MULTI-SITE STUDIES AND SINGLE IRB REVIEW

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RESEARCH PROFESSIONALS NETWORK

OVERVIEW

What we will cover:

- Multi-site studies and Single IRB regulations
- Multi-site study planning, communication, document management, and resources
- Single IRB review process and ongoing submissions

What we won't cover:

- Institution-specific policies & procedures
- Links to each RPN institution's policies will be provided at the end

OBJECTIVES

Learning objectives:

- Determine if Single IRB review is required
- Understand Single IRB reliance & review
- Identify who is responsible for specific multi-site study management activities
- Recognize ongoing submission requirements
  - amendments
  - continuing reviews
  - reportable new information
  - study closures

ACTIVITY #1: CHAT STORM

Tell us your experience with multi-site studies and single IRB!

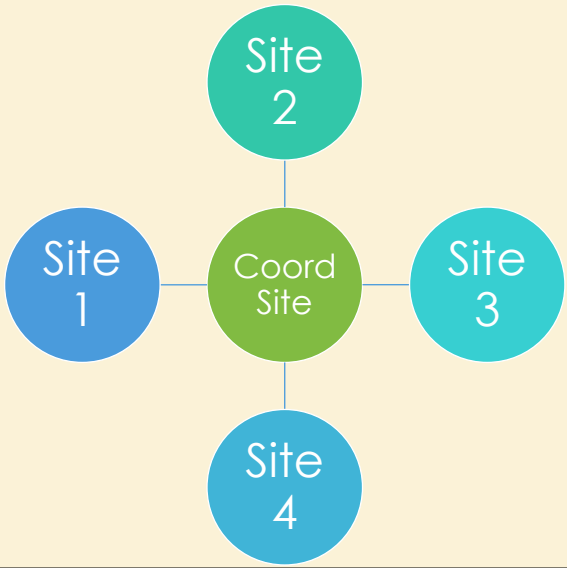
- Do you know what they are?
- Do you have experience with them?
- Does your institution have experience with them?
- Has your institution been a Lead Site? Coordinating Center? IRB of Record?

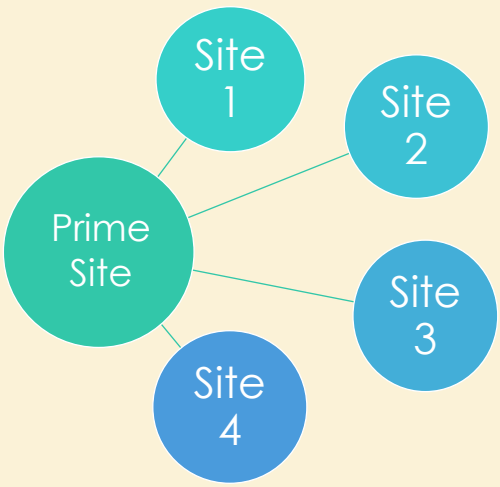
HUMAN SUBJECTS RESEARCH

An institution/individual is engaged in human subjects research if they are:

1. Receiving direct federal funding for research (i.e. Primary Awardee of the grant)
2. Obtaining data about subjects through intervention/interaction
3. Obtaining identifiable private information about subjects
4. Obtaining informed consent
5. Implementing/administering research intervention

MULTI-SITE STUDY TYPES





MULTI-SITE STUDY CONSIDERATIONS

Site selection

- Sites responsible for:
  - recruitment
  - consent
  - intervention delivery
  - follow-up

Coordinating or Lead site

- Site trainings / visits
- Communications
  - Sites
  - IRB
- Ensure protocol standardization
- Milestone tracking
- Data mgmt, compliance, and analyses
- Data use agreements
- Dissemination

SITE SELECTION & ENGAGEMENT

BY PRIME OR COORDINATING SITE

Plan	• Build partnerships and commitment by eliciting information on site specific processes and feedback on trial design
Conduct	• Sustained engagement via bi-directional communication and learning networks for enhanced site performance
Disseminate	• Leverage site and community partnerships to create locally designed dissemination plans for broader scientific reach and impact

Source: Goodlett D, et al. Site engagement for multi-site clinical trials. Contemp Clin Trials Commun. 2020 Jun 29;19:100608.

MULTI-SITE STUDY CONSIDERATIONS

sIRB selection

- Lead site
- Participating site
- Established Central IRB
- Commercial IRB

- Which site:
  - has experience as sIRB?
  - is conducting study interventions?
- What is the budget?

SINGLE IRB DEFINITIONS

Single IRB review	• legal arrangement allowing one IRB to review the research and make regulatory determinations on behalf of other engaged institutions
Multi-site research	• two or more institutions conducting the same human subjects protocol
Cooperative research	• human subjects research involving more than one institution

SINGLE IRB DEFINITIONS

Reviewing IRB	• a.k.a. IRB of Record • External IRB if ceding review to another institution's IRB • Central IRB if reviewing for a consortium/network
Relying Site	• a.k.a. Participating Site • a.k.a. P Site
Lead Site	• overall responsibility for study • often directs activities of sites • often holds grant, IND, or IDE
Coordinating Center	• designated to manage conduct of all sites • may be limited to receipt, storage, sharing, and analysis of data

SINGLE IRB REGULATIONS

NIH Single IRB Policy

January 25, 2018

Single IRB review required for NIH-funded, multi-site studies

Common Rule Single IRB Regs
45 CFR 46.114(b)

January 20, 2020

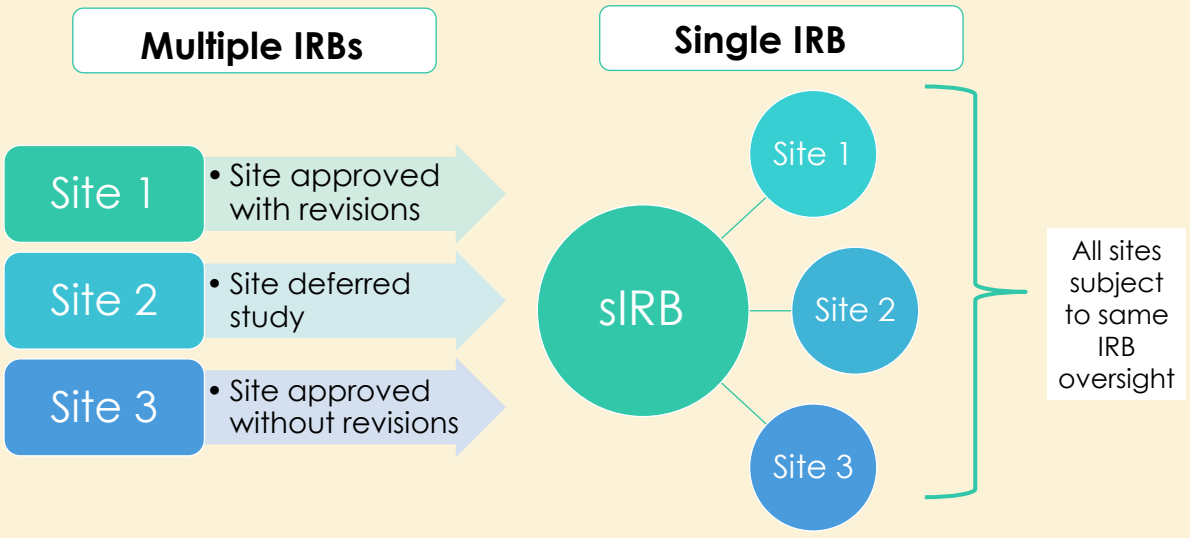
Single IRB review required for all domestic, cooperative, HS research conducted or supported by a Common Rule dep't or agency

WHICH STUDIES REQUIRE SINGLE IRB?

Common Rule Single IRB Regulation (45 CFR 46.114(b))

APPLIES TO:	DOES NOT APPLY TO:
Human Subjects Research	Exempt protocols, Quality Improvement, Program Evaluation
Federally-funded research	Industry, Foundation, or Institutionally funded protocols
Career Development (K) awards	International protocols (i.e. GDPR)
Fellowship (F) awards	Training (T) awards
	Research that must be reviewed by more than one IRB by law (i.e. tribal law)
	Research for which the supporting Federal department/agency determines & documents that use of sIRB is not appropriate

BENEFITS OF sIRB FOR MULTI-SITE STUDIES



Challenges and Solutions

- Challenge:
  - Knowing when Single IRB Review is required for your study
- Solutions:
  - Get to know the regulations
  - Get to know your institution's policies
  - Get to know the reliance contact at your institution
  - Figure it out early

ACTIVITY #2: POLL

Read the following scenarios and determine if the study requires Single IRB review under the NIH policy and/or Common Rule regulations.

We will briefly discuss the answers after each question.

QUESTION 1

- Dr. Smith at the University of Florida has received an NIH R01 grant to study the effects of smoking cessation techniques in young adults.
- This interventional protocol is considered more than minimal risk and will be reviewed at a full board level.
- Dr. Smith is collaborating with Dr. Peters at Utrecht University in the Netherlands, who will conduct the same protocol procedures including data analysis.
- Is Single IRB review required for this study?

ANSWER: NO

Though the project is NIH-funded, non-Exempt, human subjects research, there is only one domestic site. The Netherlands site is not subject to NIH or Common Rule regulations, and therefore the study does not meet the criteria for Single IRB Review.

QUESTION 2

- Dr. Jones at the Medical University of South Carolina is conducting an NIH-funded, randomized, controlled trial (RCT) evaluating the effects of exercise on recovery from orthopedic surgery.
- Dr. Jones' colleague at Boston Medical Center, a subawardee on the grant, is interviewing healthcare providers about their opinions of post-operative exercise.
- While the RCT is considered more than minimal risk, the interviews meet the criteria for Exemption category 2 research.
- Is Single IRB review required for this study?

ANSWER: YES

Under the Common Rule, this NIH-funded, collaborative human subjects research requires Single IRB Review. Collaborative research does not require the same activities to be conducted at each site, and the overall project is non-Exempt.

QUESTION 3

- Dr. Baker at the University of Vermont has been approached by the Amyloidosis Research Consortium (ARC) for participation in a repository protocol.
- Sites participating in this study would contribute both clinical data and biospecimens to the repository to be used for future research.
- The ARC is a nonprofit organization dedicated to driving advances in the awareness, science, and treatment of amyloid diseases.
- The ARC uses a Central IRB for review of its research and asks participating sites to cede review to the CIRB.
- Is Single IRB review required for this study?

ANSWER: NO

Although the consortium asks P Sites to use the CIRB, the study does not fall under the NIH or Common Rule Single IRB regulations since it is funded by a foundation (non-federal funding).

PLANNING FOR USE OF SINGLE IRB IN MULTI-SITE STUDIES

Protocol/ Grant
- Prime site? Multiple sites plus coordinating site?
- Will each site perform the same activities?
- Describe each site's responsibilities while avoiding noncompliance

Budget
- Estimate sIRB fees
- Determine which site will include in budget (prime, shared, coordinating site)

Select sIRB
- Institutional, Commercial, Government
- Will sites ceding review require local context review, as well?

PROTOCOL

Protocols for multi-site studies using sIRB should make procedures clear yet general enough to avoid noncompliance at participating sites that might have institution-specific policies or considerations:

- Recruitment
  - Local populations
  - Allowable methods
- Compensation
- Interventions
  - Local standard of care
  - Hospital SOPs
- Data management and security

- Research-related injury
- HIPAA required language
- Consent/assent procedures
- Legally authorized representatives
- Impartial witness

BUDGET IMPLICATIONS OF SIRB

IRB fees must cover

- Initial review of protocol
  - Investigator/site qualifications, informed consent plans, data collection instruments, recruitment materials
- Onboarding relying sites
  - Investigator/site qualifications, study templates edited to be site-specific
- Continuing/annual protocol review
- Periodic review of incident reports (reportable new information)
- Amendments/modifications
- Site closure
- Study/protocol closure

Consider budgeting for a project or regulatory manager as submissions for multiple sites are a significant amount of work!

ACTIVITY #3: POLL

Read the following multiple-choice and true/false questions about planning for use of Single IRB in multi-site studies.

We will briefly discuss the answers after each question.

QUESTION 1

- When creating your IRB budget, you should account for the following:
  - A) Amendments and modifications
  - B) Translation of participant materials
  - C) Study close out
  - D) Onboarding of participating sites
  - E) A, C, and D
  - F) A, B and C

- Commercial IRBs (and some institutional IRBs) may invoice for initial study approval, onboarding of sites, amendments/modifications, continuing/annual review, review of incidents & reportable new information, and site and protocol closure.
- Though translation of materials may be required of the study enrolls NES participants, it would not be considered an IRB fee.

QUESTION 2

- Data management and security policies are consistent across institutions, so language in the protocol is standardized.

A) True

B) False

- Institutions often have policies and procedures for local data management and security, and these policies might differ between P Sites. The lead investigator(s) writing the protocol should ensure that the protocol isn't so specific that it contradicts participating site policies.
- For example, a specific data transfer portal listed in the protocol isn't allowed by Site 2's IT services for secure transfer of research data.

QUESTION 3

- Institutions participating in studies under a Single IRB cede the right to local context review.

A) True

B) False

- Though P Sites cede regulatory review of the study to the IRB of Record, they do not waive the right to conduct an institution-specific local context review.
- Local Context Review may include required consent language, ancillary reviews, state laws, institutional policies, etc.
- It is highly recommended by regulatory bodies that regulatory review (i.e. ensuring criteria for IRB approval are met) is not duplicated by participating sites, but it is expected that Local Context Review will occur.

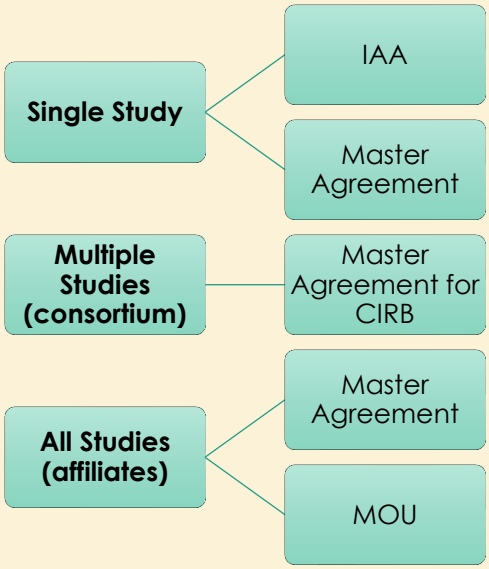
TYPES OF SINGLE IRBS

Commercial	Institutional / CIRBs	Governmental
• *Advarra • *WCG IRB (formerly Western IRB) • Aspire • Solutions IRB • BRANY • Sterling IRB • (many others)	• Universities • Academic medical centers • StrokeNet (University of Cincinnati) • Northeast ALS Consortium (Mass General Brigham) • (many others)	• National Cancer Institute Central IRB (NCI CIRB) • CDC IRB • Tribal IRBs • Foreign country ethics committees

TYPES OF RELIANCE AGREEMENTS

- **IRB Authorization Agreement (IAA)**
  - Signed by 2+ institutions engaged in human subjects research permitting ceding of review to another IRB
- **Master Reliance Agreement**
  - Type of IAA that allows an institution to rely on an External IRB repeatedly without needing to renegotiate an agreement for each study
- **Cooperative Research Agreement**
  - Either institution's IRB may review situationally
- **Memorandum of Understanding**
  - Agreement between two parties in writing; may include terms of reliance
- **Individual Investigator Agreement (IIA)**
  - Assured institution can extend its Federalwide Assurance to an independent investigator or an investigator at a non-assured institution

TYPES OF RELIANCE AGREEMENTS



ESTABLISHING RELIANCE

Reliance Agreement

Institutional Profile
Static details about a site

Local Context Form
Site info specific to the study under review

Communication Plan
Sets expectations for all parties

Master Agreement Addendum

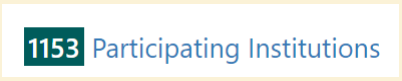
Letter of Indemnification

Challenges and Solutions

- Challenge:
  - Organizing and documenting reliance terms
- Solutions:
  - Clear lines of communication
  - Knowing who the Point of Contact (POC) is for each site
  - Online reliance systems

ONLINE RELIANCE SYSTEMS

- Streamlined, Multisite, Accelerated Resources for Trials IRB Reliance platform
- NOT a Single IRB!
- Platform that offers a master IRB reliance agreement (the SMART IRB Master Common Reciprocal Agreement) and a web-based system (SMART IRB's Online Reliance System) allowing institutions and their investigators to initiate, track, and document study-specific reliance agreements
- As of October 2023: **1150** participating institutions
- Find which institutions have signed the master agreement by going to https://smartirb.org/reliance/ and clicking on:



ONLINE RELIANCE SYSTEMS

- A freely available, web-based portal supporting single IRB review documentation and coordination for multi-center clinical trials
- As of October 2023: **510** participating institutions

ACTIVITY #4: POLL

Read the following multiple-choice question about reliance agreements and select the best answer.

We will briefly discuss the answer after the question.

QUESTION

- University of Vermont has received an NIH grant for a multi-site protocol that requires the use of Single IRB Review, and UVM has agreed to act as the IRB of Record for all participating sites.
- The participating sites engaged in the research and receiving subawards are Dartmouth, University of Maine, and University of Southern Maine.
- University of Vermont, Dartmouth, and University of Southern Maine are signatory institutions on the SMART IRB Master Reliance Agreement. University of Maine is not.
- What type(s) of reliance agreement would be appropriate to establish reliance on the UVM IRB for this study?

A) IRB Authorization Agreement (IAA) for a single protocol
B) SMART IRB Master Reliance Agreement
C) Memorandum of Understanding
D) Individual Investigator Agreement (IIA)
E) A and C
F) A and B

- IIAs between UVM and each institution for this single protocol would be appropriate.
- Also, institutions who are signed onto the SMART agreement can use it to document reliance for this study.
- University of Maine could sign an IIA, or they could become a SMART IRB signatory.
- An MOU is not necessarily legally binding and an IIA would not be appropriate as all sites are considered engaged as institutions and all have FWAs.

SINGLE IRB REVIEW: OVERALL STUDY APPROVAL PROCESS

Lead Site submits study-wide docs & templates to Single IRB

Single IRB approves study

Lead Site distributes approved study docs & templates to P Sites

SINGLE IRB REVIEW: LOCAL CONTEXT REVIEW PROCESS

P Site submits to local IRB or HRPP

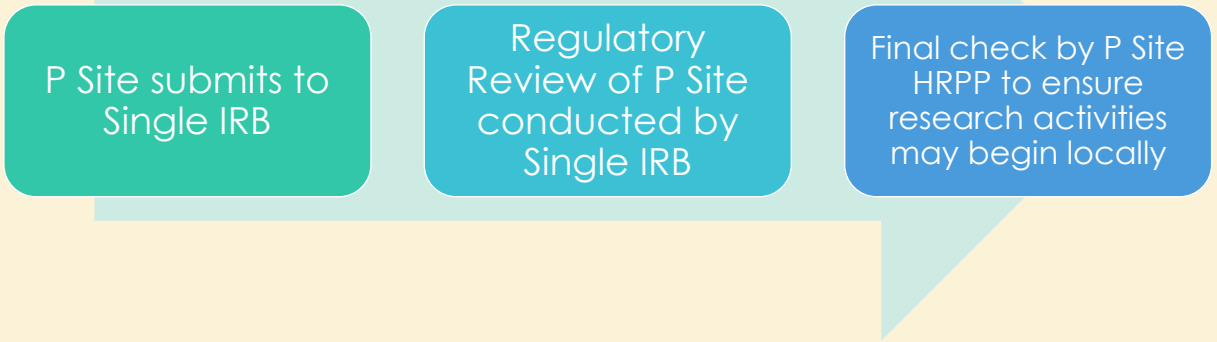
Local Context Review ensures institutional policies & local laws are addressed

Institutional Ancillary Reviews are completed

P Site HRPP indicates local context review is complete

SINGLE IRB REVIEW: LOCAL CONTEXT REVIEW AT RELYING SITE

SINGLE IRB REVIEW: PARTICIPATING SITE APPROVAL PROCESS



ACTIVITY #5: POLL

Read the following multiple-choice and true/false questions about the Single IRB review process and select the best answer.

We will briefly discuss the answer after each question.

QUESTION 1

- Relying sites should submit local study materials, such as consent templates edited to include locally required language, to the External IRB for approval *before* submitting to their site's HRPP for local context review.
  - A) True
  - B) False

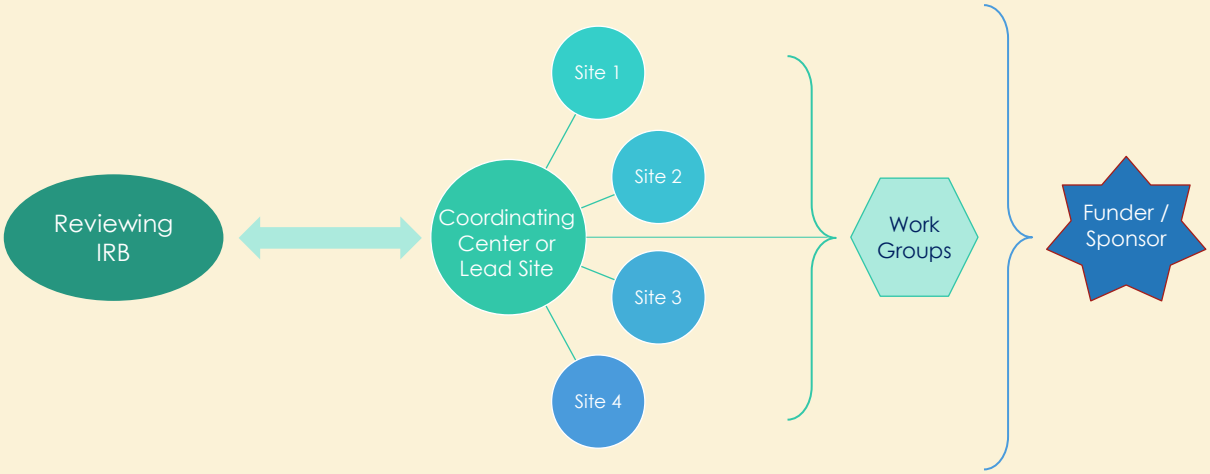
- It is best practice, and often required, for local study teams to submit study materials to their local HRPP before submitting to the External IRB.
- This allows the local HRPP to confirm that institutional policies and state laws are being followed before the materials are approved for use by the External IRB.
- This can avoid lengthy and confusing back-and-forth between the External IRB and local HRPP. If the HRPP approves documents that contradict local policies, the documents will have to be edited and resubmitted for another review and approval.

QUESTION 2

- Which of the following activities are the responsibility of the Relying Site?
  - A) Institutional Ancillary Reviews
  - B) Local Context Review
  - C) Conflict of Interest Management
  - D) Ensuring PI/Personnel Training and Qualifications
  - E) Compliance
  - F) All of the above

The Relying Site / institution retains responsibility for not only local context review, but other institutional reviews including contracts and grants, PI and key personnel training, qualifications, and conflict of interest management, and compliance with the External IRB's determinations and federal regulations.

INSTITUTIONAL RELATIONSHIPS IN MULTI-SITE STUDIES



COMMUNICATION NEEDS IN MULTI-SITE STUDIES

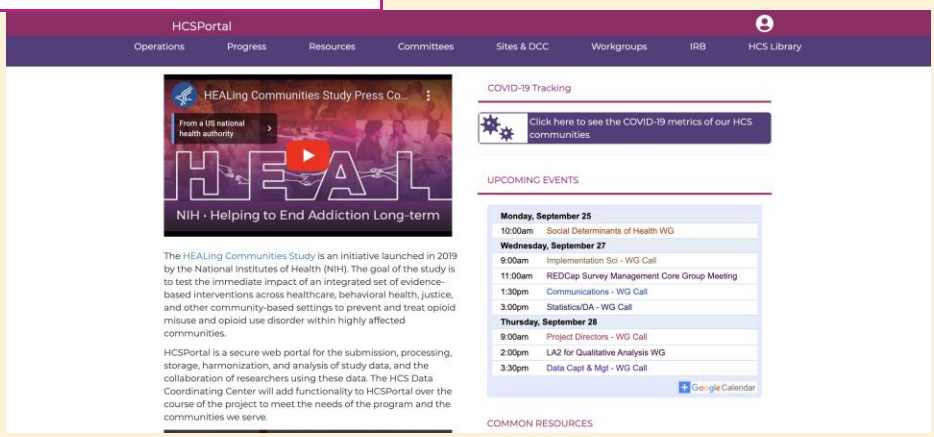
- IRB materials
  - Protocol and data collection instruments
  - Participant materials, e.g. informed consent, participant communications
    - Masters
    - Site-specific versions
- Staff directory
- Centralized publication and presentation review and approval system
- Consortium work group calendar, meeting minutes, SOPs, instructional memos, data schedule and receipt tracker
- Branded templates
- Project schedule and milestone tracker
- Centralized document search

Challenges and Solutions

- Challenge:
  - Organization of study documents and communications across multiple sites
- Solution:
  - Study specific portal
  - Commercial document management and communication platforms

SECURE ONLINE STUDY PORTAL

- One-stop shop for all cross-site IRB materials, study documentation, milestone and data tracking
- Manuscript and presentation library
- Consortium calendar



DOCUMENT MANAGEMENT & COLLABORATION OPTIONS

SmartSheet

Pros

- Task management features
- Permission based collaboration tools
- Automatic data aggregation and visualization features
- Multiple project management templates
- Ability to create interactive dashboards

Cons

- Live updates are not recorded
- Limited 'free' capabilities

Box

Pros

- HIPAA compliant cloud storage system
- 'Tools' features allow for cloud-based collaboration
- Can track version history

Cons

- Does not allow for simultaneous editing and auto-save
- Cross-collaboration on the same document can result in multiple user versions

Microsoft Teams

Pros

- HIPAA compliant cloud storage system with BAA
- 'Tools' features allow for cloud-based collaboration
- Can track version history
- Can record meetings

Cons

- Difficult to navigate, especially for those external to your org.

ACTIVITY #6: CHAT STORM

- Tell us about what your site does well when managing multi-site studies.
- Tell us what challenges your site faces when managing multi-site studies.

ONGOING SUBMISSION REQUIREMENTS FOR SINGLE IRB STUDIES

ALWAYS check reliance documentation and SOPs of each institution!

ONGOING SUBMISSION REQUIREMENTS FOR LEAD SITES

To IRB of Record

- EVERYTHING
- Changes to study's PI and lead site key personnel
- Study-wide amendments
- Reportable New Information from ALL sites
  - Unanticipated problems
  - Noncompliance
  - Adverse Events
  - Participant Complaints
  - Breach of Confidentiality, etc.
- Continuing Reviews
- Submissions on behalf of P Sites (amendments, RNI, CRs)
- Study closure

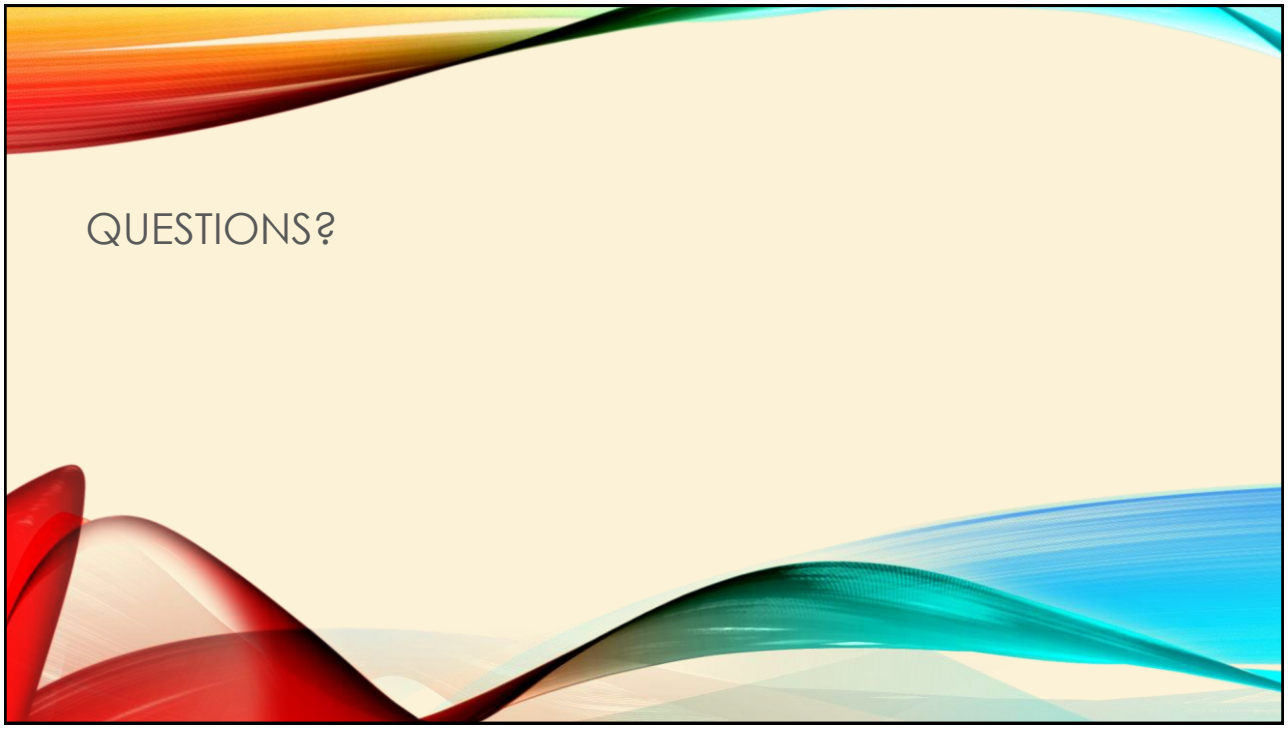
ONGOING SUBMISSION REQUIREMENTS FOR P SITES

To Lead Site +/- IRB	To P Site

• Changes to site PI (+/- key personnel)
• Site-specific materials for approved, study-wide amendments
• Reportable New Information specific to the site
• Continuing Reviews for site activities
• Site closure
	• Changes to site PI and KP
	  • Relying site is responsible for management of training, qualifications, and COI
	• Amendments per SOPs
	  • All vs. only affecting local context
	• Changes in local funding/grants
	• Reportable New Information per SOPs
	  • All vs. only UAPs and serious or continuing noncompliance, termination or suspension vs. none
	• Annual updates
	• Study or site closure

LINKS

- **NIH Single IRB for Multi-Site or Cooperative Research website**
- **Common Rule Cooperative Research Regulation**
- **Each RPN site's SOPs**
  - Medical University of South Carolina: MUSC as the sIRB of Record
  - University of Vermont: Single IRB Policies and Procedures and Single IRB website
  - Boston University: Ceding Review and Additional Resources on Ceding and Reviewing Multi-Site Studies
- **SMART IRB**
- **IREx**
- **Data management links**
  - **Check with your IT department for permissions!**


QUESTIONS?