E&HR

Stakeholder Experiences with the Single IRB Review Process and Recommendations for Food and Drug Administration Guidance

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Table 1.
Stakeholder Characteristics

Stakeholder group	*Variable*	*No. (%)*
IRB representatives (n = 10)	Institution's sIRB experience with FDA-regulated trials	
	Both the reviewing and relying institution	4 (40.0)
	Reviewing institution only	2 (20.0)
	Relying institution only	4 (40.0)
	Type of IRB	
	Academic health system	6 (60.0)
	Community-based health system	2 (20.0)
	Independent	2 (20.0)
	IRB role	
	Director of IRB or human subjects protection office	3 (30.0)
	Executive officer of human subjects protection office	3 (30.0)
	Chair of the IRB	1 (10.0)
	IRB manager	3 (20.0)
	Years of institutional involvement with sIRBs	
	1 to 2 years	3 (30.0)
	4 to 5 years	1 (10.0)
	5 or more years	6 (60.0)
Industry representatives (n = 9)	Role	
	Director	7 (77.8)
	Manager	2 (22.2)
	Type of medical product produced*	
	Drug, therapeutic, or preventive	7 (77.8)
	Biologic	4 (44.4)
	Device	4 (44.4)
	Combination products	2 (22.2)
	Size of company	
	Micro-sized (market cap under $300 million)	1 (11.1)
	Small-sized (market cap of $300 million to under $2 billion)	1 (11.1)
	Midsized (market cap of $2 billion to $10 billion)	1 (11.1)
	Large-sized (market cap over $10 billion)	5 (55.6)
	Prefer not to respond	1 (11.1)
	Years of experience with sIRBs	
	Less than 1 year	1 (11.1)
	1 to 2 years	1 (11.1)
	5 or more years	6 (66.7)
	Unsure	1 (11.1)

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Table 1.
Stakeholder Characteristics (continued)

Stakeholder group	*Variable*	*No. (%)*
Investigators (n = 9)	Specialty	
	Emergency medicine	2 (22.2)
	Medical oncology	2 (22.2)
	Pediatric cardiology	1 (11.1)
	Cardiology	1 (11.1)
	Neurology	1 (11.1)
	Family medicine	1 (11.1)
	Pediatric nephrology	1 (11.1)
	Type of organization	
	Academic health system	6 (66.7)
	Community-based health system	2 (22.2)
	Dedicated research site	1 (11.1)
	Years of investigator experience	
	1 to 10 years	2 (22.2)
	11 to 20 years	3 (33.3)
	21 to 30 years	4 (44.4)
	Type of FDA-regulated clinical trial*	
	Phase I	
	Drug, therapeutic, or preventive	4 (44.4)
	Biologic	1 (11.1)
	Device	1 (11.1)
	Phase II	
	Drug, therapeutic, or preventive	7 (77.8)
	Biologic	4 (44.4)
	Device	1 (11.1)
	Phase III	
	Drug, therapeutic, or preventive	9 (100.0)
	Biologic	2 (22.2)
	Device	3 (33.3)
Regulatory/study coordinators (n = 6)	Type of organization	
	Academic health system	3 (50.0)
	Community-based health system	3 (50.0)
	Years of clinical trials coordinating experience	
	1 to 10 years	3 (50.0)
	11 to 20 years	1 (16.7)
	21 to 30 years	2 (33.3)
	Coordinators' institutions' experience with FDA-regulated clinical trials*	
	Reviewing institution	1 (16.7)
	Relying institution	6 (100.0)
	Years of coordinators' experience with sIRBs	
	Less than 1 year	3 (50.0)
	More than 5 years	3 (50.0)

* The respondent selected all that applied.

Table 2.
Stakeholder Quotations on the Benefits of the sIRB Review Process

Benefit	Quotation
Section 1: Consistency and standardization	
Consistency or coordination across sites	The assurance [is] that the study is being conducted the same across our consortium. —IRB representative, academic health system IRB
	The benefits have been that the standardization is available throughout the study and across multiple sites. Essentially, if something is discovered or applied to one site, we know it's going to then be applied to all the other sites that are participating through that IRB as well, and it's very helpful. —Regulatory/study coordinator, community-based health system
Informed consent documents	You can often work to streamline and consolidate how the patient informed consent is presented so there's equitable information across multiple sites. When you use individual or academic sites and their individual IRBs, sometimes there's just a lot of differences and multiple different levels of reviews that sometimes go into it. —Industry representative
	[Y]ou already have a consent template from the central IRB that works really well for patients. It doesn't have 50 pages that aren't needed. We don't change the wording very much at all . . . for consistency's sake across the board, every patient on the study is getting the same type of information in their consent form. —Regulatory/study coordinator, academic health system
Section 2: Speed and efficiency	
Faster review and approval process	With so many different sites, if you have a centralized IRB . . . it's more efficient from a standpoint of moving the process along. With a central IRB, you have a calendar date that you've set, "Okay, I want to have the IRB review completed by this date." If you had allowed several other different sites or multisite IRBs to review, they may not meet as often, they may not meet as consistently, so it would slow the whole process down. —IRB representative, community-based health system IRB
	I think, for me, [the benefit] is the speed of IRB approval. My experience has been using the central IRB that you can submit on an ongoing basis whenever you're ready to. Typically, you will get approval within a couple weeks' time. Once you have that approval, then any new sites that come on board would have an already approved consent form, aside from some site-specific changes that might be needed. The process for each individual site usually takes less time than it would if each site was using their own local IRB. —Industry representative
Reduced time to starting up a site and to adding new sites	Speaking from the perspective of our role in trying to serve our research community, [the sIRB review process] allows us to work very closely with our researchers to initiate the study and review it in an efficient manner to get all the sites up and running as quickly as possible . . . —IRB representative, academic health system IRB
	I think the main benefit for that is that trials can get started up faster. For example, if you're looking to add on a site during the trial, they can get added on pretty quickly. They already have a template ICF [informed consent form]. It just has to be modified for the site. The approval of the study has already been reviewed by the IRB, so when adding on a site, they already know that the protocol they have set up is ethical. They've done the paperwork already, so they just need to issue [an approval] for the new site. I think there is a huge element there in helping trials get up faster—which ultimately leads to—hopefully—getting drugs out there a little quicker. —Industry representative
	From an operational perspective of launching the study and getting it enrolled, the first and foremost [benefit] is speed. Going to one IRB that approves many sites' IRBs—or there's that one IRB approval—drastically has an impact on my

Benefit	Quotation
	ability to activate sites rapidly. When I have to go to multiple sites for their own individual IRB, then you're dealing with those IRB challenges and schedules again and again and again. —Industry representative
	I think for one thing, [the benefit is] the shortened time period for study startup. It's incredibly efficient. . . . At our institution, we aim to open a trial within 90 days of receipt. When we use the center IRB for any cooperative group trials, we can have those [studies] open in a week or two . . . I feel like [the sIRB review process] exponentially speeds up the entire process. —Regulatory/study coordinator, academic health system
Section 3: Streamlining and simplification	
Decreased administrative burden or workload	Right now, I would say a benefit of relying on another IRB is after the initial review, once we get into the modifications and continuing review time point. The benefit, of course, is that our workload is reduced as far as what we have to process through our IRB. That, from an administrative standpoint, is a plus. We have less workload. —IRB representative, academic health system IRB
	From a practical operational administrative standpoint, I see there just being less paperwork, less documentation to have to manage when working with a single IRB than with multiple IRBs. . . . When we amend a protocol, or if a change to informed consent needs to happen, that is managed just through a single IRB. That's much easier from a time perspective, and a money perspective, than if we had to do those same administrative tasks with more than one IRB. —Industry representative
Section 4: Quality	
IRB member expertise	[Another benefit] is also taking advantage of expertise that we may not have on our own IRB that the single IRB might [or] would have. —IRB representative, academic health system IRB
	[I]ndependent IRBs [have] access to a significant number of people as IRB members, so you get access to an enormous amount of expertise and is at your fingertips, which doesn't exist at an institution. —IRB representative, independent IRB
	[Other benefits] are the ability to get a better review by being able to concentrate more resources in an expert review panel. I think that at any given local institution, you wouldn't be able to usually put together a panel that had a lot of either medical specialty or regulatory specialty expertise because it's just only so much expertise at any given institution. When you have a national panel, you can draw from a much bigger audience, and it's much easier to put together a panel that is filled with research oncologists to review oncology trials, for example, where you wouldn't be able to do that at the local site where most of the research oncologists at that site are probably on the application. . . . The idea of a central or single IRB being able to pull together that kind of expertise is much more plausible in the distributed model. —Investigator, academic health system
	I think they're more credible [independent IRBs] because that's what they tend to do for a living as opposed to local sites that are constituted by well-meaning people but not necessarily truly understanding what their role as IRB is. —Investigator, community-based health system
Quality of review	A single IRB review allows for increased quality. . . . You're working with an IRB that would then have a much stronger positioning around the signs and the medicine, as they would be the IRB that would see your asset through from start to finish versus one IRB seeing you do your phase I work . . . a broader range of IRBs seeing your phase II . . . and a subset of those see your phase III. I think to get a single IRB view across your assets, they become much more familiar with that. Plus, they have to build their therapeutic area knowledge as well. From a quality perspective of the review, their knowledge of your assets and their knowledge of the therapeutic area becomes much stronger. And so, I think it increases the quality. —

Benefit	Quotation
	Industry representative
	I think the most important potential value to a single IRB is the equity of the performance of the IRB function. And the most important part of the equity of IRB review is that, if you can imagine that we actually had some measure that we could measure the quality of IRB review. Then, the quality of IRB review across sites would be a bell curve, would be the average quality, and then a few places that do better reviews and a few people who do worse reviews. The thing that is of greatest potential risk to human subjects, I think, are IRBs that do inadequate reviews, low-quality reviews. The fact that a single IRB may only do an average quality review gets rid of all those low-quality reviews. . . . We get the opportunity to make sure that low-quality IRB reviews get replaced by an average quality or slightly above average. I think that's the most important advantage. —Investigator, academic health system

Table 3.
Stakeholder Quotations on the Challenges of the sIRB Review Process

Challenge	Quotation
Section 1: Uncertainty at local institutions	
Lack of control and duplication of effort	I think that you have to be able to accept other institutional requirements, the same as I ask other IRBs to accept mine. I think that is very difficult . . . . I've had my IRB staff try to change titles in a consent form to match ours. I said, "No, they don't have to use our template. They have their own template. It's okay as long as the information's there." Again, many ways to do the right thing . . . .There's a lot of "it's not our way" when we're the IRB of record, and so I think it's hard for IRBs when they're used to their cookie cutter. . . . That's the other thing I stopped when I came here is everybody'd take the sponsor template and switch it to our template. Why? Why? Why are we making people retype things? . . . You shouldn't have to do them multiple times, and you shouldn't have to change things because it's your way of doing it. —IRB representative, academic health system IRB
	One major [challenge] is the expectation that we thoroughly review the protocol and tell the [single] IRB all the specific institutional requirements that might apply to the protocol. That's where I think there's actually an increased workload because we're essentially now doing a shadow review when we're not supposed to be doing any review at all. I prefer telling another institution here, in general, are the areas where there are unique [name of state] laws, here's some specific areas where we require certain consent form language, and things like that. I'd rather not do a review of the protocol to tell the reviewing IRB exactly what they have to do. . . . It's the sort of duplication of effort that the people who come up with the IRB review policy don't recognize happens. They think that IRBs are making things more difficult for themselves, or they're trying to hang on to work, or something like that. But, in reality, the single IRB is also putting work back on the institution, and that is work that is not counted as an official review. —IRB representative, academic health system IRB
	Sites have created processes whereby IRB review and approval is part of their whole institutional research administration. They've spent a lot of years integrating that, making it very efficient, and now are pulling this one function out of an integrated system. It creates local inefficiencies. For example, all of my investigators need to enter all the information still for an [sIRB] application into their local research administration system, because there [is] still a lot of stuff the institution needs to do even in a central IRB world. There's a lot of other approvals. . . . There's duplicate effort created by making people go through their institution for some approvals and another place for IRB approvals. —Investigator, academic health system
	I have to go to my own IRB to let them know that I'm going to [an sIRB] for this because they still feel somewhat of a fiduciary responsibility to the protection of patients at the center, and they still are responsible. At the end of the day, the buck stops with them, so there is more work for the investigator sometimes.—Investigator, academic health system
Local context information	I think there's such a wide range, depending on the site, as to what they consider local context. It makes it very challenging to accommodate all those requests. As a single IRB, we've had to decide these are within the scope of what we can do for local context, these things are outside of that scope. —IRB representative, academic health system IRB
Section 2: Decreased timeliness	
Delayed timeline	What often ends up happening is that [relying sites] end up having their initiation of their startup delayed or they're behind in recruitment because it took so long to get their final approved documents in place, while other sites that didn't have those requirements or didn't sort of throw up those roadblocks were enrolling months earlier. —IRB representative, independent IRB

Challenge	Quotation
Inefficient IRBs	One of the challenges is when you rely, you therefore become dependent on that IRB's efficiency. If that IRB is not efficient, you actually end up waiting a lot of time for things to go through that IRB that then come back to you. Like a simple, continuing review: you're dependent on the person there to put everything through [before] you could go back to your IRB and submit it. —Investigator, academic health system
Additional reviews	Even though our IRB doesn't do the safety review, there still is a series of in-house administrative steps which happen locally that seems to slow the process down. I'm still trying to figure out why that's happening. But, even though we don't do the review to our full IRB and it goes through an administrator review process, my university still has to sign off and accept the decisions of a central IRB. That takes time, and in our place, takes too long. —Investigator, academic health system
Section 3: Variable processes	
Different sIRB systems	The workflow is different for every different single IRB and different IRB system. So, it's very confusing for investigators to know exactly who they contact at their IRB, what happens, and who's facilitating contact with the single IRB. I think that a lot of the information flow, just in terms of getting it up and starting, is at times very challenging. It seems like the IRBs are sort of making it up as they go along and as the rules change. —Investigator, academic health system
Lack of policies	[One challenge faced when reviewing is] the division of responsibilities when it comes to event reporting and incident reporting, and I mean this in two ways. One is, what kind of things need to be reported to the IRB? The second meaning of that is, what happens if the IRB determines that something is serious noncompliance, or an unanticipated problem? Who's responsible for reporting? I think there's been sort of an eagerness for single IRBs to be the reporting entity, but the reporting responsibility in the regulations and the assurances, really rests with the institution conducting the research, and where the problem happened. I know we've had a couple of cases where there've been some turf battles about reporting out to OHRP or the FDA in multisite research where there's a single IRB. —IRB representative, academic health system IRB
IRB readiness	The single IRB that doesn't have an infrastructure in place quickly stands out as maybe their reviews are fine, but their ability to internally manage volume and complexities for our studies becomes a challenge. We end up finding ourselves escalating things to them quickly because a site is complaining that we submitted whatever the IRB's requesting and they haven't heard a response, or what the IRB's asking for doesn't make sense, which usually is because they don't understand the study. —Industry representative
Section 4: Insufficient communications	
Between the relying institution and the sIRB	Because of experiences we've had as being a relying institution and having trouble with communication, as a reviewing IRB, we've tried to set up paths that make it very easy for communication to occur. But within that model, you have to have the institution be willing to provide you with the right contact people and to keep that information up to date. —IRB representative, academic health system IRB
	It's very difficult to be in a situation where you're relying on an outside IRB and you're not able to get questions answered, and you're not able to talk directly with, for example, the IRB chair in case you have questions about how they reviewed something. If your only access is through an administrative coordinating center and you're prevented direct access to the IRB or to those making the decisions, we have found that to be extremely challenging. —IRB representative, academic health system IRB
	In a situation where you have a single IRB that you're relying on, and let's say they make a serious noncompliance determination . . . there's no indication that we would know about it before they'd report it to the FDA, and so then you leave the institution in a situation of they didn't know anything about it, and all of a sudden, they have a report that has gone to the FDA without any communication with the institution what has occurred. —IRB representative, academic health system IRB

Challenge	Quotation
Between the investigator and the local IRB	We still require protocols to be submitted to our IRBs so we can do an additional review of them. This is an administrative review really, not a scientific review. . . . But we've had a couple instances where our investigators didn't go through that process, they went directly to the commercial IRBs, and the commercial IRBs went ahead and approved those even though they know our process is they're supposed to get a sign-off from us. And it was just a breakdown in the process. —IRB representative, academic health system IRB

Appendix.
Recommendations for the U.S. Food and Drug Administration's
Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials[1]

This appendix lists all participant recommendations for content to clarify, add, and remove from the guidance document, divided by section. During the interview, we tailored the review of the guidance document's sections for each participant group, to align with their specific roles:

- All participants reviewed the sections on roles in ensuring IRB review and addressing local aspects of IRB review.
- IRB representatives reviewed the sections on IRB records and using a central IRB at unaffiliated sites.
- IRB and industry representatives reviewed examples of cooperative IRB review models.

Section	Section description	Study population and number of respondents	Section recommendations
Roles in ensuring IRB review	This section describes the roles and responsibilities of all entities involved in the sIRB process.	n = 32* IRB members (n = 10) Investigators (n = 8) Regulatory admin/study coordinators (n = 6) Industry representatives (n = 8)	Clarify • language throughout, making it more directive and less suggestive (n = 10); • roles of local versus single IRB, ensuring consistency to the Common Rule (n = 4); • terms, including better defining the various types of IRBs mentioned (n = 3); • terms, including ensuring consistency between FDA recommendations and other documents related to implementing sIRB (n = 2); • the role of the investigator's local IRB in the sIRB process (n = 2); • language throughout, making it patient-centric rather than institution-centric (n = 2); • how an institution's IRB can serve as an sIRB (n = 1) • procedures to follow for site refusal to participate in the sIRB process (n = 1); • the role of the Human Research Protection Program versus the IRB's role (n = 1); • language to indicate the focus is for U.S.-based sites (n = 1); and

Section	Section description	Study population and number of respondents	Section recommendations
			• who the sponsor is for investigator-initiated research (n = 1). Add • a matrix illustrating institutional roles and detailing the responsibilities of each entity (n = 7), • language that sIRBs must provide greater transparency in their compliance and review process (n = 3), • templates for reliance agreements (n = 3), • a rationale and supporting evidence for using sIRBs (n = 1), and • references to appropriate codes of federal regulations (n = 1). Remove the statement about an institutional IRB's ability to review, as it may lead to duplicate reviews (n = 6).
Addressing local aspects of IRB review	This section provides guidance for addressing issues related to the communities where the research will take place and describes possible mechanisms to ensure meaningful consideration of relevant local factors.	n = 33** IRB members (n = 10) Investigators (n = 9) Regulatory admin/study coordinators (n = 6) Industry representatives (n = 8)	Clarify • most relevant aspects of the local context that should be considered (n = 13); • the process for reviewing local context information, including how local information should be shared with reviewing IRB, who should oversee the process to ensure local context is being considered, and how to document consideration of local context (n = 12); • how the relying IRB can ensure local context is represented, particularly for vulnerable or underrepresented populations (n = 4); • terms including "limited review" and "local" (n = 4); • language throughout, making it more directive (n = 3); • language throughout, making it easier to read (n = 2); • IRB membership and qualifications, emphasizing appropriate representation of scientific expertise (n =

Section	Section description	Study population and number of respondents	Section recommendations

			1);
			• concepts including liability in sIRB review (n = 1); and
			• concepts including that giving consideration to local context is different from ensuring diversity in study populations (n = 1).
			Add
			• instruction for reviewing IRB membership to ensure adequate ability to review local context (n = 5);
			• a general local context form (n = 5);
			• language that other mechanisms, such as hybrid reviews, may be appropriate and provide additional examples (n = 3);
			• language identifying populations who are considered vulnerable (n = 1); and
			• contact information for questions about the guidance (n = 1).
			
			Remove
			• the section on local context, as it is not helpful (n = 8), including the information on the
			  ○ requirements for IRB membership/member expertise (n = 4),
			  ○ participation of consultants with relevant expertise in central IRB deliberations (n = 2), and
			  ○ limited review of central IRB-reviewed studies, focusing on issues of concern to the local community (n = 2);
			• consideration of local context, as it may not always be necessary to consider (n = 7) (e.g., local context is relevant only for studies involving special populations, and therefore, this should simply be added as an exemption to sIRB mandate); and

Section	Section description	Study population and number of respondents	Section recommendations
			• consideration of local context, because it is never practical to review, even at institutional IRBs (n = 4).
IRB records—documenting agreement and procedures Using a central IRB at unaffiliated sites	The section on IRB records describes recommendations designed to help IRBs fulfill the requirements to prepare and maintain adequate documentation of IRB activities and to follow written procedures for the conduct of initial and continuing review of clinical research and for reporting their findings and actions to the investigator and the institution. The section on using a central IRB specifies that at clinical sites that are not already affiliated with an IRB, the central IRB should document in meeting minutes or other records how it considered relevant local factors for the various communities from which research subjects are to be drawn and that it must also document its action in agreeing to conduct IRB review for the site.	n = 12*** IRB members (n = 10) Regulatory admin/study coordinators (n = 2)	Clarify • communication plans, including how relying institutions will assess qualifications of reviewing IRB, procedures for reporting noncompliance or unanticipated problems, and who is responsible for establishing the reliance agreement (n = 3); • the general scope of all reliance agreements (n = 2); • the purpose of this section (documenting agreement) by providing agreement examples (n = 1); • the various acceptable ways agreements can be documented (n = 1); • guidance is related only to U.S.-based sites (n = 1); and • terms, using them consistently (n = 1). Add • templates, including reliance agreements and memoranda of understanding (n = 3); • examples of different review committees, such as NCI's central IRB (n = 1); • specific documentation required to establish an agreement between an unaffiliated site and an IRB (n = 1); and • suggestions for how to resolve difference between reviewing and relying institutions (n = 1). Remove • the fourth example in section B ("How the central IRB assesses the ability of geographically remote sites to participate in the study") (n = 1).

Section	Section description	Study population and number of respondents	Section recommendations
Examples of cooperative IRB review models	This section provides examples to illustrate possible mechanisms that may be used to distribute IRB review responsibilities between an institution's IRB and a central IRB.	n = 16**** IRB members (n = 8) Industry representatives (n = 8)	Clarify • what is specifically mandated (n = 4), • who ultimately approves studies and amendments (n = 2), • how an institution's IRB serves as an sIRB (n = 1), and • the role of smartIRB (n = 1). Add • information on how communication between reviewing and relying institutions should occur (n = 4), • the potential benefits and value of each model (n = 3), • best practices (n = 1), • a model using commercial IRBs (n = 1), and • an updated list of other therapeutic-based sIRBs to model B (n = 1). Remove • models that are no longer relevant or are outdated (n = 3) and • language suggesting the optional nature of cooperation (n = 2).

* Data are missing from one investigator and one industry representative.
** Data are missing from one industry representative.
*** Two regulatory/study coordinators also provided feedback on this section.
**** Data are missing from one industry and two IRB representatives.

Reference

1. U.S. Department of Health and Human Services, Food and Drug Administration, *Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials* (Rockville, MD: U.S. Food and Drug Administration, March 2006), at

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/using-centralized-irb-review-process-multicenter-clinical-trials.