Partnership and Innovation

Exploring Single IRB Models to Support Clinical and Translational Research

Yale CTSA Supplement

SESSION II: MODELS FOR ASSISTING INSTITUTIONS RELYING ON sIRB

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Yale CTSA Supplement Project Goals

- **Specific Aim 1:** To develop and apply innovative approaches to facilitate sIRB review for multi-site research across the range of research funders and IRB models. To address Aim 1, we will collaborate with academic and commercial IRBs to develop models and supporting tools to foster effective communication and single review approaches to multi-site research.

- **Specific Aim 2**: To develop tools and approaches to address local requirements that will facilitate sIRB review for multi-site research. The implementation of a centralized IRB review process involves addressing a number of issues related to the communities where the research will take place, including not only IRB requirements, but specific institutional and national research requirements. To address Aim 2, we will collaborate with internal centers (Yale Cancer Center, Yale Diabetes Research Center, Yale Child Study Center); academic collaborators (Rockefeller University Center for Clinical and Translational Science, University College London, and Puerto Rico Science, Technology, and Research Trust and its Puerto Rico Consortium for Clinical Investigation); and commercial IRBs.

- **Specific Aim 3**: To explore technology aided approaches to facilitate sIRB review for multi-site research. To address Aim 3, we will collaborate with our commercial vendor partners that are supporting critical systems: (IRB: Huron's Click platform and CTMS: Forte's OnCore/E-regulatory platforms); commercial IRB partners utilizing their own platforms; and academic partners with a combination of customized solutions to develop standards-based approaches, which can support critical IT needs in a vendor agnostic method.

Yale CTSA Supplement – Projects Goals

- Yale's goal is to present the use of commercial IRBs (CIRBs) **as *an* option** to comply with the sIRB Policy.
- It is ultimately up to each institution as to how they would like to use CIRBs as part of their sIRB strategy.
- Yale believes that materials developed as part of the CTSA Supplement will also benefit those institutions that choose not to use CIRBs at all.

sIRB Options

There are several possible options for complying with the NIH single IRB policy:

- Having the IRB at one of the participating sites agree to serve as the single IRB;
- Using an independent IRB not affiliated with an institution (*e.g.*, a commercial IRB, etc.);
- Using the IRB as required in the Funding Opportunity Announcement (FOA) or Request for Proposal (RFP)

sIRB Options

Most of the NIH initiatives to date have focused on helping institutions act as a sIRB or the establishment of an NIH or collaboration specific IRB.

In order to serve as the sIRB, those institutions are often required to make major changes to their IRB and HRPP infrastructures. Depending on the number of studies falling under the Policy and the number of participating sites per study, those institutions may need to:

- hire and train additional IRB and HRPP staff;
- increase the number of IRB meetings; and/or
- modify their electronic IRB systems to handle all of the study and site materials.

This may be feasible for some institutions, but not for others, depending on the resources allocated to IRB and HRPP operations. Even if feasible, those infrastructure investments may not be the best use of institutional resources.

Additionally, if the volume of studies for which an institution may act as a sIRB is small, the investment in infrastructure changes will not be worth the return.
For example, it may make sense for institutions to serve as the sIRB themselves for certain studies, but to rely on CIRBs for others.

sIRB Options

Use of commercial IRBs

- CIRBs have the infrastructure to support the review of multi-site research.
- CIRBs have been operating for decades and have established robust processes and systems to handle hundreds of sites for industry-sponsored and federally funded research.
- CIRBs have the site coordination capabilities required for managing multi-site research.
- Each participating site is unique and has their own institutional requirements that must be addressed. CIRBs have the ability to manage these site particulars efficiently and to connect those records with their review tools to maximize efficiency.
- Direct charging of commercial IRB review to an award is now allowable.

Industry-financed commercial ventures are now running six times more trials than NIH-funded trials led by academic investigators and commercial IRBs are now overseeing an estimated 70 percent of US clinical trials for drugs and medical devices. [1-2]

The Yale Experience

- In 2015, the Dean of the Yale School of Medicine and the former Institutional Official launched a comprehensive quality improvement Plan.
- The purpose was to look for solutions to support the continued growth and expansion of clinical research in order to increase Yale's capacity to provide timely and quality protocol review without diminishing the important work and review performed by the Yale IRBs.
- Acknowledged a changing research landscape as many NIH grants, including large Center grants, strongly recommended utilizing a sIRB for multi-site human subjects' research.
- Leadership believed that such an approach also would be advantageous in terms of attracting industry sponsors and critical in order for Yale to be able to continue to expand its research enterprise in a planned way.

The Yale Experience

- To facilitate the review the Yale Center for Clinical Investigation (YCCI), the administrative hub for Yale's Clinical and Translational Science Award (CTSA), was asked to lead effort.
- The Dean and IO appointed a committee of senior faculty members to serve as the Commercial IRB Evaluation Committee. Members of the Yale Human Research Protection Program also participated in the effort.
- The committee was asked to explore the potential for contracting with a CIRB for review of certain categories of human subjects' research.
- As part of the process, Yale solicited proposals in response to a Request for Information (RFI) for commercial IRB service and possible selection of multiple service providers to perform IRB services.
- Yale also initiated a CIRB survey to key stakeholders across the university and gathered benchmark data related to other Academic Medical Centers and their use of CIRBs.

Based on its assessment, Yale decided to send a greater number of studies to external CIRBs and not to develop infrastructure to serve as the sIRB for NIH studies

The Yale Experience

Consistent with the final recommendations of the committee, the HRPP under the direction of the Yale Institutional Official:

- Entered into master agreements with a number of commercial IRBs.
- Developed policies and procedures to support the use of an external IRB for review and oversight of research involving human subjects and outlined which types of studies may be sent externally and which should generally be reviewed by the Yale internal IRB.
- Reorganized the HRPP office and workflow in order to manage the increase in studies sent to an external IRB.

Yale reaped tremendous benefit from others as we implemented the expanded use of sIRB and commercial IRBs; however, Yale identified challenges that must be addressed to improve the collaborative research model.

Yale CTSA Supplement –
What We Did and What We Will Continue to Develop

- Leveraged information learned based on Yale's experience
- Met with CIRB partners to solicit feedback
- Developed tools
- Evaluated Technological Solutions
- Drafted whitepaper regarding the use of CIRBs to support multisite research.

Yale continues to develop additional tools and technological solutions to support the use of CIRBs for multisite research. Yale will also continue working with CIRB partners.

Idea for the Future State – Central Vetting Process

Most, if not all, institutions are in agreement that there needs to be a vetting process when choosing a sIRB, whether it be for a single study or multiple studies, and are wise to consider an IRB's capabilities and reputation.

The amount of vetting for CIRBs can also vary depending on an institution's comfort level working with CIRBs.

Yale has identified three (3) levels of CIRB vetting that are typical for institutions:

1. Comfortable with Use of CIRBs (Minimal Vetting)
2. Have Some Experience with CIRBs (Medium Vetting)
3. Have Never Used CIRBs (Extensive Vetting)

Idea for the Future State – Central Vetting Process

- Yale is proposing information be made available in a central location (**a centralized CIRB information hub**) to aid institutions going through the CIRB vetting and selection process.

- The goal is to reduce, or even eliminate, the need to go through expensive and lengthy RFI/RFP processes for CIRBs.

- Ideally this type of information could be collected for other institutions that serve as sIRBs and posted in a centralized location to aid in the sIRB vetting and selection process.

Idea for the Future State – Central Vetting Process

- In evaluating CIRBs to serve as a sIRB, there are *qualifications* and *attributes.*
  - **Qualifications** include items such as accreditation status, FDA audit history, number of IRB meetings per week/month, disease- or therapeutic-specific review specialties, IRB member rosters, etc.
  - **Attributes** include the unique services CIRBs provide and streamlined review processes available to institutions.

- Building off of CTTI's Central IRB Evaluation Checklist, Yale's CIRB RFP experience and feedback from CIRBs themselves, Yale has identified a set of common CIRB qualifications and attributes that many (if not most) institutions would use to vet and qualify a CIRB.

- Yale has divided these common CIRB qualifications and attributes into two (2) categories:
  - **Core** qualifications and attributes: Items that are often the most important when doing an initial evaluation of CIRBs and provide enough information about each CIRB to gain an understanding of their business and review capabilities/experience.

  - **Detailed** qualifications and attributes: Items that are more detailed in nature and mirror questions that are most often asked during a CIRB RFI/RFP process.

CIRB Core Qualification Examples

Commercial IRB Core Qualifications Template		
	ITEM	CIRB #1
General Info	Legal Name of Company	
	Name of IRB	
	Website URL	
Board & Reviews	Total number of IRB committees/panels	
	Specialty IRB committees/panels	
	Number of IRB meetings per week	
	Kind(s) of research review experience	
	Types of research not reviewed (e.g. emergency research)	
	AAHRPP accredited?	
	Date of original AAHRPP accreditation	
	Date of most recent AAHRPP accreditation	

Metrics	Total number of active studies (all study types)	
	% of active studies that are industry sponsored multi-site studies	
	% of active studies that are industry sponsored single-site studies	
	% of active studies that are Federally funded multi-site studies	
	% of active studies that are Federally funded single site studies	
	% of active studies that are Other study types	
	Total number of active sites	
	Convened IRB Review	
	New study: submission to review at a convened IRB meeting	
	New study: submission to convened IRB approval	
	Amendment/Mod: submission to convened IRB approval	
	Expedited Review	
	New study: submission to Expedited Review	
	New study: submission to Expedited Review approval	
	Amendment/Mod: submission to Expedited IRB approval	

Compliance	Number of FDA inspections in the last 10 years	
	Number of FDA 483 and Warning Letters received in the last 10 years	
	Number of OHRP inspections in the last 10 years	
	Number of OHRP determination letters received in the last 10 years	
	Number of inspection from other agencies in the last 10 years	
	Number and description of major and critical observations/finding received by other agencies in the last 10 years	
Other Services	Types of services provided other than IRB services	

CIRB Detailed Qualification Examples

Commercial IRB Detailed Qualifications Template

	ITEM	CIRB #1
General Info	Location of company offices	
	Number of years in operation	
	Type of ownership	
	Name of Organizational/Institutional Official and link to information	
	Name of Executive Director/President/CEO and link to information	
	Name of Primary IRB Contact and link to information	
	Link to Company Leadership Information	
	Link to IRB Compliance Statement	
	Link to IRB Rosters	
	Link to publicly available Investigator Handbook, Guidance, etc.	
	Hours of operation, including holiday hours/closures	
	Total number of employees	
	Number of employees (not including IRB members) that directly support IRB operations	
	Number of employees with other responsibilities (e.g. corporate, marketing, sales)	
Board & Reviews	Total number of IRB members/alternates	
	Number of employed (salaried) IRB members/alternates	
	Number of IRB members/alternates receiving honorariums/stipends	
	Number of uncompensated IRB members/alternates	
	Training IRB members/alternates receive	
	IRB member/alternate resumes/CVs/job descriptions, and training records maintained and available for review?	
	Submission deadlines	
	Previous experience working with an Academic Medical Center (AMC) or a hospital system?	
	Organizational certifications or accreditations for other services provided	
	Offer certified trans	
	Accept certified tran to use its own transl	
	Electronic IRB manag	
	Sites and/or sp	
Metrics	Total number of new studies reviewed during the last calendar year (all study types)	
	Total number of new sites reviewed during the last calendar year (all types)	
	Number of studies disapproved by the IRB during the last calendar year	
Compliance & QA	Organization have a plan to ensure data privacy, confidentiality and security?	
	Organization have a business continuity and disaster preparedness plan?	
	Organization have a systems and data backup/recovery plan?	
	Organization have an internal quality management program?	
	Organization perform background checks on employees, contractors, and IRB members to ensure individuals have not been convicted of a criminal offense or subject to disciplinary action, debarment, or disqualification by a government agency?	

Tools

One Example

- Yale recommends use of the budgeting and billing tool to assist in the calculation of CIRB costs and building an accurate budget.
- The tool should also include a number of commonly asked questions.
- Non-site specific information could also be included on a CIRB information Hub.

Yale's Budgeting and Billing Guidance Tool

Example

Human Subjects Research Budgeting and Billing
When Using an External (Commercial) IRB

	IRB Name 1	IRB Name 2	IRB Name 3	IRB Name 4	IRB Name 5
Does each external IRB have different pricing depending on the type of study and activity? For example, industry, federal, other, etc.?	YES Fee Schedule	YES Fee Schedule	YES Fee Schedule	YES Fee Schedule	YES Fee Schedule
Does the External IRB have special IRB pricing for Federally Funded studies, including sIRB?	YES <<*>>	YES <<*>>	YES <<*>>	YES <<*>>	YES <<*>>
Does the External IRB offer free IRB budget estimate assistance for grants/proposals?	YES Email Contact	YES Email Contact	YES Email Contact	YES Email Contact	YES Email Contact
What information should I provide when requesting the budget estimate for the grant application?	You should send study information to the contacts above when requesting assistance with the budget development for sIRB fees. Information that is generally requested by the IRBs is included in the budget questionnaire.				Budget Spreadsheet
How long does it take to get the IRB budget estimate from the external IRB?	Allow 2 – 3 days for the proposed sIRB to review the information.				
Contact at the IRB	Email Contact	Email Contact	Email Contact	Email Contact	Email Contact
Access to the electronic system	IRB 1 System Link	IRB 2 System Link	IRB 3 System Link	IRB 4 System Link	IRB 5 System Link

Yale's Budgeting and Billing Guidance Tool

Example

Additional Information for Grant Application and sIRB Plan				
Who is Yale's institutional contact for assistance with IRB budgeting and billing?	The PI and the Business Office are strongly encouraged to work with the Yale Center for Clinical Investigation (YCCI) on budget development. YCCI offers a Research Budget Development service and can help investigators with budgeting, free of charge. Please contact clinicalresearchresources@yale.edu to request the service.			
Who is Yale's primary and secondary IRB and HRPP billing contact?	When Yale cedes review to an external IRB, Yale HRPP is listed as the primary billing contact and YCCI (or the PI's business office or other designated billing department) as the secondary contact. The HRPP will work with the external IRB and designated billing contact to ensure payment to the external IRB.		**Primary Billing Contact:** Human Research Protection Program (HRPP) hrpp@yale.edu Attention: <<>>	**Secondary Billing Contact:** Yale Center for Clinical Investigation (YCCI) Research Budget Development Unit clinicalresearchresources@yale.edu Attention: <<>>
What information should be included in grant applications?	**A plan describing the use of a sIRB:** The plan should identify the IRB that will serve as the sIRB and should address any requests for exceptions from the policy. This information should be in the human subjects section of the grant proposal.	**Letter of support from the Yale HRPP to use a specific sIRB:** While letters of support from the participating sites are not required, the PI must ensure that the sites' HRPP/IRB Offices agree to use the proposed sIRB.	**IRB review fees as direct costs:** IRB fees for a single site study reviewed by a local IRB are part of indirect costs covered under the Facilities and Administration (F&A). Fees charged by independent IRBs may be charged as a direct cost when they are serving as the sIRB. For more information, see the Cost section of the NIH FAQ and guidance document.	**A description of the resources (personnel, budget) you will need to manage IRB communications:** Multi-site studies will require additional resources ('IRB Liaison') to manage across-site communications associated with the use of a sIRB. It is typically a staff member on the research team at the lead site.
Which Yale office approves studies to be sent to an external IRB?	**Prior to the grant application**: **Contact Yale Human Research Protection Program to discuss the single IRB Plan**. Request a Letter of Support for use of a single IRB by sending the following information to HRPP@yale.edu: the name of the PI, list of the participating sites, name of the proposed sIRB, the RFA number, and the funding opportunity title. **After the research is funded:** Request to send the study to an external IRB by submitting the protocol and the consent templates via IRES IRB. See the step-by-step instructions.			
Does the HRPP charge a local oversight / administrative fee if studies are sent to an external IRB for review?	Yes, but only for industry-sponsored trials. See the following link to the IRB Fee Schedule and HRPP Policy 110, HRPP Local Oversight and IRB Review Fees. There are no HRPP administrative fees for the NIH funded studies requiring single IRB review and where the IRB review is ceded to another IRB.			

Disentangling IRB Review and HRPP Responsibilities

Ensuring that there is a clear division and delineation of IRB and HRPP responsibilities is the first step to prepare an institution for implementing processes to support sIRB review.

- Becomes increasingly important when either relying on a sIRB or serving as the sIRB for multisite research.
- Because it is often convenient for institutions to layer additional responsibilities on the IRB review process, it is necessary to uncouple these responsibilities especially when relying on a sIRB or having a CIRB serve as the sIRB.
- This can be overlooked as some institutions have had these additional ancillary requirements always built into the IRB review process so it can sometimes be mistaken that these ancillary requirements are by default IRB requirements.

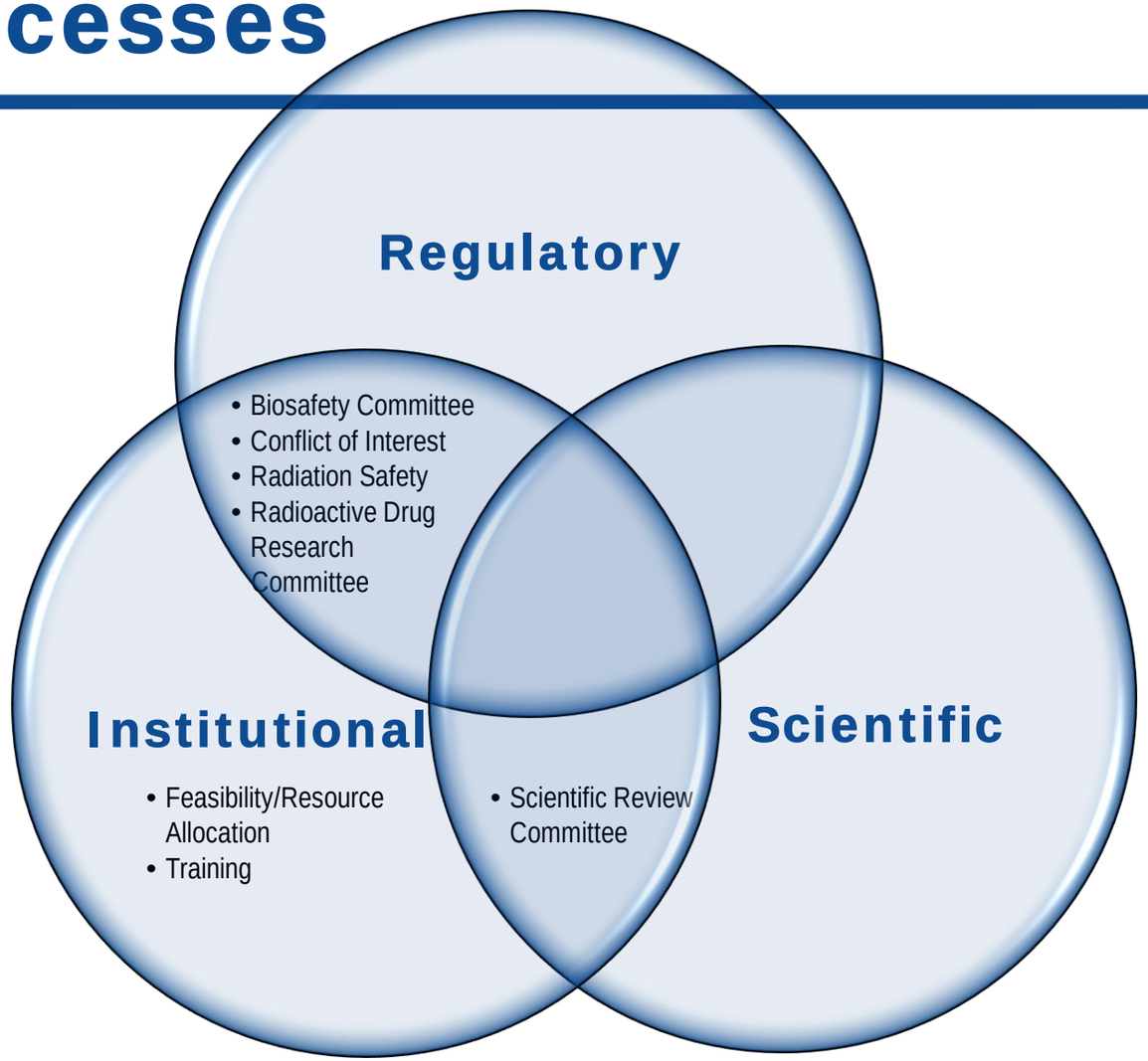
IRB vs. HRPP Responsibilities*

HRPP	IRB
Composed of other review committees, the Institutional Official, and staff supporting the administration of the IRB (and other committees depending on the institution)	Composed of a certain number of members representing the diversity of the University and local community.
Facilitates the review process of all studies/projects	Reviews all studies/projects and reportable events (e.g., non-compliance, unanticipated problems, etc.) and votes to approve, disapprove, suspend, terminate, etc.
Facilitates the monitoring process of approved studies	Monitors approved studies via continuing review
Tracks all IRB-investigator study/project-specific conflicts of interest	Reviews all IRB-investigator study/project-specific conflicts of interest
Performs study/project audits	Reviews information reported to the IRB
Manages the accreditation process	Ensures accreditation by upholding institutional policies and maintaining high standards of human subjects research requirements
Facilitates communication between the IRB and investigator(s) throughout the life of a project	
Tracks all required human subjects training and conducts investigator education, etc.	
Works with other organizational committees, review processes, officials, etc. during the review process of a project	
Provides educational outreach and facilitates communication with research participants	

** Based on table from University of Nebraska-Lincoln HRPP*

Non-IRB Approvals and Processes

- While it is clear the best strategy for facilitating a multisite study is the use of a sIRB, IRB approval is only one element of the process.
- Yale's project addresses the additional approvals and process required to facilitate the interconnected regulatory and grant required elements related to initial approval and on-going monitoring.
- To accomplish this aim, the Yale CTSA partnered with several internal centers focusing on developing and evaluating the need for tools and processes to facilitate the requirements of NIH mechanisms and other institutional functions.
- **Yale considered and is continuing to evaluate how to manage ancillary reviews and other necessary approvals as part of the review of studies that are sent externally.**



Non-IRB Approvals and Processes

Example

PHS 398 Research Plan (Protocol Review and Monitoring System)
Research Strategy: In addressing Research Strategy for Protocol Review and Monitoring System (PRMS), the applicant must adhere to the general guidelines below.

- A critical activity for Centers involved in clinical research is a mechanism for assuring adequate internal oversight of the scientific aspects of all the cancer clinical trials in the institution or institutions that formally comprise the Center (i.e., consortium Centers should document that all protocols are reviewed through a central PRMS). This function is complementary to that of an Institutional Review Board (IRB), which focuses on the protection of human subjects.

- **For multi-site institutional trials, the PRMS of the lead site is responsible for the full scientific review of the protocol (if the PRMS has been approved). The other participating sites are responsible only for an expedited review focused on prioritization, competing studies, and feasibility at that site. Should the PRMS at the lead site be conditionally acceptable or unacceptable, participating sites may select a single, acceptable PRMS at a participating NCI-designated cancer center to conduct the full scientific review.**

Relying Site Gatekeeper Considerations

- The lead site “project manager” interacts with individuals at each relying site. These individuals at the relying sites are the gatekeepers of information flow for those relying sites.

- CIRBs prefer for each relying site to have only one gatekeeper for all reliance scenarios. That way, there is a consistent relationship for all institutional-specific considerations.

There are three distinct gatekeeper models that relying institutions can employ:

1. The “Hold Submission” Model
2. The “Hold Letter” Model
3. The “Free-for-All” Model

Leveraging Technology

- Technologies supporting clinical and translational research have evolved to include electronic health records (EHRs) enabled to support scientific and research missions. Many centers have implemented the same systems to support their enterprise, including clinical trials management systems (CTMS) and IRB management systems (eIRB).
- Although the same systems have been implemented by many centers, the multiple instances at each of the centers do not communicate even in the case of multicenter studies. Additionally, many commercial IRBs have developed their own IRB management systems.
- **Many of the challenges could be facilitated if CTMS and IRB systems could exchange or transmit information in an electronic format consumable by other systems.**

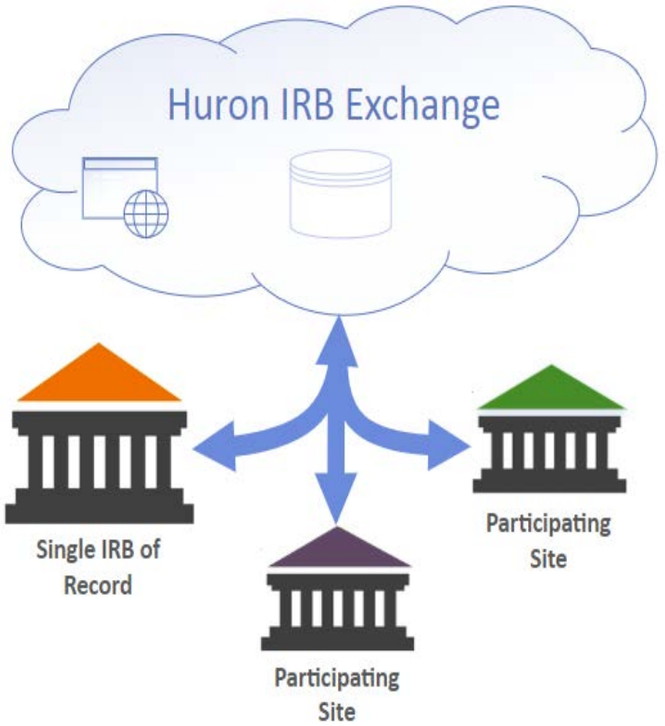
Leveraging Technology: Short Term Solutions

- As the relying institution, ensure that the local e-IRB system clearly distinguishes the research protocols under an external IRB purview from the protocols under local IRB purview.
- Keep a shell of the research record in the local e-IRB system, not the complete ‘shadow’ file (if possible), but gain access to the systems used by the commercial IRBs.
- As the awardee institution, request ‘sponsor access’ to the research records.

Leveraging Technology: Long Term Solutions

One of the key technological advances would be for the ability of each institution's eIRB system to communicate directly with each other in order to eliminate duplicate data entry and eliminate the need for a manual conduit to relay information between the sIRB and all relying sites.

One solution that is available now is the Huron IRB Exchange, which is a cloud service for enabling secure data exchange between institutions acting as the sIRB and relying sites on the same multi-site research study.



Leveraging Technology

- **The development of a standards-based model to facilitate data exchange and/or sharing would be a pivotal change in the clinical and translational research enterprise and allow a process to be implemented at the site or vendor level regardless of the IT solution.**
- Such an approach would allow the sIRB to share information with all relying sites directly enabling:
  - the institutional HRPP and compliance efforts for initial and on-going monitoring to occur;
  - all ancillary approval committees and systems to be aware of action and facilitate any specific actions/tracking required by granting or regulatory agencies; and
  - reduce the burden on investigators leading and participating in multisite studies.

Yale CTSA Supplement – Summary

- It is up to each institution to determine how to comply with the sIRB policy.
- Based on their established history of providing review of multi-site studies, the use of CIRBs is one option for complying with the sIRB policy.
- Selecting a few CIRBs (using a centralized vetting process) and building a relationship with them (by providing clear 'handling instructions', accessing the electronic systems as the relying institution and/or a sponsor, and leverage tools such as a budgeting & billing tool, etc.) will help institutions comply with its institutional obligations and feel more in control of the research that takes places at the institution.

References

1. Ehrhardt S, et al. Trends in National Institutes of Health Funding for Clinical Trials Registered in ClinicalTrials.gov. *JAMA.* 2015;314(23):2566-2567. PMCID: PMC4919115

2. Kaplan S. In clinical trials, for-profit review boards are taking over for hospitals. Should they?. STAT: In the Lab. July 6, 2016. https://www.statnews.com/2016/07/06/institutional-review-boards-commercial-irbs/

Questions