented (45 CFR 46.103(b)(4). OHRP has a sample IRB Authorization Agreement on its website at [www.hhs.gov/ohrp/humansubjects/assurance/iprotsup.rtf](http://www.hhs.gov/ohrp/humansubjects/assurance/iprotsup.rtf). A copy of the agreement should be provided to the investigator. If the agreement apportions IRB review responsibilities of the central IRB and the institution’s IRB, the agreement should delineate the specific responsibilities of the central IRB and the institution’s IRB for the initial and continuing review of the study.
Sample text for an Institution with a Federalwide Assurance (FWA) to rely on the IRB/EC of another institution (institutions may use this sample as a guide to develop their own agreements).


Name of Institution or Organization Providing IRB Review (Institution/Organization A): ____________________________

IRB Registration #: ____________________________ Federalwide Assurance (FWA) #: ____________________________

Name of Institution Rellying on the Designated IRB (Institution B): ____________________________

FWA #: ____________________________

The Officials signing below agree that ____________________________ institution may rely on the designated IRB for review and continuing oversight of its human subjects research described below: (check one)

☐ This agreement applies to all human subjects research covered by Institution B’s FWA.

☐ This agreement is limited to the following specific protocol(s):

- Name of Research Project: ____________________________
- Name of Principal Investigator: ____________________________
- Sponsor or Funding Agency: ____________________________ Award Number, if any: ____________________________

☐ Other (describe): ____________________________

The review performed by the designated IRB will meet the human subject protection requirements of Institution B’s OHRP-approved FWA. The IRB at Institution/Organization A will follow written procedures for reporting its findings and actions to appropriate officials at Institution B. Relevant minutes of IRB meetings will be made available to Institution B upon request. Institution B remains responsible for ensuring compliance with the IRB’s determinations and with the Terms of its OHRP-approved FWA. This document must be kept on file by both parties and provided to OHRP upon request.

Signature of Signatory Official (Institution/Organization A): ____________________________

Date: ____________________________

Print Full Name: ____________________________ Institutional Title: ____________________________

NOTE: The IRB of Institution A may need to be designated on the OHRP-approved FWA for Institution B.

Signature of Signatory Official (Institution B): ____________________________

Date: ____________________________

Print Full Name: ____________________________ Institutional Title: ____________________________
Policies: Both parties must have written procedures in place to implement the centralized IRB review process (21 CFR 56.108, 56.114).

**Institution:** Should develop policies for determining when and which studies conducted in the institution would be appropriate for centralized review and how a centralized review would be conducted for such studies.

*For example:*
- How the institution’s IRB determines that the central IRB is qualified to review research conducted at the institution.
Policies: Both parties must have written procedures in place to implement the centralized IRB review process (21 CFR 56.108, 56.114).

Central IRB: Must have written procedures describing how it implements its responsibilities under an agreement with a referring IRB.

For example:
- How the central IRB intends to communicate with relevant institutions, the institution’s IRB(s) and investigators regarding its review
- How the central IRB assesses the ability of a geographically remote site to participate in a study (e.g. whether the site has medical services appropriate to the complexity of the study)
**Assuring Local Context:** When a centralized IRB process is used, the review should include mechanisms to ensure meaningful consideration of relevant local factors such as ethnicity, education level, and religious affiliations of proposed subjects; community attitudes about the nature of the proposed research, and the capacity of the referring institution to conduct or support the proposed research.

Possible mechanisms include:

- **Provision of relevant local information to the central IRB** in writing by individuals or organizations familiar with the local community
- **Participation of consultants** with relevant expertise, or IRB members from the institution’s own IRB, in the deliberations of the central IRB
- **Limited review of a central IRB-reviewed study by the institution’s own IRB**, with that limited review focusing on issues that are of concern to the local community
Question 1:

Do you have institutional policies/SOPs discussing the need to assure local context?
Question 2:

When reviewing research to be conducted at a remote site, do your IRB minutes contain a discussion of how local context has been assured?
“OHRP clearly recognizes now that local context issues can be dealt with by an outside IRB… if you put together the ANPRM quotes with the OHRP letter and FDA letters, you could hopefully convince institutions that you actually can do central IRB review and certainly OHRP isn’t going to come after you for not dealing with local context appropriately.”

Jerry Menikoff, MD, JD, Director, Office for Human Research Protections

Responsibilities of Central IRBs and “IRB Organizations”

- Registration with OHRP
- Membership and qualifications
- Written procedures
- Quorum for convened meetings
- Approve, modify, or disapprove all research activities under 45 CFR 46 designated on referring institution’s FWA
- Ensure compliant content of informed consent
- Require documentation of consent or waiver
- Notification to investigator and institution of approval, disapproval and opportunity to respond in cases of disapproval
- Continuing review not less than once per year
- Satisfaction of all criteria for approval of research
- Compliant expedited review procedures
- Approval of waivers/alterations of consent
- Documentation and recordkeeping requirements
Responsibilities of Institutions Engaged in Human Subjects Research

- Federalwide assurance covering HHS-supported human subjects research – file and comply with terms
- Designation of central IRB(s) on FWA
- Require IRB approval before changes in approved research (except for apparent immediate hazard to subjects)
- Require IRB approval and continuing review/approval
- Require reporting to IRB of UPIRSOs, serious or continuing noncompliance with 45 CFR 46 or requirements or determinations of IRB
- Authorize IRB to approve, modify, or disapprove all research activities under 45 CFR 46 for which it has been designated
- No institutional approval of research disapproved by IRB
- Require no involvement of human subject in research without informed consent, documentation
Responsibilities That May Be Fulfilled by Either IRB or Institution

- Determining applicability of regulations at 45 CFR 46 (e.g. exemptions at 46.101[b])
- Developing written procedure which the IRB will follow
  - For conducting initial and continuing review and reporting findings and actions to investigator and institution
  - For determining which projects require review more often than annually, or verification of no material changes
  - For ensuring prompt reporting to the IRB of proposed changes and IRB review and approval before change initiated
- Developing procedures which the IRB will follow for reporting UPIRSOs, suspensions or terminations to Institutional Official, Department/Agency head, and Investigator.
Relying on an external IRB, whether it is for a single protocol or a portion of the organization’s research portfolio can be **efficient and cost-effective**. It is important to develop a formal written agreement which clearly delineates the roles and responsibilities of each party. In addition, there should be a working and communicative relationship between the two parties. Below are roles for the reviewing IRB and relying organizations that should be included in written agreements.

Duties of the Reviewing IRB:

1. Conduct review of research according to all applicable regulations and laws, including initial review, continuing review, and review of modification to previously approved research.
2. Suspend or terminate IRB approval.
3. Reviews unanticipated problems involving risks to participants or others.
4. Review incidents of serious or continuing non-compliance.
5. Notify the researchers and organizations in writing of its decisions.
6. Make available relevant IRB minutes to the relying organization upon request.
7. When appropriate, conduct on-site or remote post-approval monitoring or audits, unless delegated to the relying organization.
8. Specify the contact person and provide contact information for the reviewing IRB.
Roles of the Relying Organization and Researchers:

1. Researchers must comply with the determinations and requirements of the IRB and the organization is responsible for ensuring compliance with the IRB’s requirements at the research site.
2. Prior to IRB review, provide the IRB with any local context issues relevant to the research protocol.
3. Research may be further reviewed and approved or disapproved by officials of the relying organization, but they may not approve the research if it has not been approved by the reviewing IRB.
4. The organization and the researchers acknowledge and agree to cooperate in the IRB’s responsibly for initial and continuing review, record keeping and reporting. All information requested by the IRB will be provided in a timely manner.
Roles of the Relying Organization and Researchers (Cont.):

5. Researchers and research staff agree to disclose financial conflicts of interest according to the agreed upon process and comply with any conflict management plans that may result.

6. The organization or researchers will report promptly to the IRB any proposed changes in the research. The investigator will not initiate changes in the research (including changes in the consent document) without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to the participants.

7. Researchers will not enroll individuals in research prior to review and approval by the IRB.

8. The researchers, when responsible for enrolling participants, will obtain, document, and maintain records of consent for each participant or each participants legally authorized representative as stipulated by the IRB.
Roles of the Relying Organization and Researchers (Cont.):

9. Researchers will report to the IRB any unanticipated problems involving risks to participants or others according to the IRB’s reporting policy.
10. Researchers will provide to the IRB any data safety monitoring reports they receive, either at continuing review, upon request by the reviewing IRB, or on an emergent basis if appropriate.
11. Researchers will report to the IRB any non-compliance or protocol deviations according to the IRB’s reporting policy.
12. Emergency medical care may be delivered without IRB review and approval to the extent permitted under applicable federal regulations and state law.
Roles of the Relying Organization and Researchers (Cont.):

13. The organization and researchers acknowledge that they are primarily responsible for safeguarding the rights and welfare of each research participant, and that the participant’s rights and welfare must take precedence over the goals and requirements of the research.

14. The relying organization may conduct post-approval monitoring in addition to, or in cooperation with, the reviewing IRB.

15. The written agreement does not preclude the organization or researchers from taking part in research not covered by the agreement.

16. Specify the contact person and provide contact information for the relying organization.
Roles That May Be Delegated to Either the Reviewing IRB or Relying Organization:

1. The agreement should stipulate whether the relying organization or reviewing IRB performs these responsibilities:
   a. Reporting to organizational officials, regulatory agencies, and sponsors of serious or continuing non-compliance, unanticipated problems involving risks to participants or others, suspensions or terminations of IRB approval.
   b. Education and continuing education of researchers and research staff. The educational requirements followed should be specified in the agreement.
   c. Obtaining disclosure and management of financial conflict of interest, although if the relying organization maintains responsibility for this issue, any disclosure or management plan will be proved to the IRB in timely manner prior to the decision by the IRB.
   d. Management of organizational conflict of interest related to the research.
Relying Institutions will typically be a HIPAA “Covered Entities,” while central IRB will not.

A Covered Entity may not delegate HIPAA responsibilities to IRB. These responsibilities include privacy policies and training, security assessment, incident response, breach notification, etc.

Although some privacy-related incidents may be reportable (UPIRSO), corrective actions for HIPAA violations are generally prescribed by the HIPAA regulations, which will control over IRB directives.
HIPAA Issues

- **Unsettled issue:** whether an IRB can waive the requirement of an authorization when specific authorization language is required by law (e.g. sale of PHI).

- External IRBs are **not** “business associates” of Covered Entities.

- Covered Entity is responsible for reviews in preparation for research, data use agreements, etc.

- An IRB may review HIPAA authorizations, but is not required to do so (depending on the IRB’s policy).
AAHRPP: Either the central IRB or the referring IRB may obtain disclosure and institute management of financial conflict of interests.

- “If the relying organization maintains responsibility for this issue, any disclosure or management plan will be provided to the IRB in timely manner prior to the decision by the IRB.”

Unsettled issue: Does the central IRB have responsibility to seek disclosures of, and to manage, institutional conflicts of interest?
Question 1:

Does your IAA address responsibility for management of conflicts of interest?
Question 2:

Does your IRB inquire concerning institutional conflicts of interest?
Other Exceptional Circumstances

- Studies in progress – *De Novo* review?
- Pre-existing sanctions and corrective action plans (Investigators)
- Benchmarks – reporting – oversight
- Institutional appeals
Key Takeaways

➢ Put an agreement in place

Think about:

• What could happen in the relationship
• What each organization needs to get out of the relationship
• What is required for human subject protection
Comments - Discussion

[Image of a bird in a wetland setting]
Local and Central IRB Partnerships: Individual and Shared Responsibilities

March 18, 2015

Presented by:
Fred Hamilton, JD
Vice President, Ethics and Compliance
Mount Sinai Medical Center of Florida