Federal Initiatives Toward Single IRB Review

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About Schulman 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 IRB

- Review outcome provided within one business day of new study review
- One business day turnaround for complete new site submissions
- Dedicated streamlined processes tailored to Phase I timelines
- Expert oncology IRB members experienced in all phases of oncology research
  - National IRB for Cancer Breakthrough 2020 initiative
- Customized services for institutions
- Experienced primary points of contact for sponsors, CROs, institutions and sites
About Schulman IRB

Clinical Quality Assurance (CQA) and Human Research Protection (HRP) consulting services provided by:

www.provisionrcs.com  www.falconnest.com
The industry’s choice for central and local IRB services.

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Begin the initial review process.

Forms
Download the latest forms for your study.

Contact Us
Request more info & send feedback.
About Today’s Presenters

Michele Russell-Einhorn, JD
VP of HRP Services and Institutional Official, Schulman IRB

- VP Oncology; VP Human Research Protection Services
- Co-Chair, Subpart A Subcommittee, SACHRP
- Founding member, NCCN IRB Directors Forum
- Previously served as Senior Director, Dana Farber Cancer Institute, Office for Human Research Protections
- Lawyer by training
About Today’s Presenter

Judith Carrithers, JD, MPA
Director of Oncology Services, Schulman IRB

- Director of Oncology Services at Schulman IRB
- Previously served as Assistant Dean for Human Research Protection and Director of the HRPP, Johns Hopkins University School of Medicine
- Lawyer by training
A Changing Landscape
Overview

- Review of current regulatory provisions relating to single IRB review
- NIH Policy on Single IRB Review
- 21st Century Cures Act
- Final rule revising the Common Rule
- Views from industry and from a CRO
- Institutional concerns
- Next steps
Single IRB Review Generally

- Single IRB review = One IRB of record for research conducted at more than one site
- Many institutions use their own local IRBs
  - Some cede industry sponsored protocols
- Sponsors supporting multi-site research sometimes identifying one IRB as the IRB of record
- Federal initiatives mandating single IRB review
Why the Move to a Single IRB

- Sponsor concerns with tracking and managing divergent reviews from multiple IRBs
- Issues with individual IRB review in multi-site research
  - One subject population from which data is gathered for the data analysis
  - Different consent forms
    - Inconsistent risk language
    - Inconsistent language describing the research
    - Inconsistent safety measures
Support Trial

Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)
A controlled, multicenter trial – 2010

- Interesting study to review because of the different language contained in the different consent forms issued by the 22 participating institutions and their local reviewing IRBs
We conducted the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), a controlled, multicenter trial with a 2-by-2 factorial design, to compare two target levels of oxygen saturation and two ventilation approaches (continuous positive airway pressure [CPAP] initiated in the delivery room with a protocol-driven strategy of limited ventilation vs. intratracheal administration of surfactant with a protocol-driven strategy of conventional ventilation). The oxygen-saturation component of the trial tested the hypothesis that a lower target range of oxygen saturation (85 to 89%), as compared with a higher target range (91 to 95%), would reduce the incidence of the composite outcome of severe retinopathy of prematurity or death among infants who were born between 24 weeks 0 days of gestation and 27 weeks 6 days of gestation. The ventilation part of this factorial-design trial, which was used to control the ventilation approach and test other hypotheses, is reported elsewhere in this issue of the Journal.
Support Trial

- 22 consent forms
- 21 of 22 IRB-approved consent forms characterized the experimental oxygen arms in one or more of the following ways:
  - “standard of care” (15/22)
  - “within normal range” or “normal” (13/22)
  - “within the range currently used” (7/22)
  - “considered by some units to be the desired [or best] approach” (3/22)
- 9 of 22 consent forms described the mis-calibration of the pulse oximeters
Death and ROP (retinopathy of prematurity) were both components of the primary endpoint being assessed in the oxygen experiment and were reasonably foreseeable risks.

<table>
<thead>
<tr>
<th>13 of 22 consent forms</th>
<th>Stated: “Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby” (or something very similar)</th>
</tr>
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<tbody>
<tr>
<td>20 of 22 consent forms</td>
<td>Did not identify ROP or brain injury as a risk of the research</td>
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Current Regulatory Provisions

- FDA
- Federal Policy for the Protection of Human Subjects
- HHS Regulations
21 CFR Part 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.
Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.
New Regulatory Mandates

- NIH Policy Single IRB Review Policy
- 21st Century Cures Act
- Final Rule (revising the Common Rule)
NIH Policy on Single IRB Review
Effective September 2017 (issued 6/21/2016)

Purpose

- Establishes the expectation that all sites participating in multi-site studies involving non-exempt human subjects research funded by the National Institutes of Health (NIH) will use a single Institutional Review Board (sIRB) to conduct the ethical review
- Consistent with 45 CFR Part 46.114
- Intended to enhance and streamline the process of IRB review and reduce inefficiencies so that research can proceed as expeditiously as possible without compromising ethical principles and protections for human research participants

NIH Policy on Single IRB Review

Scope and Applicability

- Applies to the domestic sites of NIH-funded multi-site studies where each site will conduct the same protocol involving non-exempt human subjects research, whether supported through grants, cooperative agreements, contracts, or the NIH Intramural Research Program.
- Does not apply to career development, research training or fellowship awards.
- This policy applies to domestic awardees and participating domestic sites.
  - Foreign sites participating in NIH-funded, multi-site studies will not be expected to follow this policy.
- Applicants/offereors will be expected to include a plan for the use of an sIRB in the applications/proposals they submit to the NIH.
- The NIH’s acceptance of the submitted plan will be incorporated as a term and condition in the Notice of Award or in the Contract Award.
- This policy also applies to the NIH Intramural Research Program.

NIH Policy on Single IRB Review

Definitions

- The **Authorization Agreement**, which is also called a reliance agreement, is the agreement that documents respective authorities, roles, responsibilities, and communication between an institution/organization providing the ethical review and a participating site relying on the sIRB.

- A **multi-site study** uses the same protocol to conduct non-exempt human subjects research at more than one site.

- **Participating site** in a multi-site study is a domestic entity that will rely on the sIRB to carry out the site’s IRB review of human subjects research for the multi-site study.

- **sIRB** is the selected IRB of record that conducts the ethical review for participating sites of the multi-site study.

NIH Policy on Single IRB Review

Roles and Responsibilities

**Applicant/Offeror.** In the application/proposal for research funding, the applicant/offeror is **expected to submit a plan** describing the use of an sIRB that will be selected to serve as the IRB of record for all study sites.

- The plan should include a statement confirming that participating sites will adhere to the sIRB Policy and describe how communications between sites and sIRB will be handled.
- If, in delayed-onset research, an sIRB has not yet been identified, applications/proposals should include a statement that awardees will follow this Policy and communicate plans to use a registered IRB of record to the funding NIH Institute/Center prior to initiating a multi-site study.
- The applicant/offeror may request direct cost funding for the additional costs associated with the establishment and review of the multi-site study by the sIRB, with appropriate justification; all such costs must be reasonable and consistent with cost principles, as described in the NIH Grants Policy Statement and the Federal Acquisition Regulation (FAR) 31.302 (Direct Costs) and FAR 31.203 (Indirect Costs).

**Awardees.** Awardees are responsible for ensuring that authorization agreements are in place; copies of authorization agreements and other necessary documentation should be maintained in order to document compliance with this policy, as needed. As appropriate, awardees are responsible for ensuring that a mechanism for communication between the sIRB and participating sites is established. Awardees may delegate the tasks associated with these responsibilities.

Funding Institute or Center (IC). Funding ICs are responsible for management and oversight of the award, including communicating with the awardee regarding the implementation of its proposed plan to comply with the sIRB Policy. In the event that questions arise about the awardee’s plan, including the IRB that has been selected to serve as the sIRB, the funding IC will work with the awardee to resolve them.

sIRB. The sIRB is responsible for conducting the ethical review of NIH-funded multi-site studies for participating sites. The sIRB will be expected to carry out the regulatory requirements as specified under the HHS regulations at 45 CFR Part 46. In reviewing multi-site research protocols, the sIRB may serve as a Privacy Board, as applicable, to fulfill the requirements of the HIPAA Privacy Rule for use or disclosure of protected health information for research purposes. The sIRB will collaborate with the awardee to establish a mechanism for communication between the sIRB and the participating sites.

Participating Site. All sites participating in a multi-site study are expected to rely on an sIRB to carry out the functions that are required for institutional compliance with IRB review set forth in the HHS regulations at 45 CFR 46. Participating sites are responsible for meeting other regulatory obligations, such as obtaining informed consent, overseeing the implementation of the approved protocol, and reporting unanticipated problems and study progress to the sIRB. Participating sites must communicate relevant information necessary for the sIRB to consider local context issues and state/local regulatory requirements during its deliberations. Participating sites are expected to rely on the sIRB to satisfy the regulatory requirements relevant to the ethical review. Although IRB ethical review at a participating site would be counter to the intent and goal of this policy, the policy does not prohibit any participating site from duplicating the sIRB. However, if this approach is taken, NIH funds may not be used to pay for the cost of the duplicate review.

Exceptions
Exceptions to this policy will be made where review by the proposed sIRB would be prohibited by a federal, tribal, or state law, regulation, or policy. Requests for exceptions that are not based on a legal, regulatory, or policy requirement will be considered if there is a compelling justification for the exception. The NIH will determine whether to grant an exception following an assessment of the need.

January 30, 2017 NIH issued the following document:

NIH Policy on the Use of a Single IRB for Multi-Site Research FAQs on Costs

1. **What are the “cost principles” referred to in the NIH sIRB Policy?**

   The cost principles are described in regulation at 45 CFR 75 Subpart E and are implemented by reference in the NIH Grants Policy Statement (Section 7.2) and establish standards for the allowability of costs, provide detailed guidance on the cost accounting treatment of costs as direct or indirect (F&A) costs, and set forth allowability and allocability principles for selected items of cost.

2. **May direct costs be used to support administrative tasks of supporting an sIRB?**

   Direct charges for the salaries of administrative and clerical staff are allowable, but only if all of the
To protect vulnerable populations, incorporate local considerations, and support community engagement through mechanisms such as consultation with local researchers and human research protection programs, in a manner consistent with subparagraph (B); and

Ensure that human subject research that is subject to the HHS Human Subject Regulations and to the FDA Human Subject Regulations may—

- (A) use joint or shared review;
- (B) rely upon the review of—
  - (i) an independent institutional review board; or
  - (ii) an institutional review board of an entity other than the sponsor of the research; or
- (C) use similar arrangements to avoid duplication of effort.

Source: 21st Century Cures Act
Final Rule on Single IRB Review

- Final Rule: Compliance date January 20, 2018
- Delayed compliance date for single IRB review requirements: January 20, 2020
  - Acknowledges possibility of changes to institutional and IRB infrastructure to accommodate mandated single IRB review
- Provides OHRP with oversight over IRBs not operated by the institution (independent IRBs)
  - Alleviates one concern that has existed in ceding IRB review
Cooperative research projects are those projects covered by this policy that involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy.

(b)(1) 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. The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research.

(2) The following research is not subject to this provision: (i) Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or (ii) Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context. (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.

Source: Final Revisions to the Common Rule
Tools to Facilitate Single IRB Review

- SMART IRB
- IRB Choice
SMART IRB

- 151 participating institutions as of March 13, 2017
- Schulman was the first independent IRB to sign the SMART IRB agreement

- What does signing the Smart IRB agreement mean?

Source: SMART IRB
IRBchoice

A platform offering optimal flexibility in IRB reliance for multi-site studies. IRBchoice expands upon traditional IRB reliance models to support the full spectrum of research protections by:

- Providing access to a national network of collaborators
- Supporting single IRB review of multisite studies
- Establishing one platform to document and track all reliance relationships
- Allowing IRBs to customize reliance preferences on a study-by-study basis
- Generating study-specific instructions for research teams to help maintain compliance
- Facilitating transparency between IRBs to support best practices, shared expertise, and increased consistency

Source: IRBchoice
Working Group to revise standards to provide for a better integration of IRB ceding of review within the AAHRPP standards
- Proposed changes under review by AAHRPP Council

SACHRP guidance on using a single IRB
- Initial Considerations for Single IRB Review: Points to Consider
- Approved by SACHRP October 26, 2016
Observations from the Industry Perspective
Perspectives from an Industry Sponsor

Streamlining IRB Review to Single IRB

Supportive
- Improve efficiency of clinical research? Decrease delays in critical research activities?
- Decrease costs? Increased accountability?
- Support the rapid initiation of trials and patient access?
- Increase interest of researchers to participate in clinical trials with a decrease in administrative burden?
- Academic/local settings have equal timeline/opportunity to enroll subjects as central IRB settings?
- Consistency of information disseminated to subjects?

Challenges
- Concerns of specific local cultures, communities is lost?
- Protection of vulnerable populations?
- Specialized cases of local institutional IRB review?
- Access of local researchers to internal academic IRB support? Mentorship?
- Loss/improvement of oversight responsibilities?
- Local institutions lose opportunity for scientific input to protocol?
Observations from the CRO Perspective
Perspective from a CRO

- Informed consent negotiation
  - Timelines of negotiation
    - Central IRB vs local IRB
  - Areas of ICF delays
  - Time implications
  - Drawbacks to central IRB use
Institutional Review Board Usage

- Central IRB use is on the rise for sponsor funded research projects:

  CRO project data for total sites submitted
  
  - 2010 in the United States: 51% Central IRB vs 49% Local IRB
  - 2016 in the United States: 73% Central IRB vs 27% Local IRB
Informed Consent Timelines

Days from Site Selection to IRB Submission

There is a 41% difference in timelines that is dependent on IRB type.
Informed Consent Negotiation Timelines

- Average of slightly over 2 rounds of draft ICF negotiation and review between the site and sponsor prior to submission to the local IRB

- Main areas of ICF delays for central and local IRBs:
  - Compensation due to injury
  - Compensation/reimbursement for study participation
  - Privacy language (HIPAA/PIPEDA)
  - Intellectual property text
Informed Consent Negotiation Timelines

Days from IRB Submission to IRB Approval

There is a 21% increase in timelines for Local IRB sites

- Days from IRB Submission to IRB approval

Central IRB

Local IRB
Informed Consent Negotiation Timelines

- Average of 2.4* rounds of IRB comments/text modifications and between the IRB submission and local IRB approval
- Average of 1.2* rounds of IRB comments/text modifications and between the IRB submission and central IRB approval
  - Typically on the submission form prior to board review

- Fewer IRB meetings
  - Central IRBs typically meet daily
  - Local IRBs typically meet weekly
Informed Consent Negotiation Timelines

Site Selection to Site Activation - United States

There is a 56% difference in the total days from site selection to site activation between Central IRB and Local IRB sites in the United States.
Implications of Timelines

- CRO industry standards: a US central IRB site can be activated and begin recruitment 100 days before a local IRB site.
- Sites that are activated earlier meet enrollment projections before screening closes:
  - Local IRB sites with long approval timelines are at a disadvantage in competitive enrollment projects.
  - Studies that close enrollment earlier than planned complete scheduled visits sooner, which saves monitoring costs for the sponsor.
Drawbacks to Central IRB Usage

- Sites are not able to use every central IRB, so selection must be done to maximize the number of sites per project
- Local regulations are not always included into the consent forms automatically by Central IRBs
- Patients do not receive ICFs from the same site that they are receiving care from
  - May lead to questions on why it was not locally approved
  - Comfort level of local governance of study
Summary

- Sites able to use central IRBs typically have shorter activation timelines as a result
- Patients are able to be recruited sooner
- Time and cost savings to the sponsor
- Participants may be reluctant to sign consent forms that are not issued by their hospital/institution
Institutional Concerns and Next Steps
What Entity Can Be a Single IRB?

- Can be an institution
  - Investigator qualifications
  - Verification of use of most recently approved consent
  - System to handle revised consents and protocol related events from multiple institutions
  - Resources to train investigators on submission systems
  - Resources to respond to questions

- Can be an independent IRB

- How many should you work with?
sIRB Decision

- Will the sponsor/funder permit multiple IRBs or reliance on one IRB?
- Will an institution rely on another IRB or assume the role of sIRB? This requires:
  - Assessment of technology
  - Assessment of resources
  - Assessment of institution’s willingness to assume liability of acting as sIRB
  - Generally will require investment in additional staff and IT
Relying Institution

Managing:

- Multiple authorization agreements
- Variations in investigator responsibilities
  - Will eligibility exceptions be considered
- Variations in institutional responsibilities
  - How will conflicts of interest be managed
- Variations in availability of regulatory tools
  - Will short form consents be permitted
  - Which policy on reconsenting will be applied
  - Which policy on who can consent will apply
Relying Institution

- Implementation of any necessary and appropriate internal changes to facilitate local reviews that will still be required when relying on an external sIRB
  - Example: COI and radiation safety
  - Policies and procedures will need to be developed to communicate the results of these reviews to the sIRB
Serving as the sIRB

Managing:

- Extension of courtesy notices to external sites (e.g., CR notices at 60 days, 30 days)
- Assuring any duplication does not result in inadequate information to sIRB
  - Subject complaints can be submitted to either relying institution or sIRB
- Verification that relying institution investigators used current, approved consent form
- Training on submission system and forms
- Availability to respond to questions from all sites
  - Adverse events, unanticipated problems
Single IRB Review: Next Steps

- A general uniform IRB authorization agreement (SMART IRB)
- Need uniform policies and procedures to implement this or any other authorization agreement
Single IRB Review: Next Steps

- General guidance for relying institutions
- General guidance when serving as an sIRB

Topics relevant to both roles:
- Technology considerations
- Human resource considerations
- Cost considerations
  - Cost incurred as a relying institution
  - Cost incurred as an sIRB
  - Charging for costs incurred after the initial charges have been established
Dialogue on managing more nuanced issues:

- Cede review but decide the sIRB is not conducting reviews in compliance with the regulations
- Cede review but decide the sIRB is not acting in a timely fashion (minutes and amendments)
- Cede review but the sIRB has failed to incorporate your local reviews
Single IRB Review: Next Steps

- sIRB says no FDA IND is required; relying institution says yes one is
- sIRB makes a pediatric determination with which relying institutions disagree
- sIRB determines on amendment 2 that additional safety measures are required and relying institutions disagree
- sIRB finds unanticipated problem is reportable and relying institution disagrees
- sIRB disagrees with relying institution over the COI management of a financial interest
Single IRB Review: Next Steps

- Is your only option to withdraw from the research?
- What if this occurs midway through the conduct of the research?
Conclusion

- Beginning stages
- Progress will be made if we work together
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