

Practical & Ethical Considerations for Single IRB Review

AN EXPLORATORY WORKSHOP

Sponsored by the
Office for Human Research Protections (OHRP),
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Practical and Ethical Considerations for Single IRB Review

OHRP Exploratory Workshop: September 16, 2020

Welcome and Introduction

- Jerry Menikoff, M.D.; Director, Office for Human Research Protections (OHRP)
- Yvonne Lau, MBBS, MBHL, Ph.D.; Director, Division of Education and Development, OHRP

Dr. Menikoff, Director of the U.S. Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP), welcomed everyone to this 3rd annual exploratory workshop. He explained that the goal of these annual workshops is to provide an open forum among stakeholders in the research community to discuss important topics related to research and how these topics intersect with the Common Rule. He warmly thanked OHRP staff from its Division of Education and Development (DED) for steering, planning, and conducting these exploratory workshops.

This year's workshop explores single Institutional Review Board (IRB) review, an important topic in the research community since it is now required for multi-site studies under the new Common Rule. The National Institutes of Health (NIH) also now require grantees engaged in multi-site research to use a single IRB. For many Human Research Protection Programs (HRPPs), single IRBs (sIRBs) are a new venture and raise new questions. For example, how should reliance agreements work? How can work best be overseen at each participating institution, ensuring quality and consistency? The use of a single IRB can facilitate protocol review, and IRBs can benefit from hearing from others who have used this approach successfully.

The Director explained that OHRP staff are present in order to listen, along with others in the research committee, as speakers share information and brainstorm about the best ways to support efficient review of regulated research when single IRBs are used. The opportunity is offered in a spirit of collegial collaboration. Dr. Menikoff expressed appreciation for the moderators and presenters who have come forward to share their ideas and experience.

Dr. Lau, Director of DED, also welcomed everyone to the workshop. She explained that DED's mission is to conduct public outreach and education to promote awareness of ethical issues related to the rights and wellbeing of human subjects. These annual exploratory workshops provide a high-level platform for open dialogue and exchange of ideas among stakeholders in the regulated community. The panel has been chosen to represent diverse experience, expertise, and perceptions. The objectives of this workshop include:

- To share and discuss ways to ensure quality IRB review under the sIRB model;
- To consider the importance of concerns related to local context and ways to incorporate and manage them in sIRB review;
- To discuss and promote best practices for the sharing of oversight responsibilities and separation of roles in IRB review and oversight of research under sIRB; and
- To spark interest in research, scholarship, and collaboration that could inform future practices for sIRB review to better protect research participants.

Session I: Providing Options and Ensuring Quality in Single IRB Review

- *Moderator:* Stephen Rosenfeld, M.D., MBA: Freeport Research Systems, LLC

Session I Introduction

- Stephen Rosenfeld

Dr. Rosenfeld introduced himself and each of the speakers in the session, welcoming each one.

Single IRB review of collaborative multi-site research can reduce inconsistencies and improve the quality of reviews. However, the single IRB mandate could result in a small number of IRBs amassing more responsibility and importance over a large proportion of federally funded research. Encouraging more institutions to serve as single IRBs is one way to diversify single IRB options and could promote a culture of quality reviews that inspires confidence. In this session, speakers shared their experience in creating options for single IRB reviews at their institutions and explored measures to promote quality ethics review and human research protections.

Ensuring Quality IRB Reviews: Lessons Learned from NCI's CIRB Initiative

- Linda K. Parreco, RN, M.S.; Nurse Consultant, Office of the Deputy Director, Division of Cancer Prevention, National Cancer Institute

Ms. Parreco presented lessons learned from two decades of evolution by [the National Cancer Institute's \(NCI's\) Central IRB \(CIRB\) initiative](#), which was established because multiple reviews were limiting subjects' ability to participate in trials. The initiative was launched in 2004 and accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) in 2012. It now comprises seven NCI research networks, 2700 enrolled institutions, 22,000 investigators, and 650 NCI-approved protocols.

The speaker noted that producing quality reviews requires attention to three elements: people, processes, and tools. She observed, however, that we don't always know how to define or measure quality.

Addressing the first key element – people – Ms. Parreco stressed that doing a quality review requires bringing the right people to the table. For example, NCI determined that, in order to assure the board's independence, no one who serves on a CIRB can be affiliated with NCI. Three-year appointments are made for the board's 15-20 members, with reappointment by invitation. Consultants are used as needed. Processes are also important, and NCI has continued to reimagine them and improve them. For example, instead of replacing members one at a time – resulting in time-consuming individual orientation for each member – the NCI now brings new members on once a year as a cohort. An open call for applications to serve on the CIRB is issued in the spring, and members are oriented in the fall so they are ready to join the Board in January.

NCI seeks members who are diverse in terms of race and ethnicity, geography, and experience and requires all members to do a robust self-evaluation annually. To assure the board's independence, the CIRB Operations Office (a contracted service) handles all communication. Members are not named in the minutes, and Standard Operating Procedures (SOPs) require members to report any efforts to influence their deliberations.

NCI has also developed several tools to help the Board. For example, the NCI Stipulation Analysis Review Tool (StART) codes stipulations to assess adherence to regulatory criteria (Rooney et al. 2019). Board reviewer worksheets have been redesigned, and several decision aids have been developed. Board members are offered workshops in stipulation writing. Once a month, a 15-minute talk delivers helpful information on a topic identified by the Board and staff. All protocols undergo NCI scientific review and approval prior to CIRB review, and findings are provided to the CIRB – a procedure that keeps the Board from asking and trying to answer questions that have already been addressed.

Transparency with stakeholders is a key priority for NCI, and the CIRB is proactive in presenting information about its deliberations. For example, the CIRB frequently gives presentations at meetings attended by researchers and offers a help desk where they can reach out to the CIRB and get answers to their questions. The CIRB publishes minutes of its meetings, and its [website](#) has been designed to allow more transparency to the general public. The names of all Board members and their affiliations are published, and SOPs are also available on the site. The Board has also produced numerous publications in the oncology and IRB literature that share aspects of its experience with the research community (see References).

NCI also works to foster appropriate dialogue with the study team. The Principal Investigator (PI) has an opportunity to talk to the CIRB and make sure that any questions they have are answered. Dialogue with the research team continues during protocol review as questions arise, and a determination letter to the PI explains how and why the Board reached its decision. The PI can request a subsequent call with the CIRB to discuss questions or concerns in the determination letter.

Through its 20 years of operation, the CIRB has steadily sought to improve. Ms. Parreco stressed the importance of allowing time to reflect, evaluate, and correct any problem areas. She urged other central IRBs to find opportunities to apply a systematic approach, which can be beneficial. She stressed the importance of meticulous attention to communication: listen to stakeholders, be a presence in their community, and offer clear and accurate communications over time.

Dr. Rosenfeld observed that NCI is the public entity that has the most experience with central IRBs, and its experience is particularly relevant today.

Diversifying Options for Single IRBs: An Institution’s Experience with Extending their IRB Services to Outside Institutions

- Ann Johnson, Ph.D.; IRB Director, University of Utah

Dr. Johnson explained that the University of Utah is relatively new as a single IRB. As it became aware that NIH’s policy and the Common Rule would be changing to require the use of single IRBs, the university’s HRPP reflected on how it might engage in the new space. This required holistic thinking about the things it valued.

Four key values emerged as relevant and important in making this decision.

- 1. We value having a positive influence in the IRB and research ethics space.* The program wanted to have a voice and add to positive movement.
- 2. We value having empirical evidence in the IRB and research ethics space.* Although it is hard to measure, the program realized it valued quality and wanted to ensure IRB reviews were evidence-based.

Staff and members wanted to contribute to empirical evidence that helps IRBs achieve more consistent quality in their reviews.

3. *We value dialogue, differing perspectives, and voices when considering research protections and ethical conundrums.* This value and underlying ethical principles must be reflected in SOPs so that they are reflected in the way different studies are reviewed.

4. *We value getting research done.* This translates into a concern for finding efficient and appropriate ways of making decisions and getting promising research “out the door.”

After a thoughtful review, the University decided to establish a single IRB “not just for us, but potentially for anyone who needs one in the new space.” While it should have a sound business model, the sIRB should also have procedures that ensure its approach is ethically sound and free of conflicts of interest. The University determined that while it needed the resources necessary for sIRB members and staff to do their jobs, it did not need to make a profit and it did not need to undertake to review any study submitted. The sIRB has the discretion to accept studies that are a good fit and pass on those that are not and can better be addressed by other review boards.

Dr. Johnson reviewed the key considerations that had to be addressed as the transition to single IRB moved forward. These included:

1. *Relationship management.* Building relationships with institutions outside your own is critical, and transparency becomes “a huge issue.” An institution that becomes a single IRB will need to reach out more than it usually does to build solid working relationships and trust.

2. *Cost and fees.* To fulfill its new role, the HRPP needed to expand its capacity for business accounting and for analysis of the time and effort it put into reviews. Dr. Johnson stressed the importance of collecting and using data to support decisions about which reviews to undertake: How long will this one take? What will it cost? In the past, the IRB could rely on intuition, but intuition alone usually cannot yield a reliable estimate of human hours needed.

3. *Electronic systems capacity.* As people used the university’s services as a single IRB, facilitating external access to data became a challenge. The IRB also had to look at different ways to handle applications and build in flexibility so that relying sites could proceed on their timelines.

4. *Other investments.* Additional full-time equivalents (FTEs), both board members and consultants, were needed. Also, board members needed additional training and education, as well as liability protection. The speaker observed that concerns about liability hold many institutions back from acting as a single IRB, and this is by no means an inconsequential element of the decision. Every institution must carefully consider how to handle this issue.

Dr. Johnson also highlighted specific considerations in developing a single IRB. First, the IRB needs to maintain a reputation for quality. One consideration is allowing discretion in the studies chosen for review so that reviewers are well prepared. The research portfolio needs to be monitored periodically. Second, the IRB needs to balance timeliness with concern for making a quality decision. She noted that “efficiency is not an ethical principle.” Finally, collegial relationships must be maintained. The speaker’s university placed a value on openness to other institutions that want to learn from it. It is willing to share its policies and practices. (See the resource section of this document.)

From Relying to Reviewing: Considerations and Lessons Learned when Establishing a Single IRB

- Joshua Fedewa, M.S., CIP: Associate Director, HRPP, University of Texas Southwestern Medical Center

Mr. Fedewa said he could testify to Dr. Johnson's willingness to share resources, which were invaluable to the University of Texas Southwestern Medical Center (UTSW) as it began the process of preparing to serve as a single IRB.

The speaker explained that UTSW is accredited by AAHRPP and has about 5,000 active studies. Historically, it has served as the primary IRB for its affiliated community hospital, children's hospital, and orthopedic children's hospital. It also serves as the IRB of Record for a new partner health system in North Texas. Until recently, it had not considered serving as a single IRB for institutions in other states, but it has a good deal of experience to bring to the table.

Recent mandates from NIH and the revised Common Rule brought this possibility into sharp focus as UTSW considered its strategic direction. Internally, the decision to proceed was influenced by the desire of UTSW leadership to expand the university's portfolio in human subjects research and seek federal funding to further its contributions to this field. Also, faculty members wanted to collaborate with external partners, not only in data sharing but also in implementing intervention and interaction studies created by UTSW faculty. HRPP leadership observed that requests for UTSW to serve as the sIRB on such collaborations were increasing.

Mr. Fedewa reviewed UTSW's initial steps in setting up an sIRB. First, the HRPP convened an sIRB work group in spring 2020. All university departments were invited to participate. Members realized that each of them had attended different conferences where the subject arose and had different perspectives on what it might mean for their field. The work group identified unknowns that had to be addressed and determined what questions, tools, guidance, and policies were relevant to the initiative. It sought to identify resources at other institutions that had already established successful sIRBs so it could learn from them. The speaker expressed appreciation to the University of Utah, Johns Hopkins Medical Center, Boston Children's Hospital, the University of Wisconsin, and Vanderbilt University for their willingness to collaborate and share roadblocks so others won't trip over the same ones. He encouraged institutions seeking to become sIRBs to reach out to others that have taken this path.

Questions identified by the work group included:

- *When will we serve as an sIRB?* UTSB has restricted access to its electronic systems, so it has faced challenges in granting access to documents and managing shared access.
- *How will we collect information about local context?* What would other institutions need UTSB to consider, and how would it identify all these concerns?
- *How do we route the review of sIRB studies through the HRPP?* The speaker expressed appreciation to Dr. Johnson for being willing to share a helpful organization chart, workflow descriptions, and documentation on roles and responsibilities.
- *How will we train the HRPP staff, IRB members, and study teams, and what will that training include?* The speaker observed that study teams may receive a lot of misinformation about what a single IRB means. This misinformation needs to be countered, and correct information must be

disseminated to everyone participating in the review process about what to expect and how to fulfill their responsibilities.

- *Is our electronic system designed to facilitate serving as an sIRB? What changes are necessary?*

Mr. Fedewa noted that becoming an sIRB inevitably means that tools, guidance, and policy will all need to be updated with the new role in mind. For example, there are unique aspects of the expected workflow that need to be well thought out, and the website will have to be updated to facilitate communication with relying sites.

Finally, the speaker reviewed key lessons the new sIRB has learned.

- It is helpful to have some state-sponsored research (UTSW has 10 to 12 sites) as well as federally sponsored research.
- Expect many stops and starts as procedures are operationalized and as the sIRB learns from and collaborates with HRPPs that have not traditionally relied on other IRBs.
- Prepare a good guide for Principal Investigators (PIs) and include the fee structure.
- Make good use of existing resources such as [IREx](#), [SMART IRB](#), and experienced institutions. Many guidance documents already exist that can be adapted for specific purposes. For example, master templates for consent documents can be useful.
- Decide on a clear sIRB fee structure.
- Operationalize sIRB practices as learned from other sites.
- Perform Strength, Weaknesses, Opportunities, and Threats (SWOT) analysis as sIRB studies are submitted: Did we make any changes? Is it working?
- Becoming an sIRB affects study teams just as much as the IRB/HRPP office, if not more. Serving as an sIRB puts a burden on the institution's research teams as well as the HRPP office. It is important to put as much effort into educating those study teams as the HRPP puts into educating itself.

To operationalize its sIRB, UTSW created a new team to manage all studies. It used **Research Electronic Data Capture (REDCap) tools** to facilitate reliance requests and produce sIRB quotes and support letters for federal funding requests. Continuing reviews use a data collection tool within REDCap that allows supporting documents to be attached to primary study documents. As the initiative goes forward, Mr. Fedewa also stressed the importance of clarifying who does what within the HRPP for the sIRB effort. Finally, responsibilities for those serving as the main study team must be clearly identified and communicated.

The speaker highlighted additional work UTSW sees as needed going forward. This includes redesigning its electronic system to facilitate sIRB studies, developing more tools and guidance documents for study teams, expanding the sIRB website, tracking sIRB requests more effectively so the sIRB can anticipate when work may be coming in, and billing for sIRB work so the UTSW can maintain the resources necessary to run an effective program.

Dr. Rosenfeld observed that it was heartening to hear that institutions are working together to respond to the challenge of the new single IRB mandate.

Evaluating the Quality of Ethics Review and Promoting Transparency and Accountability in the Era of Single IRBs

- Holly A. Taylor, Ph.D., M.P.H.; Research Bioethicist, Department of Bioethics, Clinical Center, National Institutes of Health

Dr. Taylor explained that [Advancing Effective Research Ethics Oversight \(AEREO\)](#) is a consortium that seeks to advance effective research ethics oversight through empirical research and quality improvement (QI) efforts. It currently has 68 members representing 52 institutions, organizations, and agencies. These include human research protection program directors, academic scholars, and representatives of professional associations, federal agencies, independent IRBs, and health care systems. Through AEREO, institutions collaborate to learn from one another, gather data, test new ideas, and implement effective and efficient approaches to research review and oversight.

The speaker defined “effectiveness” as “doing the right thing.” It invokes an ethical framework for deliberation. Efficiency was defined as “doing the right thing well.” While not an ethical principle, efficiency is also an important consideration. She quoted the following comments about efficiency from [Investopedia](#):

Signifies a **peak level of performance** that uses the least amount of inputs to achieve the highest amount of output... It is a measurable concept that can be determined using the **ratio of useful output to total input**. It minimizes the waste of resources such as physical materials, energy, and time while accomplishing the **desired output**.

In some cases, IRBs may find efficiency and effectiveness in conflict. Examples may arise in the context of a public health challenge such as COVID 19. We need to find answers to important research questions as soon as possible. Ideally, IRBs want to find themselves pursuing the right goals *and* doing so efficiently.

The speaker raised the question: “What does effective research ethics oversight look like?” She suggested that such research ethics oversight should:

- Protect the rights and welfare of research participants,
- Promote justice in practice/outcomes of human subjects research,
- Foster a culture of ethical concern in researchers and institutions.
- Maintain and promote trust in the research enterprise, and
- Promote socially valuable, scientifically valid, ethical research.

She emphasized that effective research ethics must accomplish all of these. However, she acknowledged that there are no validated performance measures for these outcomes. AEREO and others must accept the challenge to develop tools that individual IRBs and or single IRBs can use to assess ethical outcomes. Without evidence regarding the effectiveness of IRBs and HRPPs, they could be doing more harm than good. For example, they might be failing to protect human subjects adequately, encouraging box checking over ethical quality, wasting or misallocating resources, imposing reforms that don’t work, or missing solutions that would help.

Dr. Taylor observed that the research ethics oversight system was created with the expectation that its impact on the research enterprise would be outweighed by benefits (i.e., effectiveness in achieving desired outcomes). She queried, “Is that expectation being satisfied? How would we know?” At present, we lack valid and reliable outcome measures to assess the quality and effectiveness of IRB/HRPP review and oversight. Measuring efficiency is relatively straightforward, but effectiveness is less so. It is not yet possible to demonstrate that impact of the IRB/HRPP system is justified by its effectiveness. Nor can we evaluate the effectiveness of new approaches. She pointed to the definition of accountability presented by Baum et al. (2007) as an ideal:

Transparency – “...making public and explicit one’s assumptions, justifications, and reasoning – contributes to accountability and is essential for establishing trust with the public. Credible, scientifically sound decision-making further enhances accountability, as does responsible and competent stewardship of [resources].”

This definition is relevant given the importance of accountability to the public, which in many cases is funding the research under review. A focus on effectiveness might improve the ability of HRPPs to have sound, empirical, data-driven ways of thinking about ethical quality. However, the transition to sIRBs adds complexity to this challenge. Before the sIRB mandate by NIH and the new Common Rule, a coordinating center managed the flow of information coming from the individual IRBs that were all doing their individual site-level work as part of multi-site trial. Following the mandate, much more communication is needed between the sIRB and each institution involved in the search as well as each PI. When a single PI is engaged in multiple multi-site trials, there is the potential for great complexity among lines of communication that could affect both efficiency and effectiveness.

Where does that leave us? The speaker summarized the current situation as follows:

- We lack valid and reliable outcome measures to assess the quality and effectiveness of IRB/HRPP review and oversight;
- We can’t properly evaluate IRB/HRPP quality and effectiveness;
- We can’t clearly demonstrate that the impact of the IRB/HRPP system is justified by its effectiveness; and
- We can’t evaluate the effectiveness of new approaches.

Panel Discussion for Session I

Ancillary reviews. Dr. Rosenfeld invited panelists to comment on how ancillary reviews are handled when institutions rely on a single IRB. He noted that the term is used in two different ways: to refer to reviews that may be part of an institution’s HRPP program, such as radiation safety, or alternatively to refer to research reviews conducted by local IRBs even when they are relying on a single IRB. He observed that in Dr. Taylor’s slides, administrative review is a much bigger box than ethical review. He felt this reflected the experience of many HRPPs. He wondered if an unanticipated consequence of the single IRB mandate is that ancillary reviews once gathered under the umbrella of the HRPP have had to be disarticulated from the research review instead of informing it. He asked how institutions with experience in multi-site review are handling this challenge.

NCI’s model differs from others represented on the panel, Ms. Parreco noted. Before protocols come to the CIRB, they undergo a scientific review and other reviews within the cooperative group system; the results of those reviews are given to CIRB members so they know what questions have already been

asked and answered. With the other definition of ancillary review in mind, she observed that when NCI's CIRB was initiated, many local IRBs did separate reviews. With patience and education, these duplicative "mirror" reviews are less frequent.

Dr. Rosenfeld gave the example of a radiation oncology trial in which radiation safety committees at every site must do reviews. How are these integrated? Ms. Parreco said she was not seeing that kind of issue on a daily basis and was uncertain about whether these reviews are typically conducted locally before start-up or through the cooperative mechanism.

Dr. Johnson explained that the University of Utah HRPP had reviewed the work done by the various ancillary committees and asked in each case, "What questions are we asking and why?" They were then able to determine whether the review was required by the Common Rule (which would clearly place it within the domain of the single IRB) or whether it mattered more to the specific institution. The exercise helped it distinguish between questions that matter most when the Board is acting as a single IRB and those that are relevant when it is deferring to another institution's IRB. Some questions, such as those related to privacy, apply both to the Common Rule and to individual institutions. Disentangling these potentially duplicative reviews was important for efficiency and effectiveness. This exercise made it possible for investigators to answer the right questions for the applicable review process.

Dr. Johnson also observed that ancillary committees (for example, the radiation committee) do not speak the same language as the IRB. Her IRB staff becomes the liaison, making sure that clear communication is occurring with each of these committees and across institutions. She said identifying liaisons for communication is absolutely critical to making the single IRB structure work. Dr. Rosenfeld observed that her presentation and others emphasized the importance of communication in multi-site studies.

Mr. Fedewa said that relying institutions sometimes ask his Medical Center to include aspects of their process in the single IRB's review. For example, they may want to modify recruitment plans based on their local population. His HRPP is willing to consider these requests, but it cannot allow an IRB to mandate changes that might affect other states. Local and state laws will differ. Dr. Rosenfeld observed that many HRPPs have difficulty accepting such constraints.

Ancillary reviews require a good deal of time and energy, Dr. Taylor commented. Detaching ethical review from all the other reviews underway may provide a way to highlight ethical issues and give them more attention than they ordinarily receive. Because of the many responsibilities that remain with the local IRB, the shift to the sIRB model is not necessarily more efficient, at least in the short term.

Dr. Rosenfeld observed that "we could talk about this for hours." The single IRB mandate does not necessarily mean that all the ancillary reviews conducted by relying IRBs are connected back to the center.

Is this right model? Dr. Green asked, "Is this really the right model?" The stated goals of the new mandates for the use of single IRBs in multi-site studies are to improve efficiency and to decrease the administrative burden associated with research review. Is this really happening, or have we just traded one set of problems for another?

Dr. Taylor observed that this is "the million-dollar question." She said that AEREO has not focused on specifically on single IRB reviews. She noted, however, that if the field could find ways to assess the effectiveness of the review process, the question could be answered more readily.

Mr. Fedewa said many efficiencies stem from the policies that the NCI has put in place to limit feedback from local IRBs. “We know exactly what our lane is.” If every institution could develop such clear lanes and clarify who is responsible for what, the model could be very efficient. A few institutions may develop successful models and emerge as leaders in this effort. A question is whether every institution should have the opportunity to act as a single IRB or if, instead, it would work better to have regional IRBs that act as single IRBs.

From a qualitative perspective, Dr. Johnson observed, increasing the voices and perspectives represented in reviews has been useful. One thing this mandate has done is to “create a space in which we are all talking to each other.” More institutions are collaborating and incorporating what they learn from each other. We talk more about “what’s happening at your site.” There is some measurable progress there. However, she stressed, we still need to learn how to invite and use these different perspectives efficiently. Dr. Johnson also perceived that inconsistencies in review are reduced as HRPPs talk through their differences, though this has not been pursued as a goal. If we do focus on that goal, she suggested, we can enhance quality.

Ms. Parreco commented that in the “early days” of NCI’s CIRB, a “culture of accommodation” existed. Staff would do whatever it took to make participating sites happy. Recently, however, NCI did a careful audit of the kinds of changes that had been allowed in study boilerplate and consent documents and found that most of the changes were not really necessary. She also united with Dr. Johnson’s comment that “IRB language” must be translated and made clear to stakeholders.

Dr. Rosenfeld reflected that he was at the Western IRB (an independent IRB) when the debate about the use of a single IRB began. He was initially confident that this model would work, having experienced the use of single IRBs in multi-site review on projects under the jurisdiction of the Food and Drug Administration (FDA) regulations. At the time, he was not fully aware of some of the differences that exist for research conducted under the Common Rule. He noted that independent IRBs have learned lessons about how to facilitate multi-site reviews that would be helpful in this discussion.

Capturing and analyzing data. Recalling that Ms. Parreco had said that the NCI CIRB requires members to respond to periodic surveys, Dr. Rosenfeld wondered whether the data from these surveys or from meeting minutes had been analyzed. Ms. Parreco responded that NCI has not yet done an in-depth analysis of minutes or member surveys, but she said it would be a good idea. Dr. Rosenfeld said that the Quorum Review IRB (now consolidated into Advarra) used to do an annual analysis of similar surveys and found it useful.

Dr. Taylor said that AEREO has several relevant projects underway right now, including a close look at the review process for COVID-related research. Data sources include minutes and letters to the PI from the reviewing IRB. It is interested in the question of whether secondary data analysis can help assess quality. AEREO plans to present what it has learned at the upcoming Public Responsibility in Medicine and Research (PRIM&R) meeting, and perhaps this will help answer this question.

Shifting the burden? Dr. Rosenfeld said it was striking that there is as yet no evidence that multiple ethical reviews actually improve human subject protection or that the use of a single IRB does a better job of this. He expressed concern that the single IRB mandate has caused some institutions to shift some HRPP responsibilities to PIs. Rather than reducing burden, it may simply have shifted it around and made research more challenging at a time when the field is having difficulty recruiting investigators. Dr. Green said this concern was part of what was behind his question. The new mandate has made the tasks of the PI

much more complex, which may result in a negative impact on the things we care about, which is ultimately how research is conducted. He believes the shift has on the whole been detrimental.

Dr. Johnson observed that in the initial stages of the effort, the single IRB approach may simply shift or increase the burden. However, her institution is new to this, as are many others. She suggested that “we need to allow ourselves a learning curve.” Additionally, she noted that recruitment and protocols are becoming more complex, adding further challenges. However, her anecdotal experience is that some PIs are doing well with the new system and others are still struggling. She said she didn’t know whether the learning curve will ever get to where it needs to be with the majority of investigators.

Accountability to human subjects. Dr. Thomas found the conversation fascinating, but he noted that if there is a steep learning curve for investigators, the learning curve for potential human subjects must be even greater. If the discussion does not put the subject back in the conversation, IRB-approved studies may end up generating front page news as unethical. He felt that too much emphasis was placed on reducing risk rather than building trust. Dr. Rosenfeld observed that IRB deliberations typically do not encompass accountability to the public as a whole.

Dr. Bierer asked how the use of a single IRB instead of a local IRB would affect human subjects, assuming that the IRBs in either case are fulfilling their responsibilities and addressing local context. Dr. Thomas responded that investigators and program representatives assure subjects that there is an IRB whose job is to protect them. Knowing that this IRB is actually in another state may contribute to hesitancy to participate.

What have we learned to do differently? Dr. Klitzman noted that there is indeed a learning curve and there will likely be some improvement as people become more familiar with the new approach. However, some structural obstacles may not improve. He asked Ms. Parreco whether there are things that NCI has learned to do differently over its 20 years of experience that have improved functionality.

Ms. Parreco said the biggest change has been to shift from a “culture of accommodation” in which institutions continued to conduct their own reviews as they chose, to one in which grantees that participate in NCI-sponsored research are required to use the NCI CIRB as their IRB of record. The “lanes” are clearer than they were in the past.

Session II: Effectively Managing Local Context Concerns in Single IRB Review

- *Moderator:* Liza Dawson, Ph.D.; Chief of Bioethics and IRB Chair, Walter Reed Army Institute of Research

Session II Introduction

- Liza Dawson

Dr. Dawson introduced herself and each presenter.

Some question whether local context issues receive adequate consideration in single IRB review. This session examines what might constitute legitimate local context concerns and how single IRBs could best ensure that they receive appropriate attention and accommodation.

Dr. Dawson observed that diverse issues come into play as local context is considered. For example, knowledge of each institutions' own policies and practices, usual practices, and potential subjects' perspectives about the research are all aspects of local context. Most single IRBs won't know every relevant factor for each local site. A positive side is that focusing on this concern provides an opportunity to rethink how this critical contextual data is collected and improve the process.

Addressing Local Context Issues by Single IRBs in Multi-Site Research

- Robert Klitzman, M.D.; Professor of Psychiatry, Columbia University

Dr. Klitzman said his presentation reflected the findings of two studies. One study reported the views of sIRBs held by 46 individuals serving on local IRBs (Klitzman 2011). The second interviewed 103 individuals from 20 sIRBs and reported their perceptions of challenges and solutions related to local knowledge (Klitzman et al. 2019).

The speaker cited several possible advantages of sIRBs. These could include more consistency among IRBs in multisite studies and reduced duplication of effort in IRB reviews, resulting in better protection of participants and more efficiency. However, there are also concerns (Klitzman 2011):

- Local IRBs may fear “something will be lost.”
- When there are many sites, central IRBs may not know all the relevant information for each site, especially if they do not have a prior working relationship with the local IRB.
- If “something really bad happens,” who is responsible?
- How can concerns related to different groups of subjects (for example, a local population of Haitian immigrants) be recognized and addressed?
- Will local subjects benefit from study findings?
- Will local HRPP staff lose their jobs?

Local knowledge about local participants and communities is a critical component of local context. One example is race and ethnicity, including awareness of languages other than English spoken by potential subjects. Different cultural views may be present, and socioeconomic factors such as poverty must be taken into account. Studies may not be equally relevant to different communities. “Red and blue” differences may translate into attitudes that have implications for study participation (for example, views of sexual diversity). Local laws, geography (for example, the distance from the study hospital), cost of living, and incentives to participate (for example, the lack of alternative ways to access treatment) may also need to be taken into account.

Dr. Klitzman pointed out that local institutions also may have relevant knowledge of participating researchers. They may know, for example, which of them is overextended or has a worrisome history of minor violations. They also have institutional knowledge that may affect the research, such as challenges in emergency response, differing standards of care, or differing policies and procedures. It may be difficult for single IRBs to know whether or not they have enough knowledge about the local community, especially for global studies.

Single IRBs may not have sufficient expertise to address these gaps in knowledge; on the other hand, some local IRBs may be relatively small and have their own pertinent gaps in knowledge. Some IRB members are less concerned about the issue than others and believe that local differences may matter less

than they used to (“We all have the same Starbucks”). Some feel that knowing the local population better may not “matter that much” (Klitzman et al. 2019).

A number of mechanisms have been identified to address local context. Some institutions use “local information forms” to capture data. Webinars, hotlines and phone calls can help obtain relevant information. To make this approach work, trusting relationships must be forged with specific staff members. Separate IRBs may be established to ensure concerns related to certain groups (such as Native Americans) are adequately represented. Local IRBs can submit comments on considerations related to local context to the sIRB, but some never do.

The speaker offered several conclusions that should be kept in mind as solutions are sought:

- Levels of concern vary regarding potential “loss of local knowledge.”
- Several types of local knowledge exist. Knowledge of local populations is especially important.
- Many mechanisms for local input and coordination are possible to address knowledge gaps.
- Some local institutional functions may need to be coordinated with sIRB.
- sIRBs differ in many ways (for example, history, context, and size).

Dr. Klitzman called for the development and refinement of mechanisms to obtain local knowledge. For example, sIRBs may need to have broader, more comprehensive membership to represent local subjects, including more non-scientific, unaffiliated members. Policies to address specific issues related to local context must be developed. Ongoing research is needed to assess effective strategies. One obstacle, however, is that many for-profit IRBs have so far declined to participate in such research, and their perspective and experience are critical.

Challenges to Reviewing Clinical Research when Local Context Includes Variation in Infrastructure and Practices

- Jonathan M. Green, M.D., M.B.A.; Director, Office of Human Subjects Research Protections, National Institutes of Health Intramural Research Program

Dr. Green focused his remarks on a particular element of local context relevant to medical studies: usual care. He defined usual care as the care that would typically be provided in a given clinical circumstance. Usual care is provided by a given clinician, at a given location, and at a given time. It may vary by doctor, hospital, region, payor mix, within a “condition,” and over time. Problems addressing usual care do exist when a local IRB reviews the study, but they may be exacerbated when an sIRB is the reviewer.

There is a huge amount of variation in clinical practice and it is important to know which approach is best. This challenge can be approached through clinical trials in which one or more arms represents usual care as compared to experimental care, or in which two (or more) usual care strategies are compared to each other. Such trials can increase knowledge of risks and benefits and provide data to inform treatment guidelines.

Dr. Green expressed concern that an IRB might not have an accurate understanding of what constitutes usual care for a participating site, which can lead to serious consequences. The IRB may have inaccurate data on usual care and may lump together heterogeneous study populations that require different clinical approaches. It may be unable to identify a widely accepted practice (usual care may evolve rapidly) or use expert opinion rather than data to reach its conclusions.

Serious consequences of this lack of understanding could include an inaccurate assessment of risk, failure to minimize some or all risks, unreasonable risks, inadequate data safety monitoring, or inadequate informed consent. Dr. Green cited several examples of specific trials in which aspects of usual care were not taken into account, with concerning consequences and implications. (See PowerPoints.)

If IRBs struggle to know what usual care is at their own site, Dr. Green queried, how can they know what usual care is at other sites? He stressed the need for increased understanding of the challenges of usual care research and appropriate trial design. IRBs need to understand what is comprised in usual care at each institution enrolling in the study, and they need the expertise to apply this knowledge to the study under review. Investigators and scientific reviewers must also take this into account.

Dr. Green stressed the need for IRBs – whether local or single – to do the following:

- Require data supporting usual care for each site;
- Ensure access to appropriate expertise when reviewing usual care;
- Ensure the informed consent process accurately distinguishes usual care vs unusual care;
- Ensure the informed consent process accurately discloses risks; and
- Assess risks and benefits, being cognizant of differences across sites.

How Might a Single IRB for Multisite Research Address Local Culture, Race and Social Class of Potential Human Subjects?

- Stephen B. Thomas, Ph.D.; Professor, Health Policy and Management, and Director, Maryland Center for Health Equity School of Public Health, University of Maryland, College Park and IRB member for the All of Us Program

Dr. Thomas focused his remarks on the challenges and pitfalls a single IRB might encounter in taking the local culture, race, and social class of potential human subjects into account. He noted that in the communities where he works, many potential subjects do not understand what research means.

Consequently, the University of Maryland has sought to build a community-engaged research structure “out in the neighborhoods” so that people hear about research before they are asked to participate as subjects.

The speaker raised the key question, “Who represents the community?” He said he was old enough to remember when the local community representative on an IRB might be the wife of the head of the Department of Surgery. Meaningful representation of subjects’ communities is needed. He noted, however, that when local IRBs simply “talk to themselves,” they may fail to recognize how important this is. He cited a 2019 study (Klitzman et al.) that reported that some IRB representatives do not feel local context (presumably including subjects’ perceptions) is especially significant. Efficiency is more highly valued than inclusion.

Dr. Thomas noted that “history matters” and contributes to the challenge of including diverse populations in clinical trials. For example, more African American participants are needed in COVID 19 trials, particularly given the fact that they are among disadvantaged groups that suffer a higher share of the disease burden. He reported that even today, the legacy of the notorious Tuskegee study, in which African Americans with syphilis were unknowingly denied treatment, is apparent and sometimes cited by prospective subjects. Other well-known research that contributes to distrust of research includes the use of a biopsy from Henrietta Lacks without her consent and the IRB-approved use of DNA samples from

Havasupai subjects who originally consented to the use of these samples for a different purpose. Trust must be rebuilt over time.

Dr. Thomas said the “rubber meets the road” in the informed consent process, in which the relationship between the prospective subject and the study team member is critical. The speaker suggested that it helps when websites offer pictures of the study team that include people who look like the prospective subjects themselves. He challenged researchers to consider how they approach this process:

- What methods do you use during the informed consent process?
- What strategies do you use to increase understanding of the informed consent document?
- How do you assess participant understanding?

He also offered questions that can be explored with community members:

- How do you like to learn about a study?
- What methods are helpful for understanding the informed consent document?

He noted that researchers’ methods of presenting studies are often not viewed as helpful by community members and that document formats preferred by subjects are typically not used. The literature finds that the most effective modes of presentation are face-to-face interactions and extended conversations using plain language and teach-back methods. Multiple meetings are sometimes needed to ensure that subjects comprehend relevant information.

Experience with Regionalized Ethics Review Committees in the United Kingdom and Europe

- Sarah J.L. Edwards, Ph.D.; Professor of Bioethics, Department of Science and Technology Studies, University College London

Dr. Edwards provided historical context on the effort to standardize the consideration of ethical issues in reviews conducted in the United Kingdom (UK) and Europe. She stressed, however, that ethics reviews cannot ensure that the research itself will be ethical, only that the factors the review is seeking to balance are reflected in research procedures.

In the context of global health, Dr. Edwards observed that structures invoked in review often vary depending on the cultures of research participants. For example, when conducting research in Africa, “we suddenly talk about community engagement” and may involve anthropologists to aid in understanding the community. In the UK, this is called patient and public involvement, and anthropologists are not considered necessary.

In presenting experience within the UK, the speaker stressed the importance of bearing in mind the fact that the UK does have a national health service. Therefore, the basis of study review has been guidance from its Department of Health. This means some caution is needed in extracting lessons to apply within the US.

Local research ethics committees began to be used in the UK by 1991. By 1997, however, researchers observed variations from committee to committee that sometimes hindered research and frequently resulted in duplication of effort. In response, in 2000 the Department of Health established the Central Office for Research Ethics Committees to implement, develop, maintain, standardize and oversee operating procedures for Multi-Regional Ethics Committees (MRECs) and Local Regional Ethics

Committees (LRECs) throughout the UK. MRECs now have jurisdiction over studies that supersede geographical boundaries. A 2005 study by Al-Shahi describes how this works:

A multicentre research project (taking place over five or more LREC geographical boundaries) required the opinion of just one MREC about its ethics. Once approved, its decision and details of the project had to be distributed to every LREC in the geographical location of the study, whose executive subcommittee was only allowed to consider—within a proscribed timeframe—the suitability of the local site, researcher(s) and/or facilities.

Procedural problems continue to be reported in the UK and in Europe, however. A 2007 review of 26 studies across Europe found differences in the clarifications and revisions asked of researchers regarding consent, recruitment, risks and benefits, compensation arrangements, and science (Edwards, Stone, & Swift 2007). Focusing on Great Britain, a 2011 study (Heasman et al.) concluded that it was “absurdly duplicative to require both a local ‘site-specific assessment’ (submitted by a named local investigator) as well as research and development management approval at every National Health Service site involved.” Dr. Edwards also noted that the Department of Health offers lump grants for comprehensive biomedical research, an approach that often results in difficulty capturing the diversity of the UK population.

UK laws now also require specialized ethics review for certain populations (for example, adults with impaired mental capacity). Also, all clinical trials of Investigational Medical Products (IMPs) require ethics review by one ethics committee for each European Union (EU) member state. With BREXIT on the horizon, however, “anything could happen.”

Panel Discussion for Session II

Areas of Responsibility. Dr. Dawson observed that Dr. Klitzman’s comprehensive list of concerns spans the gamut of things institutions must take into account in their deliberations, those researchers must address, and areas for which the single IRB is responsible. How do you distinguish among these three areas and determine which things should belong to the single IRB and which should remain with the institution or researcher?

Dr. Klitzman responded that there are many areas that are actually a shared responsibility. He gave the example of an international study in which the IRB asked the PI (regarding a particularly complex procedure), “Is that treatment the usual standard of care in this country?” If the researcher says yes, should the IRB simply take the researcher’s word that this is the case? He argued that while this is the researcher’s responsibility, the IRB should “trust but verify.” The different levels of verification that are appropriate will vary depending on the study.

Dr. Green agreed with Dr. Klitzman that many areas of responsibility overlap. It is not easy to parse all of them out. Investigators need to collect and provide certain information, and a scientific review committee bears responsibility for an independent perspective on the scientific design and the veracity of the information provided. At some level, IRBs have to trust the information they are given, and their responsibility is to make sure they actually have the information they need and the scientific review was thorough.

Dr. Green observed that relevant variations in local context, including more subtle questions that may not be obvious or routine, will differ depending on the study. Single IRBs are still trying to determine what

these questions should be. Ultimately, the institution remains responsible for research conducted at its site. He held that if you are a subject in the study, you do not care which IRB made the decisions that affect you. Dr. Dawson commented that she appreciated the reminder that other committees with distinct areas of expertise share responsibility; for example, the scientific review committee must take account of issues that affect the science of clinical trials, including assessing the adequacy of the standard of care and considering variations in clinical practice across different sites.

Dr. Edwards said that scientists and PIs bear the burden of proof to demonstrate that they have considered certain aspects of the protocol sufficiently, and ultimately the ethics committee must take certain things on “informed trust.” If the ethics committee is not able to discharge its substantive functions, things can go badly wrong. She gave the example of a study in which a drug company presented a study on a new drug for review in the UK. The regulator was unaware that the study had previously been rejected by a review board in Germany and approved it rapidly. The ethics committee assumed that there were no serious risks because the regulator approved it and changed key language in the consent document that turned out to make these risks less understandable. All six volunteers participating in the study nearly died. The chief investigator has the overall responsibility for preventing such incidents in the UK. She added that there must always be an appropriate process for patient and public involvement, and this is the responsibility of the investigator in charge at each participating site.

Engaging human subjects. Dr. Thomas observed that study teams often have Community Advisory Boards (CABs) that are established separately for each study. He suggested there might be value in single CABs that could contribute to a variety of studies in their area and be at the table routinely. He stressed the importance of taking into account how human subjects may view administrative changes. A question worth exploring is how potential human subjects are represented on single IRB boards. Dr. Dawson responded that the Division of AIDS at the National Institutes of Health (NIH) is advised by a global CAB that consists of representatives from local CABs.

Dr. Taylor suggested that community-based engagement may be more important for particular types of studies than for others. She contrasted a study in which the research is carried out in the neighborhood of the institution conducting the research and a multi-site trial in which the subjects all have a particular disease. In the latter case, she posited that there is less robust concern for robust local input and a different kind of engagement is required.

Such variations are important, Dr. Thomas agreed, but he stressed that when the IRB is located outside the research area the voices of subjects need to be amplified, not decreased. If administrative capacity is lacking, local voices are lost at each step of the process, making it more difficult to handle blow-ups. Community voices would provide a “buffer” if subjects have been involved all along. Even if the research simply involves collecting biospecimens in the course of hospital treatment, subjects must be informed and willing to provide them.

Agreeing with Dr. Taylor, Dr. Klitzman thought that local knowledge is more important in some studies than in others. However, deciding the appropriate level of involvement and determining how best to engage subjects is not as easy as it may seem. Even in a study of diabetes, heart disease, or cancer, there may be multiple social determinants to consider. Do we feel comfortable excluding groups of people? Although translation (for example) is expensive, investigators should think carefully before they exclude people.

Dr. Edwards observed that “we mean different things by community.” Patient populations might come from anywhere, and their backgrounds must be captured. In one study of arthritis, for example, it turned out that the most important outcome to subjects was not reducing pain, but reducing fatigue. If scientists really knew the values of the populations where their technologies were designed to be delivered, they wouldn’t need an extra layer of research to address gaps. She advocated very early involvement with subjects.

Communicating local context. Dr. Dawson invited presenters to comment on how sIRBs can access knowledge about the local context. Whose responsibility is it and how, operationally, can it occur? She was reluctant to say this is solely up to the PI, who is likely to be swamped with administrative responsibilities related to complex trials. Do sponsors have a responsibility here? Are they responsible for funding data collection and relaying some of this important contextual information to the single IRB?

Dr. Edwards said the question was an easy one for her; in the UK, the National Institute of Health is responsible. However, the chief investigator still has a lot to do. The more established the investigator, the greater the resources he or she may have to carry them out. For example, they may have financial support from a previous grant that can help them develop a proposal for another project.

Be careful about compartmentalizing this function, Dr. Green cautioned. Everyone needs to get the same information, but each has a different responsibility in evaluating that information. The biggest problem is that we are not sure about what information needs to be transferred, and we do not know what questions to ask or how to transmit what is known efficiently and effectively. In complex processes, this is especially challenging. He held, however, that community engagement is usually an institutional responsibility. Subjects live in communities. Even in early stages of drug trials, for example, an institution has an obligation to the people that surround it. PIs can’t do everything. The institution should “own” this issue and have processes and funding in place to keep the community engaged across research studies.

Dr. Klitzman held that there should be more CABs and sponsors should cover the cost of maintaining them. He also stressed the need for more unaffiliated and non-scientific members on IRBs. Perhaps 5 percent or even 10 percent of the board should consist of members from the communities. The information to be communicated is varied: socio-economic information (not just categories of racial and ethnic groups), access to health care, or the presence of undocumented immigrants. Much of the responsibility for collecting and transmitting such data remains with the investigator who initiated the study.

Dr. Dawson commented that the Walter Reed Army Institute of Research routinely receives information from local sites participating in clinical studies via a Site-Specific Addendum, which includes information about local study population, clinical care, oversight processes, responsible parties for implementation of the trial, and other data.

Dr. Thomas said the critical piece of this issue is actually caring about local subjects. Many minority communities have not benefitted from systematic efforts to educate them about research. Subjects must be prepared, educated, and empowered to participate in trials. It is important to ensure that study participants’ voices can be heard and actually matter. He added that having someone on the study team that community members can identify with helps greatly in building trust and can aid in recruitment.

Justifying local variations. Dr. Dawson asked panelists to identify situations in which it is reasonable to have variations at local sites. Dr. Klitzman said that variations are reasonable when and if there is a justification. The problem the sIRB mandate is trying to address is the need to avoid unjustified,

idiosyncratic variations that are really about personalities at the local sites or a need to control the details of the process. If the same protocol is reviewed by different IRBs in the same community with different results, it is unlikely the variation is justified. However, given two different study settings, each with different socioeconomic and geographic conditions, it might be possible to justify, for example, offering subjects housing in one setting and not the other.

When surveys ask very sensitive questions, Dr. Edwards observed, different communities may have different perceptions about who is allowed to answer those questions. When vaccine trials recruit subjects from a poor population, there may be justifiable variations in protocol compared to those that recruit subjects who are not living in poverty.

Session III: Sharing Responsibilities and Distinguishing Roles in the Single IRB Era

- *Moderator:* Megan Kasimatis Singleton, J.D., M.B.E., CIP; Associate Dean, Human Research Protections and Director, Human Research Protections Program, Johns Hopkins University School of Medicine

Session III Introduction

- Megan Kasimatis Singleton

Ms. Singleton introduced herself and each presenter.

This session will focus on how, in the era of single IRB review, responsibilities are distributed and shared between relying organizations and reviewing IRBs. This session explores how responsibilities can be articulated, the manner in which they can be operationalized, how performance of those responsibilities can be evaluated, and the ways in which reviewing IRBs and relying organizations might best work together in a single IRB model to address their collective responsibility for human participant protections.

Reliance Agreements: Considerations and Responsibilities Beyond IRB Review

- Emily Chi Fogler, Esq.; Partner, Verrill Dana LLP (as of September 21, 2020, Ms. Fogler is a Member of Epstein Becker & Green, P.C.)

Ms. Fogler began by noting the shift in the research community from viewing reliance agreements as a roadblock to viewing them as a critical piece of the roadmap for reliance.

She highlighted the many kinds of study oversight activities besides IRB review. Examples include consideration of conflict of interest, investigator qualifications, determinations related to the Health Insurance Portability and Accountability Act (HIPAA), and applicable laws and regulations. Once a study is underway, oversight includes reviewing and responding to complaints, reporting actions to sponsors and regulatory agencies, and ensuring compliance. At the conclusion of a study, participants in medical studies may need help transitioning to standard care. In short, there are many institutional responsibilities beyond IRB review, and many institutional bodies and committees beyond the IRB; it is important to ensure that none of them falls through the cracks.

Federal regulation and policy on single IRBs now reflect this broader perspective. The new Common Rule requires parties in a reliance agreement to “document the institution’s reliance on the IRB for

oversight of the research *and the responsibilities that each entity will undertake to ensure compliance with the requirements of this policy*” (45 CFR 46.103[e]) (emphasis added). The NIH Single IRB policy similarly contemplates the responsibilities of the relying institution and requires attention to how those will be fulfilled.

What institutional oversight activities should be delegated to the reviewing IRB? There are no regulatory restrictions on this decision. Various approaches could be more or less robust or more or less efficient, but there is no right or wrong answer as to whether or the extent to which to delegate these activities. The flexibility can make the decision even harder.

Ms. Fogler pointed to the [National Center for Translational Sciences SMART IRB Platform](#) as a useful resource as institutions explore how best to assign responsibilities. The Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB Platform offers a sample authorization (or reliance) agreement for multisite trials and guidance documents, among other resources.

The speaker distinguished between contractual and compliance responsibilities. *Contractual* responsibilities are determined and allocated by the contracting parties. Failure to perform a contractual responsibility may constitute a breach of contract and could result in specific performance requirements, injunctions, or monetary damages. (Injured third parties, however, generally have no rights.) On the other hand, *compliance* responsibilities are determined by laws and regulations. Unlike contractual responsibilities, compliance responsibilities cannot be reassigned. The institution with the compliance responsibility under law or regulation will still be responsible to authorities for noncompliance or other violations even if it has delegated contractual responsibility for carrying out the law’s or regulation’s requirements. The consequences could be government investigation and enforcement actions, fines, restriction of activities, or criminal penalties. Applicable laws and regulations may or may not give injured third parties rights. Ms. Fogler held that even though contractual responsibility and compliance responsibility may not always align, it is not unreasonable for an institution to delegate contractual responsibility for various institutional oversight activities to a reviewing IRB.

The oversight activity of ensuring that research complies with all applicable laws and regulations beyond federal human subjects regulations (such as state and local laws) is an example. The risk of failure to comply with applicable state and local laws and regulations may be greater when the reviewing IRB is in a different state. Ms. Fogler suggested, however, there are options that can be used to increase the likelihood of compliance. For example:

- The relying institution/site can agree to provide a representative to the reviewing IRB to assist in review with respect to application of relevant state/local laws and regulations. This approach might not be feasible in all situations, but it may be helpful for research for which local laws and regulations are more relevant. It requires more effort but may result in a lower level of risk.
- The reviewing IRB can agree that it will identify, interpret, and apply all relevant state/local laws and regulations without the need for involvement on the part of the relying institution/site. This is a more realistic expectation when the reviewing IRB has the resources to review state/local laws and regulations independently. This may be the case with an independent IRB, for example, but does require some tolerance for risk.

- The relying institution/site can agree it will identify and interpret all relevant state/local laws and regulations (upfront or study-by-study) and communicate requirements to reviewing IRB to apply in its review. Ms. Fogler considered this option to lie in the middle of the risk scale.

All these approaches are permissible from a regulatory viewpoint.

Ms. Fogler also gave examples of how an institution might approach the delegation of responsibilities related to HIPAA (see PowerPoints).

The Role of the Relying Institution in Human Subjects Protection in the Era of Single IRB

- Kelley O’Donoghue, M.P.H., CIP: Associate Vice President for Human Subject Protection and Director of the Office for Human Subject Protection (OHSP) at the University of Rochester

In determining how a relying institution could best fulfill its responsibilities in human subjects protection, Ms. O’Donoghue suggested that IRBs should understand their responsibilities, create policies, utilize existing processes when possible (there is no need to “reinvent the wheel”), and consider the capabilities of their staff. She stressed the importance of broadening the HRPP’s perspective to encompass the institutional review rather than the IRB’s own review. For example, post-approval monitoring is crucial.

Citing as a key source the [division of roles and responsibilities](#) for relying and reviewing institutions featured on the Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB Platform, Ms. O’Donoghue suggested that when research is initiated, the reviewing IRB should generally be responsible for:

- IRB registration
- IRB membership
- Compliance with regulations
- Review of local considerations, and
- Approval of the study/site.

The relying institution needs to maintain the Federal-wide Assurance (FWA) and address such institutional considerations as:

- Education for the research staff
- Identifying conflicts of interest
- Addressing special considerations such as applicable laws
- Ancillary committee approvals, and
- Ensuring local context is considered in consent forms.

Once the study is underway, the reviewing IRB should be responsible for:

- IRB membership
- Compliance with regulations, and
- Reviewing and approving modifications, continuing reviews, reportable events, non-compliance, etc.

At this stage, the relying institution should:

- Maintain the FWA
- Continue to monitor institutional considerations
- Monitor changes to conflicts of interest, and
- Ensure research staff education requirements continue to be met.

[Policies and guidelines](#) are needed to guide collaborative research, and the University of Rochester (UR) has developed several that may be useful models for other institutions. Ms. O’Donoghue noted that current IRB review and approval workflows may be modified when the institution is serving as a single IRB or is relying on an external IRB. It may be easier for researchers to adapt to a modified process that is familiar in either case; often existing resources can be modified to accommodate new situations. Examples of documents created at the UR include a policy for IRB Reliance and Collaborative Research, with associated guidelines and flowcharts for when the university is either the reviewing IRB or the relying institution, and template consent language for when the university relies on an IRB outside the university system. (See Resources.)

When relying on an external IRB, the UR has found that knowledgeable staff are essential. The processes will be different, and it is necessary to have staff who have expertise in relevant aspects of human subject protection. Ms. O’Donoghue’s office employs a reliance specialist who is dedicated to collaborative research and external IRBs.

There are many challenges that can come up for a relying institution when trying to address their responsibilities. Examples include determining who is taking the responsibility for HIPAA and how to build that into the process if needed, modifications that affect institutional considerations, and managing state and institutional differences. In addition, institutions need to be aware and ready to adapt to changing institutional requirements. For example, the UR instituted a new data security guideline that needed to be integrated into the process.

Working Together to Improve the Single IRB Model: Suggestions from a Multi-Stakeholder Project Team

- Sara B. Calvert, PharmD; Senior Project Manager, Clinical Trials Transformation Initiative (CTTI)

Dr. Calvert explained that the CTTI is a public-private partnership co-founded by Duke University and the Food and Drug Administration (FDA) that seeks to “develop and drive adoption of practices that will increase the quality and efficiency of clinical trials.” Its Single IRB Evaluation Project developed a framework from which a future assessment of the implementation of NIH’s sIRB mandate, or more broadly an evaluation of the use of sIRB as required by the Common Rule, could be developed. The CTTI project team collaborated with an NIH workgroup to design data collection activities and develop the framework. Dr. Calvert reported on findings from 360 case study interviews of 21 individuals at two universities and interviews with 13 research administration leaders from multiple organizations who provided their experiences implementing sIRBs, including their processes and potential metrics to inform framework development.

The project team found that:

- There is wide variation in how sIRBs are being implemented.

- Some participants explained that the sIRB model has improved inefficiencies associated with the local IRB model. More participants, however, indicated that the sIRB process has not simplified the ethics review process, particularly for the reviewing institution and investigators.
- Efficiency is improved by standardizing processes, experience, and IRB system adjustments. For example, resources and tools such as those available through SMART IRB have proved helpful and facilitate standardization.
- The current IRB/sIRB system is not being measured routinely. Existing metrics typically focus on efficiency and are collected primarily at organization or program level.

The [full report](#) that emerged from the framework development effort is available on the CTTI website.

Dr. Calvert highlighted a number of challenges in evaluating the effectiveness of the NIH sIRB policy alone. Notably, she emphasized the need to develop standardized, well-defined metrics to measure IRB/sIRB review. Also, there is no central database of organizations that serve as a single IRB. A list of organizations that are implementing the sIRB model must be developed to define the population for the future evaluation. Ideally, a sample of sIRB organizations will be asked to share data on the to-be-established measures annually.

The CTTI team proposed that Common Rule agencies, including NIH, develop a learning system to measure and improve the sIRB process. To accomplish this, all stakeholders involved in the sIRB process should be engaged and encouraged to communicate their needs and suggested improvements to the sIRB system, leading to the creation of a system for continuous sIRB improvement. The system the CTTI team envisioned would:

- Compile and share nationwide sIRB processes and metrics,
- Establish standards where appropriate,
- Identify areas where changes and improvements are feasible, and
- Engage stakeholders in all steps.

SMART IRB: Lessons Learned and Opportunities Ahead

- Barbara E. Bierer, M.D.; Director, Regulatory Policy, SMART IRB and Director, Regulatory Foundations, Ethics, and the Law, Harvard Catalyst (CTSC)

Dr. Bierer explained that [SMART IRB](#), funded by the National Center for Advancing Translational Sciences (NCATS), provides infrastructure support for IRBs and works to harmonize review processes nationally. Various resources are offered for IRB professionals, institutions, and investigators. For example, a large number of SOPs have been developed that provide default policies for the roles and responsibilities of the reviewing IRB and relying institution; for processes to follow and communications to manage before, during, and after reliance; and in the event of problems occurring. These SOPs are the “default,” but they can be superseded or supplemented by other written documents to which both the reviewing IRB and relying institution agree if in compliance with the reliance agreement.

The SMART IRB platform supports institutions in using or acting as single IRBs in several ways. It seeks to:

- Grow a national IRB reliance network

- Support the use of SMART IRB
- Educate and train institutions and investigators, and
- Harmonize sIRB review processes across the nation.

Available tools include a Master IRB Reliance Agreement that saves whatever time is expended in developing and negotiating inter-institutional agreements. Institutions sign the Master IRB Reliance Agreement once and can then use it for all subsequent reliance arrangements. Its flexible terms allow the agreement to cover all types of clinical research. The platform also features the Online Reliance System that enables users to request, track, and document reliance arrangements for each study – a system that is a system of record and has been utilized for reliance arrangements in over 100 COVID-19 studies. Dr. Bierer reported that the median time to achieve reliance has been 3 days, with the minimum time being 16 minutes!

Currently, 790 institutions participate in SMART IRB. Because it is often difficult to find the responsible institutional representative to answer questions, every institution is required to identify individuals to serve as the points of contact. Dr. Bierer stressed that education, coordination, communication, and trust are key elements of the program, and all are essential for its success.

Through its Harmonization Steering Committee, leaders in the field promote best practices, which are also disseminated through education and training. SMART IRB has appointed Ambassadors who are HRPP professionals knowledgeable in IRB reliance and available to help institutions join and implement the SMART IRB Agreement. Tools, templates, Frequently Answered Questions (FAQs), checklists, peer consultations, and webinars are all available through the initiative. Because turnover in HRPPs is frequent, SMART IRB developed start-up packages and resources for IRB and HRPP professionals to help them get up to speed quickly.

SMART IRB offers members a number of ways to share information and tools. Its monthly newsletter, which has 2700 subscribers, points people to new resources. It sponsors a monthly virtual talk that provides an opportunity to discuss best practices and challenges, as well as a webinar series. During the COVID crisis, SMART IRB provided a forum for leaders in the field to discuss and address emerging issues.

Going forward, SMART IRB will continue to evolve in response to the feedback it receives from the research community. It will continue to offer and improve its programs and resources in response to stakeholders' expressed needs.

Panel Discussion for Session III

Monitoring adherence to agreements. Ms. Singleton queried, “Should we be monitoring our organizational adherence to what we have set forth in reliance agreements in terms of our roles and responsibilities as reviewing IRBs and relying organizations?” Ms. O’Donoghue responded that this is a difficult issue and needs more thought. The UR tries to push consistent use of SMART IRB agreement to ensure consistency is requirements, but this is not always possible; it can be difficult to monitor differences between reliance agreements to ensure we are always meeting our responsibilities. One way the UR is trying to achieve this is to hold the highest standard regardless of what the agreement indicates. For example, in relation to audit reports, many reviewing IRBs only want reports when they are bad or indicate a problem. The UR sends all audit reports of its monitoring activities, regardless of whether the

sIRB wants them or not. Right now, Ms. O'Donoghue said, we don't have a good plan for monitoring the terms of each agreement, outside of a spreadsheet.

Dr. Bierer said SMART IRB's Harmonization Steering Committee has just finished a project on for-cause and not-for-cause auditing. One component of this is a description of when and how one would think about monitoring the reliance process itself. In addition to the SMART IRB agreement, institutions may have a number of different agreements with which to comply; the challenge is especially difficult for study coordinators who are trying to meet a variety of different expectations and timelines. It will help greatly if the field could reach consensus on a common set of expectations for reviewing IRBs and relying organizations.

Ms. Fogler asked Dr. Bierer whether people ask SMART IRB questions about this. Dr. Bierer responded that people do ask. Ms. Singleton asked Ms. Fogler whether, when formulating reliance agreements, the question of monitoring compliance with the agreed-upon roles comes up. Ms. Fogler responded that people are concerned about this. Ms. Fogler noted that from a legal perspective, institutions don't typically look at reliance agreements after they are signed unless a problem develops. In this case, however, some monitoring of compliance with the agreements may be warranted; many institutions are engaging in new, trust-based relationships. Ms. Fogler suggested it may be helpful for parties with reliance agreements to select studies about which to have formal reviews or even informal conversations after the study is complete to identify what aspects of the reliance relationship worked well or did not work well and what may need to be changed.

Dr. Bierer noted that SMART IRB tools include a regulatory binder that allows people to keep policies and other study materials together in an organized way. An electronic version will soon be available for download. Dr. Bierer suggested that separate toolkits might be developed for study startup and close down to help people remain compliant.

Addressing new needs for professional development. Ms. Singleton observed that the single IRB mandate has raised new challenges for investigators and study teams in learning the requirements related to sIRB review and questioned whether there are best practices to help educate researchers about these complexities.

Dr. Bierer observed that many investigators may conduct only one study in their lives that is subject to the sIRB review requirements, and all these procedures and issues are new to them. Dr. Bierer shared that SMART IRB has developed a suite of 6-minute YouTube resources for investigators and their study teams, with "cheat sheets" to help them track who is responsible for what. However, Dr. Bierer said this is still just "touching the surface" of the need. It is very hard for study coordinators to negotiate the requirements of different studies, PIs and IRBs, and they are always "at the sharp edge of a mistake." Checklists, resources, and tools to help track workflow are needed. She added that during the COVID crisis, the consent process was different in different locations for the same research study depending on the incidence and severity of infection, social distancing, and institutional policy. While some institutions have seen no COVID cases, others are overwhelmed.

Ms. O'Donoghue reported that UR has instituted a Study Start-Up Consultation that can be used to train and educate the "one-off" investigator. The consultation program helps the new investigator understand roles and responsibilities, including where to go when questions arise.

Learning to speak SMART. Dr. Taylor observed that one interesting development is the new language disseminated through SMART IRB. If everyone "speaks SMART," it should help people collaborate. Dr.

Bierer agreed, noting that it once could take up to 120 days to establish a new reliance agreement. That process can now move as quickly as a couple days.

Challenges and benefits of collaboration. Ms. Singleton noted that a common theme throughout the workshop has been the power of working together. Perhaps we should place more emphasis on how to collaborate more effectively and how to foster a collaborative approach. Would this emphasis decrease efficiency?

Dr. Taylor observed that while on the one hand, everyone wants to do high quality IRB reviews, there must be a commitment to undergo change and take some risks in the short term. Creating SMART IRB took investment, energy, and resources, and the result has been increases in efficiency. Can we create an environment that is tolerant of risks and delays in the short term in order to have a collaborative approach? She believed that if the answer is yes, we can make progress.

Ms. O'Donoghue noted that collaborations are key to the success of the relying model, even if it may decrease some of the efficiency. Reviewing IRBs are becoming far less collaborative in recognizing and accommodating institutional policies (for example, compensation for injury). Where reviewing IRBs used to recognize this as an institutional policy, the pendulum may have gone too far in the opposite direction. For example, the UR encountered situations where it was told it must either accept the standard consent form language related to compensation for injury or pass on the study. She felt that some reviewing IRBs need to collaborate more than they do at present.

What are the challenges on which we need to collaborate? Dr. Bierer observed that some require collaboration and some are relatively simple and straightforward. She would like to see a deeper understanding of local context and diverse participation in research, areas she believes IRBs have not yet shouldered as their responsibility. A new level of analysis is needed to address the responsibilities to society in clinical research.

Dr. Johnson opined that certain types of studies and issues call for more voices and greater involvement on the part of relying IRBs. One example is exceptions from informed consent, an issue on which participating sites need to be able to provide meaningful feedback to the single IRB.

Ms. Singleton said that while Johns Hopkins has had numerous positive collaborative experiences in the last few years with many good outcomes and products, she still sees gaps in tougher areas and conflicts among deep-seated institutional philosophies and approaches. While a good base has been built to assist in collaboration, perhaps a new SMART work group is needed to tackle some of the thorny issues that still require commitment to a more collaborative approach.

Diversity and inclusion. Dr. Bierer said she had been part of a 2 ½ year project on diversity and inclusion in clinical research (see the MRCT Center guidance and Toolkit available at: <https://mrctcenter.org/diversity-in-clinical-trials/>). Social justice issues are now in the forefront and have given us new insights into “just how problematic our system has been for so many years.” While some may disagree, Dr. Bierer believes that it would *not be* “scope creep” for IRBs to accept responsibility for addressing inclusion in clinical research.

Dr. Dawson said “amen” to the focus on diversity. She noted that the HIV research world has had this issue in focus for many years. There should be a larger conversation about how to ensure project budgets allow sufficient resources to support meaningful community engagement. This effort needs to be

underway well before the protocol begins its search for subjects. The field needs to have a larger conversation about how to really do this, not just give “lip service” to the concern.

What we need to know. Ms. Singleton highlighted the need to determine whether the single IRB model is working as well as it could or whether reviewing IRBs and relying organizations should be interacting with each other in different ways. Dr. Calvert noted that answering this question should be a major focus of an evaluation of the sIRB model, which should investigate how sIRB is being implemented and what does and doesn't work.

Noting that use of the model is no longer an option but a requirement, Dr. Bierer stressed the need for IRBs to engage in the evaluation process. Admittedly, they may fear exposure in research like Dr. Taylor's, but such efforts are critical to improve quality and understand its elements. Dr. Klitzman emphasized the need for data to capture various perspectives on efficiencies, cost savings, expenses, and other issues associated with the use of single IRBs. Dr. Calvert cautioned that future research should include investigators, whose satisfaction with the process seems to vary greatly from study to study, in part because of frustration in process variations (e.g., the sIRB process for an industry-funded study may vary from the process used for an NIH-funded study).

Dr. Taylor expressed concern that two tiers of research may be created – one that is done less effectively because resources are lacking, and one that is more robust. She would like to know more about how young or new investigators can be prepared to participate in this type of system and would like to encourage self-reporting. It would also be helpful to hear the perspective of more senior investigators regarding their experiences with the sIRB requirements.

Many of these questions are not new, Dr. Rosenfeld noted. Similar discussions occurred as independent IRBs began to serve as central IRBs. How can institutions make data-driven decisions? There is certainly a need for research, which requires money and someone to put these issues on a research agenda. However, Dr. Bierer observed, there is also a need for IRBs willing and able to engage in such research. Many of them are not compensated for their roles in the HRPP and participating in a research study, on top of other unpaid duties, may not be feasible.

Dr. Green added that the IRB is only one part of the HRPP and lives within the institution and a whole. Addressing the issue of collaboration therefore goes beyond the IRB itself.

Summary Panel: Where Do We Go from Here?

Reflections from moderators. Ms. Singleton invited each of the moderators to share closing thoughts.

Dr. Rosenfeld: The workshop has been wonderful, and everything that was said is of vital importance. It has also been an extension of a conversation the field has been having for a long time. He observed that all the speakers represent “outlier institutions” that have more resources, better trained staff, and more committed leadership than are common “in the rest of the world.”

Noting that it is power relationships that guide decision-making, he stressed the importance of giving greater power to research participants and increasing accountability to the public. This should be handled structurally, not as something dependent on leaders. He observed that while people, processes, and tools

are all important, tools and processes can become ends in themselves. We need better ways to address the issue of decisional quality and ensure that the right decisions are reinforced by appropriate incentives.

Dr. Dawson: The conversation was inspiring and highlighted issues that matter to everyone. Everyone agrees that there are many shared responsibilities, but it is still important to clarify who is responsible for what and to whom. This includes clarifying how local context can best be communicated and understood. Geographic and socioeconomic issues, including access to care, all have implications for potential subjects' receptiveness to research participation. Single IRBs need more clarity on what they actually need to know in this regard and what kinds of information are salient for various types of studies and situations.

Ms. Singleton: One area in which more dialogue is needed is how to identify types of studies that do not work well with the single IRB model and should qualify as exceptions. It should not fall on the shoulders of the PI to make this case on a study-by-study basis.

The idea that HRPPs can leverage resources across organizations through collaborating under a sIRB model is an exciting one. She would love to consider ways to further the collaborative nature of sIRB review in order to enable reviewing IRBs to tap into the expertise available at relying institutions to improve communication and share knowledge.

While the general perception is that IRBs are not willing to be part of the evaluation process, in fact this is often due to lack of time and resources. IRBs need support to make their participation possible (for example, resources to support the collection and sharing of HRPP data).

Reflections from panelists. Ms. Singleton invited panelists to share closing reflections.

Dr. Klitzman: It would be helpful if OHRP, PRIM&R, and the IRB community encouraged NIH to fund the research needed to make this model work. One challenge is getting participation from IRBs at major for-profit organizations, which must be part of the discussion.

Dr. Green: It has taken an enormous amount of effort to try to make this system work without even knowing for sure that it is a good idea. He hopes that data demonstrates it really does add value but remains skeptical.

Dr. Taylor: The single IRB approach has not changed the burden, but where it falls. It would be great if all our decisions could be empirically informed and data driven. However, the likelihood of the Common Rule being changed again in our lifetimes is probably slim. We need to think of the single IRB mandate as an opportunity and make the best of the situation. She hoped that the same conversation will not have to continue for years to come.

Dr. Dawson: She shares Dr. Taylor's approach – we need to make the best of it, hoping that in some future iteration of the policy world we will learn how best to reduce administrative burdens. That would give us a win out of this challenging situation.

Ms. Parreco: She hopes we will get closer to closer to defining quality as research progresses. The discussion of local context was super, both fascinating and frightening. We collect “tons” of data, but is it the right data? Are we evaluating and using it well? Finally, she appreciated the discussion of inclusion and would like to see this focus maintained throughout the review process.

Dr. Bierer: The workshop opened many questions about how we should and wish to work together to move the field forward, and SMART IRB would like to be helpful. She wondered where and how future discussions might take place. She believed that OHRP is open to hearing about settings where the single IRB option does not work well, but the only way to explore this is to have these continued conversations.

Dr. Rosenfeld. Anyone who participated in AEREO's discussions realized it was an act of charity for most participants. Leadership and resources are both critical, and it is important to remember that the HRPPs represented in this workshop are not typical of the way everyone works.

Megan thanked everyone for the robust discussion.

Closing

Dr. Lau thanked everyone involved, including those who have participated by watching the discussion. She also expressed appreciation for the NIH technicians who responded to the challenge of facilitating a workshop on two web platforms.

She agreed with panelists that the workshop has been only a step and hoped that leaders in the field would accept the challenge of carrying the discussion forward.

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Online Resources

[AEREO: The Consortium to Advance Effective Research Ethics Oversight](#)

AEREO is a consortium of leaders in human subjects research oversight, research ethics, and empirical methods. Consortium members work collaboratively to advance an empirical research agenda to support evidence-based approaches to research ethics review, oversight, and policy. Its site offers research and resources aimed at improving effectiveness and efficiency.

[Central Institutional Review Board for the National Cancer Institute](#)

The NCI Central Institutional Review Board is dedicated to protecting the rights and welfare of participants in cancer clinical trials.

[The History of the CIRB](#)

[CIRB SOPs](#)

[Clinical Trials Transformation Initiative](#)

The initiative is a coalition of 80 organizations that seeks to “develop and drive adoption of practices that will increase the quality and efficiency of clinical trials.” CTTI has developed a variety of publicly available tools, including resources to improve informed consent and tools to promote patient engagement in clinical trials. It also has single IRB Projects that have developed resources and a framework to assess NIH’s single IRB mandate.

[Single IRB Projects](#)

[Evaluation Framework for the NIH Single IRB Policy](#)

[National Center for Translational Sciences SMART IRB Platform](#)

[RedCAP](#)

REDCap offers a “free, easy-to-use, and secure method of flexible yet robust data collection.” The REDCap consortium continues to actively develop the software.

The [Streamlined, Multisite, Accelerated Resources for Trials \(SMART\) IRB Platform](#), designed to help grantees comply with NIH’s mandate that single IRBs be used in multisite trials, offers a sample authorization (or reliance) agreement and guidance documents, among other resources. Selected resources include:

[Institution vs. IRB responsibilities](#)

[Authorization agreement](#)

[Worksheet for developing a communication plan](#)

[Evaluation Checklist for the use of Central IRBs](#)

[University of Rochester Office of Human Subject Protection](#)

The University of Rochester has developed a number of tools for its own use that may provide useful models for other institutions.

[Guideline for Human Subject Research Data Security Requirements](#)

[Guideline and Flowcharts for when the University of Rochester is the Reviewing IRB](#)

[Guideline and Flowchart for when the UR Relies on a non-UR IRB](#)

[University of Utah Single IRB](#)

The website offers the Electronic System Site-Control Model, fee model video, sIRB Education videos, and reliance consultation. Email to request internal process documents, organization chart, and job descriptions.

[The sIRB Process](#)