

NIH Grants Conference PreCon Event, Human Subjects Research: Policies, Clinical Trials, & Inclusion

Day 1, December 6, 2022

Essentials of sIRB Requirements

And I am Dr. Pam Kearney. I'm the Director of the Division of Human Subjects Research in the Office of Extramural Research. I am going to be your moderator for today's presentation. I'd like to introduce you to Ms. Lyndi Lahl. Ms. Lahl is a nurse practitioner by training. She has very extensive experience in human subjects research requirements, both working professionally and independently as an IRB member. She is currently the NIH Human Subjects Officer in the Office of Extramural Research. And, Lyndi, take it away.

Lyndi Lahl: Thanks, Pam. So as Pam mentioned, I'll be doing the Essentials of Single IRB Requirements. So the objectives that I'm going to cover during this session are reviewing the single IRB requirements under the revised Common Rule and the NIH Single IRB Policy. I'll be reviewing scenarios, so you'll be able to recognize when the single IRB requirements apply to an NIH-funded study, and I'll be identifying the type of justification needed for a single IRB exception request both to the revised Common Rule and to the NIH Single IRB Policy.

So let's talk about those single IRB requirements. So I'm going to first start off talking about the NIH Single IRB Policy. Now, this was initially released in June of 2016, so it's been around for over 6 years. Now, the effective date of the policy was changed a couple of times, and this was to provide institutions more time to ready themselves for the single IRB requirements. So the final effective date for the NIH Single IRB Policy was for competing grant applications with due dates on or after January 25th of 2018 and for contract solicitations issued on or after this date. Now with note, ongoing noncompeting awards with more than one domestic site conducting the same protocol are not expected to follow the policy until the recipient submits a competing renewal application. So this means that the date of the noncompeting award must be - that it must be compliant with the NIH Single IRB Policy would be the date that the competing renewal award is issued, and we've been seeing a number of those in the last year or so that have been coming up for competing renewal, have been renewed and started off they were not subject to the Single IRB Policy, but now they are. And the whole purpose, the reason that the policy was written this way was, it was the expectations that all multi-site research being done in the U.S. would eventually fall under the single IRB requirements. Now I do want to note that if an application that proposes an ongoing multi-site human subjects research study being conducted in the U.S. that did not previously have NIH funding but now has received funding, it will become subject to the NIH single IRB requirements when that award is issued. So even if it didn't have a single IRB in place when it started because there was no requirements because it

was not NIH-funded, once they receive NIH funding, then the single IRB requirement would likely apply if there's more than one U.S. Site conducting the same research protocol.

So let's talk about a little bit more detail on the NIH Single IRB Policy. The policy applies to domestic sites of a multi-site study when those sites are conducting the same nonexempt human subjects protocol. Now, there are some built-in exclusions to the NIH Single IRB Policy requirements, and these include international sites that are conducting the same multi-site protocol as domestic sites. The international sites do not need to be part of the NIH or do not need to fall under the single IRB. This also includes certain awards. Career development or K awards, institutional training awards or T awards and fellowship awards or F awards were not subject to the Single IRB Policy requirements. In addition, the NIH Single IRB Policy does not apply to other transaction awards or OT awards. Now, there are three types of exceptions to the Single IRB Policy. The first two exceptions are automatic, and that means that if automatically accepted, there's no need to submit a single IRB exception request. So the first automatic exception is when a single IRB review is prohibited by federal, state or tribal law, regulation or policy, and the second automatic exception is a time-limited exception for ancillary studies that are associated with multi-site ongoing studies. Now, the parent study and the ancillary study will become subject to the single IRB requirements when that ongoing parent study has its competing renewal award issued, and then the other type of single IRB exception must be requested by the investigator and will need to include a compelling justification, and we're going to talk about requesting exceptions a bit later.

So note that the Single IRB Policy applicability is in part when sites are conducting the same protocol, so I want to talk a little bit about what that means. So in general, the same research protocol means that the protocol is addressing the same research questions involving the same methodologies and evaluating the same outcomes. Now note I did not use the term identical when I was describing same protocol because there may be some variations in the protocol procedures due to local context. Also, to be conducting the same protocol, it doesn't mean that one award is funding all the sites that are conducting the same protocol. There can be multiple awards, including a different award for each site that is conducting the same protocol, and sites don't have to be conducting the entire protocol to be considered conducting the same protocol. They can be conducting only part of the same protocol and still fall under the NIH single IRB requirements. An example of this would be a site that is only recruiting participants, determining their eligibility, obtaining informed consent from the participants and performing select study procedures. This site would most likely be considered to be conducting part of the same protocol and then would be subject to the single IRB requirements when it's a multi-site study that involves more than one U.S. institution. I also want to talk about prime recipients. So when a prime recipient has subawarded all nonexempt human subjects research activities to another domestic site, now note that the prime recipient must perform a substantive role in the conduct of the planned research. They cannot just merely serve as a conduit of funds to another institution or party, and for this reason, NIH considers the prime recipient to be conducting the research as well, and therefore the Single IRB Policy applies.

So the original NIH Single IRB Policy required that applicants and offerors include a single IRB plan in their application or proposal. Now, the single IRB plan was intended for the applicant or offeror to describe the plans for use of the single IRB that will be selected. Now, since the release of Forms F and other later grant application packets, applicants no longer need to submit a plan that describes the use of a single IRB at the time of application submission. Now that being said, applicants that are required to use a single IRB are required to provide the name of the single IRB during the Just-in-Time submission before the award is issued, and I talked a little bit about Just-in-Time submission during the last session. Now when the applicant provides the name of the single IRB, this satisfies the Single IRB Policy requirement for a single IRB plan, and I do want to remind you that although applications no longer require that a single IRB plan is included, this does not mean that the applicant doesn't need to have a plan in place. Applicants will still need to develop and carry out a plan for using a single IRB when applicable because without a single IRB plan, a recipient will most likely have delays in implementing the portion of the research project that involves human subjects, and I have to say that I have seen this a number of times, and there isn't much that we can do except tell them, "You just need to get it in place."

So let's move now from the NIH Single IRB Policy to talking about the other single IRB requirement under the revised Common Rule. Now, the revised Common Rule at 45 CFR 46 was published in January of 2017, and the single IRB requirements in the revised Common Rule are found at 45 CFR 46.114, and these are known as the Cooperative Research Provision. Now, the compliance date for the Cooperative Research Provision pertains to research subject to the single IRB requirements that receives initial IRB approval on or after January 20th of 2020, and as was asked in the last session I want to repeat it here. Institutions conducting the same exempt research protocol and that need limited IRB review are not subject to the single IRB requirements. They can all use their own local IRB for exempt research that's being - multi-site research that's being done at more than one institution.

So now let's talk about the details for the revised Common Rule single IRB requirement. Any institution located in the U.S. that is engaged in cooperative research must rely upon approval by a single IRB for that part of the research that is conducted in the U.S. I know this sounds familiar because Yvonne talked about this as well. So I have one word and a phrase that I'm going to focus on, and it's not what Yvonne focused on. So the term engaged, this term is used in the phrase that the institutions are engaged in the cooperative research. Now, OHRP considers an institution engaged in a particular nonexempt human subjects research project when its employees or agents either, one, obtain data about the participants of the research through interventions or interactions with them, or two, obtain identifiable private information about the participants of the research, or three, obtain the informed consent of participants for the research. Now the phrase that I want to highlight in this same section is cooperative research, and this is defined by the revised Common Rule as research projects that involve more than one institution. Now please note that the single IRB requirements apply to all domestic multi-site nonexempt human subjects research regardless of funding mechanism.

Now, just as the Single IRB Policy has exceptions, the revised Common Rule also has some exceptions to the single IRB requirements, and the first is when more than a single IRB is required by law, and the second is when any federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular research context. Now please note that the federal department or agency for HHS-supported research is OHRP. It's not NIH. NIH does not have the authority to make determinations on exceptions to the revised Common Rule unless OHRP has determined a particular category for which the cooperative research single IRB requirements are not appropriate, and this leads us to the third exception. So the last type of exception to the revised Common Rule single IRB requirements is limited during the COVID public health emergency. This is the only exception for which NIH can review and potentially approve the use of this exception. I do want to note that this exception can only be used during the ongoing COVID public health emergency, so once the public health emergency is declared over by the Secretary of HHS, NIH will no longer have the authority to approve exceptions for research that is subject to revised Common Rule single IRB requirements.

Now, similar to the NIH Single IRB Policy, institutions that are the prime recipient of an NIH award directly from NIH for nonexempt human subjects research are considered engaged in the research project. This is true even when all activities involving human subjects are carried out by employees or agents of another institution. So if both institutions are located in the U.S., the revised Common Rule single IRB requirements will apply.

Now I want to spend a moment talking about reliance agreements. A reliance agreement or IRB authorization agreement, which is what OHRP calls them as well as how they're referred in the Grants Policy Statement from NIH, is a written agreement that details the responsibilities of the institution that's relying on the IRB and the reviewing IRB's responsibilities under that institution or organization that is serving as the single IRB of record and performing the IRB review. Now, to be eligible to serve as the IRB that is reviewing any NIH-supported research, the IRB must be registered with OHRP, and you did hear that from Yvonne with the last session. So it's the responsibility of the NIH recipient to ensure that there is a reliance agreement in place and ensure that there is a mechanism established for communications between the single IRB and the participating sites. The recipient will need to maintain a copy of the reliance agreement to document compliance, and I did see in the chat with the last session that somebody had mentioned SMART IRB, and SMART IRB is a mechanism that helps facilitate that reliance agreement, and if you don't know about it, you can go to the NCATS website, N-C-A-T-S, write SMART IRB, and you can learn more about this SMART IRB platform.

Okay, so there are a lot of similarities between the two sets of single IRB requirements, and this slide and the next compare the single IRB requirements to show the similarities and highlight the differences. So the applicability of the two single IRB requirements is similar. Now, the effective dates are different. As I mentioned, the NIH Policy has been around for longer. Its effective date was January of 2018, and the revised Common Rule was January 20th of 2020.

Now, the revised Common Rule does not have automatic exceptions for certain types of funding that are found in the NIH Single IRB Policy. The revised Common Rule also does not include any language that mentions the need for a single IRB plan. The revised Common Rule limits automatic exceptions to when more than a single IRB is required by law. Now if you think about the NIH policy, it says that when it's prohibited by law, regulation or policy, so the revised Common Rule does not allow those automatic exceptions if it is from a regulation or policy, only if it's a law. And under the revised Common Rule, new ancillary studies are not grandfathered in, and they will be subject to the revised Common Rule single IRB requirement. Again, if it meets the requirements that it is cooperative research being done at more than one U.S. institution, nonexempt human subjects research, and the exception request justification is different depending on which single IRB requirement the research project is subject. So speaking of exception requests, let's now spend a little bit of time talking about exception requests and justifications and other logistics.

Now, the applicant, offeror or the recipient will need to include the correct type of justification for the single IRB exception request, and this will be dependent upon if the research is subject to the NIH Single IRB Policy or if it's subject to the revised Common Rule single IRB requirement. Now, if the research is subject to the revised Common Rule single IRB requirement, the justification will need to address why a single IRB is not practical during the COVID public health emergency. If the research is only subject to the NIH Single IRB Policy, the exception request will need to include a compelling justification. Now please be aware that if the research is subject to both single IRB requirements, the exception needs to address the revised Common Rule justification. If an exception request is approved for research that is subject to the revised Common Rule single IRB requirement, it is also automatically approved for exception to the NIH Single IRB Policy. This means that it is not necessary to include a compelling justification for an exception to the NIH Single IRB Policy when the research is subject to both requirements. I do want to make sure I state this last sentence on the slide. Exceptions to the use of a single IRB are rare.

So let's talk about the details for the revised Common Rule single IRB exception justification. Now, research that is subject to the revised Common Rule requirements and that is ongoing or initially reviewed by the IRB during the COVID public health emergency is eligible for consideration of this exception. The justification needs to describe why reliance on a single IRB would not be practical during the COVID public health emergency. Now the request should be consistent with the scenarios found in the OHRP Guidance Document on Exceptions During the COVID Public Health Emergency, and the guidance includes the scenarios for which OHRP anticipates that it may not be practical to rely on use of a single IRB during the ongoing public health emergency. I recommend that you review the guidance for additional information, and I want to remind you once again that once the public health emergency is over, NIH will no longer have the authority to approve exception requests for research that is subject to the revised Common Rule single IRB requirement.

Now, if the multi-site protocol is only subject to the NIH Single IRB Policy, the request will need to provide sufficient information that demonstrates a compelling justification to the Single IRB Policy, and this justification should include why the single IRB cannot serve as the reviewing IRB for a particular site that's asking for an exception and why the local IRB is uniquely qualified to be the reviewing IRB for that specific site.

So I want to talk now about submitting an exception request. So during the pre-award phase, the process for submitting a single IRB exception request will start with the applicant sending a written request to the program official or program director. Offerors will need to follow the instructions in the RFP for submitting an exception request. So in general, the request will be submitted as an attachment with the contract proposal. Now please note the applicants and offerors do not submit the single IRB exception request directly to the NIH OD. They will need to submit the request to their respective PO, PD or CO. I also want to mention that applicants and offerors should not assume that their exception will be granted when they're considering what single IRB costs to include in the proposed budget. In other words, the proposed budget needs to reflect all necessary single IRB costs without an approved exception. And after an award is issued, the grants and cooperative agreements recipient seeking an exception to use of a single IRB should submit a prior approval request in writing to the NIH Grants Management official, and that needs to be done no later than 30 days before the proposed change and signed by the Authorized Organization Representative, and that's described in the NIH Grants Management Grants Policy Statement. NIH contract recipients should submit the single IRB exception request and justification directly to their contracting officer.

Now for NIH-conducted or supported research, NIH will review the exception request and determine if the exception can be approved. So it's the NIH Office of Director staff that process all exception requests. The OD staff will review the request to ensure the request includes all required information and confirm that the appropriate justification was included with the exception request, and it's OD officials that determine if the request meets the requirements for exception. After that's done, and it's done at a meeting, OD staff will notify the applicable PO, PD or CO of this determination via email. Now for grants and cooperative agreements, it's going to be the program officer or program director that will notify the applicant or the recipient of this determination, and for contracts, it's the contracting officer that notifies the offeror or the recipient of the determination.

So NIH OD staff and reviewing officials see a number of common issues with exception requests, and these issues include incomplete information that is submitted with an exception request. Perhaps there's no single IRB of record identified or there's no plan to put the single IRB in place or not all sites that need exception are listed. There could be an incorrect justification such that there's a compelling justification that is provided for a study that is subject to the revised Common Rule single IRB requirement. The one that should be submitted is why it's not practical during COVID to have a single IRB. There may be a justification based on the cost of the single IRB or the inconvenience to the researchers. Those are not appropriate

justifications, and they will not be approved. And the last thing I have on for this bullet is that there is a decision requested within a few days of submission because, "Gee, the award needs to be issued within a couple of days, so we need to get this exception request approved so we can issue the award." Well, that doesn't work very well. It takes a minimum of a couple of weeks from the time the OD receives the request until the meeting where the OD officials review, and then there is a letter that's written. So it does take a few weeks, and sometimes it takes months because we're not getting the information that we need.

So I do have some single IRB resources on the next page. There are a number of NIH guidance documents on single IRB. Certainly the revised Common Rule is also a good resource, and that OHRP Determination of Exception During the COVID Public Health Emergency is another one. When you have questions, I would direct you first to your program officer, program director or contracting officer for questions about single IRB. If you have questions that they cannot answer, there is a single IRB policy mailbox that you can submit those questions.

And now the last activity that we'll do before we go to the question and answer session is reviewing a few single IRB case studies, and I do want to disclose that all these case studies are based on actual scenarios that occurred with NIH awardees. So case study number one, you have applied to an NIH funding opportunity announcement with a due date of January 20th of 2023. You respond to question 3.2 in the PHS Human Subjects and Clinical Trials, or HSCT, Form, "Is this a multi-site study that will use the same protocol to conduct nonexempt human subject research at more than one domestic site," with a response of no. Your application identifies one domestic collaborative site where all nonexempt human subject research activities will be performed. This site has not yet received IRB approval. There are two questions for this poll. Is the study subject to the single IRB requirements? And two, which single IRB requirements apply? So thank you, DeRon. You just launched the poll. So I would like you to answer the two questions, and you need to type your answers in, limit of 200 characters for each. Is the study subject to the single IRB requirements, and which single IRB requirements apply? So we'll wait about 30 more seconds. Oh, and the poll just closed. Okay, so let's go ahead and look for the answers. So question one, is the study subject to the single IRB requirements? So the answer is yes. The study is subject to the single IRB requirements, even though you answered no in that question, and it looks like the majority of you got that right, so good job. Now the second question, which single IRB requirements apply? And it looks like there's kind of a split answer here. The study is subject to both the revised Common Rule single IRB requirement and the NIH Single IRB Policy. Now, the receipt date or due date for funding opportunity announcement is after January 25th of 2018, and the initial IRB approval date will be after January 20th of 2020. So this is a case where you're not only subject to the two requirements, it's because the applicant who is being considered for funding will be engaged in the nonexempt human subjects research when all human subject research activities will be conducted at a subrecipient institution. Remember, prime awardee that subs out everything to another U.S. site is considered engaged and under both NIH and the revised Common Rule, and therefore the single IRB requirements apply.

Okay, let's go on to case study number two. You are the PI of an NIH-funded multi-site domestic study with an award date of September 22nd of 2022. You received initial IRB approval from your local IRB in November of '22 and have begun to enroll participants. However, your IRB decides that they do not want to serve as the IRB of record for the other two sites. You submit a compelling justification that the study will be delayed if all sites must rely on a single IRB, and this is going to negatively affect the study accrual. You also state that the budget does not include the fees for a commercial IRB. There are two questions for this poll. One, which single IRB requirement applies, and two, is the single IRB exception request or exception justification sufficient? So please go ahead and write your short answer responses to this. We'll give you a little bit of time to address this, and when you're done ... Okay, it looks like the poll closed and ... waiting for the results, and okay, thank you. So for question one, which single IRB requirements apply? So it looks like most of you put that both requirements apply, and that's true. The study is subject to both the revised Common Rule single IRB requirement and the NIH Single IRB Policy. So the initial IRB approval date is after January 20th of 2020, and although the receipt date for funding opportunity announcement is not included in the case study, I know that it was in January of '22, and that means that the study is subject to both single IRB requirements. So, sorry for not giving that second piece to you, but it looks like most of you figured that one out on your own. Okay, so ... Whoops. Oh, there, okay. So now you have that. So let's go on to question two, and is the single IRB exception justification sufficient? And it looks like a lot of you said, no, it's not sufficient, and that's true. It is not sufficient. There is no information about why having a single IRB is impractical during the COVID public health emergency, so this request would not be accepted. It wouldn't even be considered. The request does not mean that the compelling justification would be met either if it was only subject to the NIH Single IRB Policy. Now, the PI should have been aware that the single IRB requirements would be applicable when she or he submitted the application and had months to get the single IRB in place, and cost is not considered a compelling justification from the NIH single IRB requirements. And as unfortunate as this is, I must say that I think the investigator would have benefited from having a single IRB plan in place. It probably would have been very helpful to them.

Okay, the third and final case study; you are the PI of a competing renewal application with an estimated award date of January 20th of '23. The original grant was awarded in May of 2016 and received initial IRB approval in June of 2017. There are seven sites involved in the research, including three in New York, one in Maryland, one in Washington state, one in Puerto Rico and one in Canada. There are three questions in this poll. One, which single IRB requirements apply? Two, which sites do not need a single IRB? And three, which single IRB exception justification must you address? So thank you, DeRon. You launched the poll. So we have three questions. They all require or they all ask for short answers. So please go ahead and take a moment to address if you think the single IRB requirements apply, which site would not need a single IRB, and which single IRB exception justification will you need to address? So we'll give you a little bit longer before the poll is ended. Okay, so the polls ended. So let's go ahead and

see the results, and it looks like the majority of you said yes, the single IRB requirements apply. So that is correct. So this award is subject to the NIH Single IRB Policy only. Note that the initial IRB approval date is before January 20th of 2020, so the revised Common Rule single IRB requirements do not apply. Now, when the competing renewal award is issued, the NIH single IRB requirements will apply, so the recipient will be expected to comply with the policy on the date that the award is issued. Okay, and now for the second question, which sites do not need a single IRB? And it looks like everybody or almost everybody said Canada. That's correct. Now I see a few that identified Puerto Rico as not needing a single IRB. So it is the site in the Canada that will not need a single IRB. I want to mention that Puerto Rico is a territory of the U.S. and therefore counts as a U.S. site, so Puerto Rico would fall under the single IRB requirements. And then for question three, which single IRB exception justification must you address? And it looks like the majority of you put compelling justification, and that is correct, compelling justification, since this study is subject to the NIH Single IRB Policy. So excellent, thank you very much.

So we are down to the end here. I had mentioned before that we have a single IRB policy mailbox, if you do have questions after the session, that you can send it to, and now I'm going to turn this over to Pam to see if we have any questions that I can address. Thank you.

Pamela Kearney: Great talk, Lyndi. We actually have a ton of really good questions in the Q&A, and we'll go to about 3:57-ish. I think it won't take us very long to wrap up. So the questions, as I was sorting through them, are kind of grouped together, so I'm going to try to get the general gist of some of the questions, but one of the questions that we have ... and there was at least four that were in this same vein about, which one should I follow, the NIH Policy or the revised Common Rule? That's the general gist of about four or five ones, and so I'll just throw that out to you. Which one should we follow?

Lyndi Lahl: Okay, well, it just depends. I don't like when I get the answer, "Just depends," but it's so applicable for this because it depends on when your NIH funding came in and when the initial IRB approval date was. So remember you have those two dates, and so you have to look and see when it's applicable. So if you're subject to both, guess what? You have to follow all of the requirements. If you're only subject to the Single IRB Policy, you need to follow the Single IRB Policy. If you're only subject to the revised Common Rule, and that does happen sometimes when ... think about an other transaction award, it's not subject to the Single IRB Policy. It would only be subject to the revised Common Rule. Then you'd have to follow the revised Common Rule, but essentially if you're subject to either one of those single IRB requirements, you have to have a single IRB in place for any site in the U.S. that is conducting the multi-site research.

Pamela Kearney: So and then, specifically there was a question about our training awards, the KTNF awards and which ones should they follow because the NIH policy doesn't include them, but there was a guide notice a little bit later that said, "If you are subject to the revised Common Rule, then you would have to have a single IRB." So that if you had IRB approval on or after January 20, 2020, then you would have to have a single IRB for the Common Rule. Another

question, can the single IRB be associated with one of the participating institutions, or does it have to be an outside commercial IRB?

Lyndi Lahl: Great question, and we certainly don't mandate that a certain IRB is going to be serving as the single IRB of record. We see often that it is one of the sites that is conducting the research for the award, so it could be the participating site. What we see sometimes is when there's a prime recipient, and they sub the award with all the human subjects research being done at a participating site, often the participating site will be the one that serves as the single IRB of record. So they would be reviewing on behalf of the prime recipient and on behalf of the research that's being conducted there. There, as Yvonne said earlier, commercial IRBs are another option. They tend to be on the costly side, but that's why you have to have your single IRB plan and you have to budget, and in your budget when you submit your application.

Pamela Kearney: We had about four or five questions regarding the prime awardee and the sub sites and what happens if one is doing one part or if the prime awardee was only doing analysis. Would these folks have to have single IRB? You basically answered that, but just because we had so many questions, why don't you address it again?

Lyndi Lahl: Yeah, so you remember the prime recipient of an award, even when all the human subject research activities, nonexempt human subject research activities, are being done not in the institution but in the subawards, they would still be considered engaged in the research, and therefore, if it's more than one domestic site, then single IRB would apply, and there would need to be single IRB for all of those domestic sites that are engaged in the research.

Pamela Kearney: Sadly, there's a whole bunch more, but you guys will have an opportunity. We have a big question and answer at the end of tomorrow's sessions where it's going to be all of the panelists. You can try to fit your questions in then, if your specific question we didn't get to it, but right now we need to wrap up. So a great big thank-you to Lyndi and the other panelists from today.