**Transcript**

**Humans Subjects Research Policies, Clinical Trials, and Inclusion**

**Day 2**

Lyndi Lahl: So, hello, and welcome to day two of the Human Subjects Research PreCon event. Thank you for taking the time out of your busy schedule to join us today. This NIH PreCon event is part of the larger 2022 and 2023 NIH Grants Conference presentation series. We have a fantastic team of experts from NIH and OHRP with us today, but before we begin, I would like to go through a few logistics. Now, today's overall event will run about 4 hours, and it'll include several breaks. The event begins at 12 o'clock and ends at 4 o'clock p.m. Eastern Standard Time. At the end of the event, we request your feedback. A short survey will pop up directly in Zoom. Now, please consider taking a moment to complete the survey, which the planning team will use to improve the quality and content of future virtual events. Now, during this live event, we invite you to be part of the discussion. For Q&A, all questions that you want to pose to the presenters should be submitted through the Q&A box. We will try to respond to as many questions as we can, but as there are hundreds of you and limited time, we may not be able to get to everyone's question. So to help us identify the most relevant questions for our audience, we invite you to use the thumbs-up feature in the Q&A to upvote a question. Now, the chat feature will also be open throughout the presentations. Please note that the chat should be used to share comments and answer questions that the presenters may pose to the audience, but do not chat to pose questions to the presenters. You need to do that through the Q&A. Some people find the chat to be distracting. Now, if you fall into this category, I recommend that you click the little arrow next to the chat tab in the navigation and turn off those notifications. Now, you can find all of the PowerPoint presentations in the NIH Grants Conference Center once you're logged in. You need to look for the Human Subjects PreCon Event page and in the Agenda Planning section of the lobby. Now, outside the conference center, you can find the PowerPoints on the Grants Conference website, and we're going to be putting the page with the listing in the chat, as well. Now, the current versions that are posted do not include case study Q&A, but we will be uploading those versions by the end of the week. I want to address a frequent question that we've been receiving. Will there be a recording? So the answer to that is yes. The recordings will be posted in 7 to 10 business days in the same locations within the conference site. So today, our day will consist of three different presentations that are focused on NIH policies: an Overview of the NIH Policies on Clinical Trials; Including Diverse Populations in NIH Clinical Research; and Using the eRA Human Subjects System. And at 3:15 p.m. Eastern Time today, we will be continuing the conversation with Q&A and include a panel of all of our OHRP and NIH experts who have presented during this two-day event, so don't miss out on a valuable opportunity to get your other questions answered that we haven't been able to get to previously. And, finally, I would like to remind you that this is a live event, so we ask all attendees to be respectful of one another in the chat. Please don't enter specific names of people or complaints in the chat. Instead, please direct any issues or concerns that you have via e-mail to our team at nihgrantsevents@nih.gov. Now, as we begin day two of our event, we would like to find out a little bit more about who has joined us today, so let's take a moment for a few polling questions to solicit this information, and here we go. So the two questions that we would like you to respond to are, "What is your primary role at your institution?" and, "What is your experience level?" So if you can take just a moment to address these two questions, that will be very helpful. And the poll is closed, and let's see who we have in the audience today. We have almost 1,000 folks. It looks like the majority of you are administrative and then scientific programmatic and other. Okay, and that's, I think, about the same as yesterday. So in terms of your experience level, most of you have at least 5 years' experience, and then almost 30 percent have between 1 and 5 years' experience, and then there's a smattering of other experiences. So thank you very much for providing that information to us. Okay, so thank you. We know that you're eager to get started on our first presentation, so let's go. So thank you for joining this presentation, which is on an Overview of NIH Policies on Clinical Trials. This presentation is 1 hour and 15 minutes long, and it will include not only valuable information on NIH policies related to clinical trials but also provide an opportunity for you to engage in some case studies and Q&A. My name is Lyndi Lahl, and I'm serving as the moderator for the first presentation. I'm the Human Subjects Officer in the Division of Human Subjects Research located within the NIH Office of Extramural Research. I am pleased to introduce to you your expert for this presentation, Dr. Pamela Kearney, who is the Director of the Division of Human Subjects Research in the Office of Extramural Research at NIH. Dr. Kearney is an otolaryngologist by training and has served as an IRB Chair of the combined neuroscience IRBs in NIH's intramural program for almost 10 years. Pam, I'm going to let you take it away. Thank you.

Dr. Pamela Kearney: Well, welcome, everybody. I'm really excited that you could come back for day two. This presentation, the very first one of the afternoon, we are going to talk about NIH policies on clinical trials. Let me see if I can ... All right. It's not going to work. All right. Before we get started, a couple of housekeeping things, you'll notice that this particular presentation wasn't uploaded yet on the resources pages. It will be almost immediately after this. At the end, we have some interactive cases, and all the answers are there in the presentation, and we didn't want all the answers to be there when you were going through this. For this presentation, you'll notice that there's a fair amount of text on the slides, and I did that on purpose because I want you guys to be able to utilize this presentation as a resource later, and I don't want you having to guess what was said on the slide. We'll still try to make it very interesting for you. And also, if I repeat a few things, I've done that on purpose throughout here. Pay attention to that because you may need that later on when we do our cases at the end. So let's get started. So our goals for today is, we are going to review NIH clinical trial policies. We're going to review how to go about determining if you are doing a clinical trial, and we're going to do some practice cases, and I want you to be able to understand where you can find clinical trial resources after you leave this presentation today. All right. Let's get started on NIH-defined clinical trials. So first of all, what is a clinical trial? And at one point or another, I feel sure that all of you have seen any number of these terms associated with clinical trials. Now, the NIH definition, which was released in a guide notice back in 2014, and people still refer to it sometimes as the new definition of a clinical trial. It's really not so new anymore because we're pushing almost a decade. And the definition covers a wide variety of types of clinical trials. And the definition, in short, is, number one, a research study in which one or more human subjects, number two, are prospectively assigned to one or more interventions. Number three, the study is designed to evaluate the effects of those interventions, and then, number four, the effects being measured are health-related biomedical or behavioral outcomes. And you can see from this little graphic that it's not just your classic applied drug study that a lot of people think of when they think of clinical trial. An NIH-defined clinical trial can be a mechanistic trial. It can be a pilot study. It doesn't even have to be powered. It can be a pilot clinical trial, and it can be even basic science, and we'll talk about that a little bit as we go. All right. So when you are filling out your application to get a grant at NIH, you're going to run across these four questions, and these four questions are going to look very familiar because they are literally pulled right out of that definition. And these four clinical trial questions, number one, does the study involve human participants? Are the participants prospectively assigned to an intervention? Is the study designed to evaluate the effect of that intervention on the participants? And, number four, is the effect that will be evaluated health-related biomedical or behavioral outcome? If you answer yes to all four of those questions, then NIH considers that you are doing an NIH-defined clinical trial. And what will happen in the application is, it will then direct you to fill in more information. You'll have trial-specific information that you'll be required to give NIH in order for it to be properly reviewed as a clinical trial. All right. So why do we even care? Well, number one, NIH has clinical-trial-specific FOAs, and we're going to talk about that. And then there are specific clinical trial requirements. Again, we're going to talk about each of these, the registration, results-reporting requirement, the GCP training requirement. There are monitoring requirements for certain clinical trials, and also importantly, if you misclassify your study, and you submit a misclassified clinical trial, it might even be withdrawn prior to it even being reviewed. So this is actually quite important. So the very first policy we're going to talk about, you are getting ready to apply to NIH. And the first one you're going to run into is the clinical trial funding opportunity announcement policy. We call it the FOA policy for short. It was announced in this guide notice, and you'll notice throughout my presentation I have a number of links to guide notices and web pages and that sort of thing. And what I've done is, at the very end of this presentation, there are about four slides where I pulled all of those links, and I've put them all in one place. So if you're utilizing this presentation as a resource, you don't have to guess and try to go through 70 different slides trying to find the link that you're looking for. So that will be there at the end. So the FOA policy at base says that applications that are involving clinical trials have to be submitted to clinical-trial-specific FOAs. Now, the purposes of this policy is really to allow NIH to better identify and track proposed clinical trials, and it ensures that key pieces of trial-specific information are submitted with your application, and it allows NIH to uniformly apply those trial-specific criteria during the review process. So the FOA policy requires that all applications after January 25 of 2018, so basically all of the ones that you are proposing now, all of the new ones, that are proposing one or more clinical trials have to be submitted to a clinical-trial-specific FOA. And applications that are submitted to an incorrect FOA are supposed to be administratively withdrawn without even being reviewed. So these are the different types of FOAs you may run into. There are actually more than this, but these are the basic ones. You might see a clinical trial not allowed FOA. You might see a clinical trial optional FOA, and you might see clinical trial required. There's also a special type of FOA that we'll talk about a little bit later on, which is a basic experimental studies with humans, or BESH, FOA, and those FOAs accept only applications that are proposing clinical trials that are also basic science. So what does the FOA policy mean for you? Well, what you're going to need to do is, you need to very carefully consider the work that you're proposing and make sure whether or not it is an NIH-defined clinical trial. And be sure because, as we mentioned earlier, NIH-defined clinical trials are much more than just that classic drug study that people may think of when they think of clinical trial. And you must choose a concordant FOA that matches your study. All right. Now, you've been funded. Congratulations, so now you need to actually do your study. So what's one of the first things that you need to do when you are putting your clinical trial together? Well, one of the first things you need to do is, you need to be compliant with the policy on Good Clinical Practice training for NIH awardees involved in NIH-funded clinical trials. We call it the GCP policy for short. It's outlined in this particular guide notice for your reference. There's also a web page if you want to do a little bit of a deeper dive after this and read more about that. I provide that link for you. The bottom line is, this policy was effective back in January of 2017, and it outlines GCP training requirements. Now, the purposes of the study is to make sure that everybody that's involved in the clinical trial has fundamental knowledge of the quality standards for doing a clinical trial, for designing and conducting it and recording, reporting, et cetera. And also, if everybody is trained in the fundamental knowledge of doing a clinical trial, it will help assure the safety of the participants in the clinical trials and make sure that the quality of the clinical trial is high. So the GCP training policy requires, number one, basically anybody that is involved in your clinical trial has to be trained, so this is the policy reads "staff involved in the design conduct oversight or management." So basically anybody who breathes on this clinical trial needs to be trained in Good Clinical Practice. The training is supposed to be consistent with the International Conference for Harmonisation. It's ICH. Harmonisation is spelled correctly there. It is for the document. The document link is here if you want to go in that document and see what those principles are. And the training needs to be refreshed every 3 years for those that take it. And when you do do this with your clinical trial, you need to make sure that you retain documentation of the training of the folks in your study. Now, there's no specific course or program that is outlined as required. So the GCP training can be achieved through any number of ways. You can have a class, a course. You can do an academic training program. You can do a certification from a recognized professional organization. The only thing that matters is that all of the principles of that ICH are included in the training. So NIH actually offers some free-of-charge GCP training. NIAID offers one. The link is here. Again, all of these links will be at the end of the presentation, as well, so you don't have to search through it to find it. The Drug Abuse Institute, NIDA, offers one. If you're doing social-behavioral research, you might want to consider looking at OBSSR's training. They have one, as well. Keep in mind, though, GCP training doesn't have to be done through NIH to meet the NIH requirement. Your own institution can have your own GCP training tailored to your own investigators and the work that you do, and that is completely appropriate and completely fine. So there are no specifications as to which training has to be done. Now, what does it mean for you? We've basically gone over all of this. You need to identify the relevant staff on your study that are subject to the requirement, and you need to arrange for them to get adequate initial GCP training, and then make sure you retain the documentation. Whichever way that you do this, whatever administrative way that you keep up with these sort of things, make sure that the person charged with this, which ultimately is the PI, but whoever on your study is charged with this, make sure that they keep the documentation because when 3 years rolls around, these people have to do the training again, and you'll need to retain documentation that they got the refresher trainings, as well. So now, you are moving on in your study. You've got everybody trained, and your study is underway. You have to be also compliant with the NIH Policy for Data and Safety Monitoring. Now, there are two guide notices here. You can see that they are from a while ago. One is from '98. The other one is from 2000. And we also have a web link, a web page, here that you can read. But the bottom line for this requirement is that every clinical trial has to have provision for data and safety monitoring. Now, this policy is required for all NIH-defined clinical trials, and keep in mind this is a misunderstanding that I hear frequently. Data and safety monitoring is distinct from IRB review, okay? The IRB is going to approve your data and safety monitoring plan, right? But the IRB is not your data and safety monitor, so keep that in mind. The IRB review is different. And the data and safety monitoring is the method that you put in your protocol to monitor the safety of the participants in your study and to make sure that you have integrity of your data. And the type of monitoring that you choose needs to be commensurate with the risk of your study. Now, there are a number of different types of monitoring that you can choose. If you have a very low-risk study, the principal investigator may be the one who is the named monitor. If it's a little bit more risky, you might have an independent monitor, someone who isn't involved with the study, but there's only one person, and they're doing the monitoring of your study. It could be even stepping it up a little bit more. You could have an independent monitoring committee of several independent people who work together as a committee to monitor your study. And then the highest level of monitoring is a Data Safety Monitoring Board or Data Safety Monitoring Committee. The word is dependent on your institution, which one they use: DSMB, DSMC. And this particular type of monitoring committee, the FDA has some guidance, and the link is here. And that guidance outlines requirements for the DSMB, its requirements such as, what is the makeup? What is the note-taking requirements for the committee? It's a little bit more formal. And those are generally reserved for higher-risk studies. Now, the Data Safety Monitoring plans have to be submitted for all NIH-defined clinical trials, and you have to submit a DSMP, and I highlighted the P because people get confused with DSMC, committee, DSMB, board. The DSMP, or the Data Safety Monitoring Plan, has to be submitted in your NIH application. And that plan has to address the overall framework of your monitoring that you are going to do. You have to identify the monitor that you have chosen, your IRB has approved, and it needs to describe the procedures for adverse event reporting to your IRB, to the FDA and to NIH. Now, each IC has different requirements for adverse event reporting. Some ICs require that all adverse events need to be reported to NIH, and others only require a summary report, so make sure that you know the requirements of the IC that has funded your study. Now, DSMB or DSMCs, NIH actually has some requirements for clinical trials that have to have this highest level of monitoring. And in general, all NIH-defined Phase III clinical trials have to have the DSMB, and all multisite clinical trials, regardless of risk, have to have a DSMC, and again, here is that same link to the FDA guidance. Now, there is one exception that I will say about the all multisite clinical trials. If you are doing a clinical trial that is Exemption 3, and, yes, it is possible for a clinical trial to be exempt, largely exemption, you'll see it in Exemption 3, which is the Benign Behavioral Interventions. If you are doing a study that is multisite that's an Exemption 3 study, NIH says you do not have to have a DSMB. You can use a type of monitoring that is more commensurate with that lower-risk type of study. All right. So what does the data and safety monitoring policy mean for you? Of course, you're going to choose the appropriate monitoring based on your study, the complexity, the size and the risk. Use the DSMB or DSMC if it's required. Submit the appropriate DSMP, your plan, with your application. Monitor the study, per that plan, and report the AEs as required. Remember, you have to monitor your study per your plan because that plan becomes part of the terms and conditions of your award, and if you don't monitor your study per your plan, you are in violation of your terms and conditions of your award. So make sure that you submit the plan, and you follow the plan. Right now, you're almost done with your study. You've conducted your study. You're getting close to the end, and now you need to be compliant with the dissemination of NIH-funded clinical trial information policy. Now, this policy, we generally refer to as the registration and results reporting policy. The guide notice is here, and it is complementary to a couple of other regulations. There's a section in FDA, and there's 42 CFR part 11. Again, it's beyond the scope of this talk to go into the details, but the links are here if you want to take a look. The bottom line is, all NIH-defined clinical trials have to register and report results in clinicaltrials.gov. And this is regardless of the study phase. It's regardless of the type of intervention. It can be a drug study. It can be a benign behavioral intervention. It can be basic science. It's subject, and it's regardless of whether or not you're subject to the regulation to register and report. And here is the website if you want to do a deeper dive on looking through that if you've got a lot of time to read. Now, the clinical trial registration and results reporting policy requires that you submit a plan on how you're going to be compliant with this with your application. And, again, like the DSMP, this becomes part of your terms and conditions of your award, so you have to follow your plan. You also have to include a statement in your clinical trial consent form that notifies the participants that summary results are going to be posted on clinicaltrials.gov. You have to register your clinical trial in clinicaltrials.gov no later than 21 days after you enroll that first participant, so pretty quickly, so once you enroll someone, you've got to get your study registered. And you've got to report summary results in clinicaltrials.gov no later than 1 year after your primary completion date, and these are very important. Now, there are some potential consequences of noncompliance. Registration and reporting are going to be verified by NIH before any remaining funds or funds for a future grant are given, so if you are looking to get funds later in the study, we can't release those funds if we see that the registration reporting hasn't been done the way it's supposed to. And you're not going to be able to submit your RPPR if your registration and results reporting are overdue. And if you are doing an applicable clinical trial, there are some actions and federal regulations that might kick into play. Right now, let's talk about a particular type of clinical trial because there are some temporary flexibilities for this type of clinical trial, and these are your basic experimental studies with humans. These studies are both a clinical trial for the NIH definition, and they also meet the definition for basic research. We have some great resources. There is a BESH website on the OER website that is really nice. It was put together by some program officials that handle these type of studies, and it's a really nice resource even for people who aren't doing basic science studies to take a look. There's also a podcast that you might want to take a listen to if you're interested or you do that type of study. Now, basic research, here's the definition. This is basically a systematic study that's looking for knowledge or understanding of fundamental aspects of phenomenon or observable facts. And there isn't a specific application towards processes or products in mind, and if it is both basic science and clinical trial, then it is a BESH, and this is important because some BESH have some temporary flexibilities for registration and reporting, okay? Here's the latest guide notice on that, and if the BESH is submitted to a designated BESH FOA, and remember in the beginning of the presentation, we talked about the different types of FOAs, clinical trial required, optional, and these designated BESH FOAs. If a BESH comes in through a designated BESH FOA, they can register and report in platforms other than clinicaltrials.gov through September of 2024. But it's only for those that come in through the designated BESH FOA. So what does the registration reporting policy mean for you? It means you have to submit the plan in your application. You have to register no later than 21 days after you enroll that first participant. You have to report your results no later than 1 year after the primary completion date, and you need to include a statement in your clinical trial consent that the summary results are going to be reported in clinical trials that go. All right. Now, there is one more requirement that we need to talk about, and this one, I'm always surprised that this is one that people aren't as familiar with. There's a requirement that you need to post a consent form if you are doing a clinical trial. This is a consent form that was used at some point during your trial. The requirements are here. It's actually in the revised common rule, and NIH put out a guide notice regarding our implementation of this, and I'm going to talk about here NIH's implementation of this. And the bottom line is, all clinical trials have to post a copy of the consent form used on a federal website. And for NIH studies, if you had an English-language consent form, you have a choice of posting it on clinicaltrials.gov, and the instructions on how to do that, I've also linked to that here. Again, all of these links will be at the bottom of this presentation, so you can find them easily. Or, you can submit them to a docket on regulations.gov, and that docket is also linked here. Now, if you have a non-English-language consent form, you have to post it on regulations.gov because clinicaltrials.gov is not equipped to take the non-English-language consent forms. All right. Now, here is a caveat for this. It sounds very easy, about posting your consent form, but there is a really tight window of time that will make you compliant. You can't post this until after enrollment closes, and then you can't post it any later than 60 days after that last study visit by any participant. So if you are doing your study, and you think you're going to get ahead of the game, and you just go ahead and post one of the consent forms, but your enrollment hasn't closed, your not in compliance. So you need to make sure that you wait until enrollment closes. So, again, whichever admin person is taking care of your timeline, again, it's the PI's responsibility, but make sure that you have this marked on your clinical trial timeline that when enrollment closes that you post this clinical trial consent form. And if you post it before enrollment, it doesn't count. All right. Now you're experts in the clinical trial policy, so now it's important to find out, am I actually doing the clinical trial? So let's take a look at clinical trial determinations. All right. We looked at these before. I'm not going to read them again because what we're going to do is, we're going to go through each one of these questions, and we're going to talk about some rules and pitfalls of each of these questions. Remember, if you answer yes to all four of these, you are doing an NIH-defined clinical trial. And a reminder, the devil is always in the details. I've had people come to me, an investigator added an aim four. They weren't doing a clinical trial, and then they added an aim four, which added this kind of pilot type of efficacy clinical trial, and it kicked them into clinical trial territory, so be careful that you don't have a paragraph or two in there that has kicked you into clinical trial territory when you didn't think you were doing one. And remember, if any one part of the application is a clinical trial, the application is a clinical trial, so even if it's aim 10 or it's one part of one of your studies kicks you into clinical trial territory, the whole project has to be classified as a clinical trial. And remember, NIH-defined clinical trials are so much more than those classic drug studies. So, people, if you're not thinking about, what exactly is an intervention, that it can be a probe, it doesn't have to be a drug, you might get tripped up. So keep this in mind. So let's take a look at question number one. Does the study involve human participants? I'm not going to spend a lot of time on this Lyndi Lahl did a very nice presentation yesterday, and OHRP actually did some presentations on engagement of research and human subjects participants. But the bottom line is, a human subject is a living individual about whom an investigator gets information or biospecimens through intervention or interaction and then uses studies, analyzes that information or biospecimen, or they obtain, use, study, analyze or generate identifiable private information or identifiable biospecimens, and that will make it human subjects. All right? Now, remember, exempt human subjects research is still human subjects research, and it is possible for certain exempt human subjects research to be clinical trials, and I'm thinking specifically of Exemption 3, the one with benign behavioral interventions, okay? So don't think just because it's exempt that it can't be a clinical trial, because it can. All right? And we've got some resources here. You can go to our human subjects website, and then I've got a couple of links to the Revised Common Rule if you want to take a look at those. Now, let's move to the second question. Now, the second question actually has two parts: the prospectively assigned and the intervention. So let's talk about prospectively assigned first. Now, prospectively assigned is just that predefined process that you have specified on how you're going to assign your research participants to one or more arms. In other words, you have decided in advance that this is the way it will be done, prospectively assigned, okay? So it doesn't matter if they're randomized. It doesn't matter how many groups. You can have one group. You can prospectively assign people to have an intervention in one group, and it doesn't matter how that group assignment is made. You can decide in advance that the participants are going to pick their own group. You can decide in advance that the physician is going to assign somebody based on their medical need. You can decide the investigators are going to put people in one of two or three groups. So it doesn't matter about how it's assigned. It only matters that you decided in advance that this is how it's going to be. All right. Again, I'm repeating this for a purpose. Randomization doesn't matter. It is the most common reason people come back to me and say, "I can't be doing a clinical trial. It's not randomized." Yes. Yes, you can, because randomization doesn't matter. All right. So, now, the second part of this is, are the participants prospectively assigned to an intervention? Now, an intervention is a manipulation or a probe of the participant or their environment for the purposes of modifying one or more health-related biomedical or behavioral processes or endpoints, okay? And remember that this is a probe. It doesn't have to be a drug. It doesn't have to be a big, risky procedure, okay? This can be health-related education training programs. It can be a computer application you're asking them to do. It can be a task that you're going to ask them to do in an MRI scanner. You can show them emotional faces. That is a task. It's a manipulation. It's a probe, and you're looking for the effect of that on something. Now, the one thing you need to remember is the intervention has to be done as part of the study. All right? So if you are just taking advantage of a program that somebody else is doing, a health department, an HR department or something like that, and you just say, "Hey, I'd like to know what the effect of that is going to be," but you are not doing the intervention, it's being done by somebody else and will happen regardless of whether you do your study. It's not a research intervention, okay? So that is not an intervention that you would count. All right. The pearls and pitfalls, question number two, again, randomization, number of groups, how the group assignments are made, types of manipulations or folks do not matter. I'm repeating this for a purpose. It's helpful to think of the intervention as the independent variable, and I think if you start thinking that way, you might be able to start identifying these. And don't mistake the intervention for a measurement. This is very, very common. Just because you're doing an FMRI doesn't mean that this a measurement, per se, okay? The BESH website actually has a really nice little paragraph on determining intervention versus measurement, and I would encourage you to take a look at that. I think the folks that put that together did a nice job. All right. Now, let's take a look at question number three. Is the study designed to evaluate the effect of that intervention, which you just identified in the previous question, on the participants? What I generally do when I'm looking at these is that I go through a proposal, and I look at all of the effects that an investigator is proposing to measure. And these are anything including changes in behaviors, changes in knowledge, intent to change behavior. Have you changed their intent to do something? So, vaccine study, you've got a program to increase vaccines, and you're going to measure whether or not folks had changed their intent to get the vaccine. That counts. It's often helpful for me to isolate how the effect is being measured so that I can kind of better identify the effects. If I can find the questionnaire and look at the questions, that kind of tells me what they're evaluating, and I find that a helpful step and that you might be able to use that, as well. All right. So, pearls and pitfalls, remember. Effect does not necessarily mean effectiveness. You don't have to be looking at the effectiveness of something, a drug or something. You're just looking at, did it affect it? Was there an effect of your manipulation, of your probe? Now, are these effects on the participants or an institution? Because if it's just on the institution, it's not a clinical trial. But be careful. Be careful, because if you're looking at institutional effects, sometimes, remember, devil in the details. Sometimes what happens is that investigators measure effects on participants, as well. Even though the main purpose is the institution, they've kicked themselves into clinical trial territory because they're also measuring things on the participants and the effects on the participants. So be careful. Any one part is a clinical trial, the whole project is a clinical trial. And it's helpful to think of the effects as the dependent variables, which are tested and measured. And remember, the words, designed to, simply means that you plan to do it, not that it's the main purpose of the study. I once had an investigator who was very upset that his study was classified as a clinical trial because the clinical trial part was in aim three, and he said, "That's not the design of my study. That's not what I'm intending to do. That's not what my study is designed to do." Well, it wasn't the main effect. It wasn't the main purpose. But you did design your study to measure it. It's an aim three. It's only a minor aim, but it is. So designed to doesn't mean main purpose. It just means that you're planning on doing it. Okay, so now, let's look at the last question, number four. Is the effect that you're going to evaluate a health-related biomedical or behavioral outcome? If the questions one through three are yes, in my experience, question four is almost inevitably yes, as well. I had one of my colleagues from OBSSR once joke to me that if you're applying to NIH for money, do you really want to say that you're not looking at biomedical behavioral outcomes? It was a joke, but it rang rather true. While this is not always the case, I find that it usually is. So once you've answered yes to one, two, three, look at question four very, very carefully, okay? And remember that these can include health-related knowledge and learning and intents to change behavior. Okay, now you've gone through all of that, and you're still unsure. Okay, that's good. We've got some resources for you. I would refer you to the NIH clinical trials website. On that website, there is a clinical trial decision tool. It's very basic. It walks you through the processes that we just talked about, but it's a helpful exercise if you're really having trouble sorting out the details. You can look at our BESH website, which I find to really help you kind of think about the issues. And then I would urge you to seek help from your program official. If you don't have a program official there's a nice tool that NIH has called NIH Matchmaker, and you can find this off of NIH Reporter. When you go to that website, I found it was a little bit hard to find, so I wanted to point it out to you. You kind of have to scroll down just a tick, and it's on the right-hand side near the bottom, and this arrow is pointing to it. If you click on that link, you're going to get this field and this text field here. You can type in your abstract. You can type in some text. What it will do is match you up with program officials and ICs who manage similar types of work as yours to help you identify folks that have expertise in your field. All right. Now, all right. So let's do some examples. Let's do some exercises, and for this I'm going to have you guys answer the questions here. So when I get to certain questions, I'll say, "Put your answer in the chat." And I actually am able - they've set it up here so that I can actually see the chat. There are so many of you. Don't worry about getting things wrong. I'm not going to be able to - I can see names, but there's so many I'm not going to be focusing on names. I'm just going to be focusing on the answers. So let's go through these examples and test our knowledge. All right. This example, FYI, is theoretical. It's completely fictional. Please don't do a critical dive into the science here, okay, because this example was put together just to demonstrate some points. All right. So let's look at it. We have a study that's going to design and implement a workplace mindfulness program. They're going to enroll employees of a company. They're going to randomize them to experience this mindfulness program versus not, and at baseline and then in 1 month, they're going to measure the participants' blood pressure, their cortisol levels, and they're going to administer a survey about stress levels. So is this an NIH-defined clinical trial? I'm already seeing some answers here, and I'm loving what I'm seeing. So this one is pretty straightforward on purpose, but we're going to go through each one of these questions, and we're going to talk about it a little bit. So does the study involve human participants? It does, so, yes, yes, yes, I am loving this. You guys are awesome, amazing, amazing. Okay, yeah, yes, the employees of the company. All right. What about, are the participants prospectively assigned to an intervention? And I'm seeing tons of yeses. I've yet to see a no. It's going so fast, some of them. Somebody wrote in some text that I couldn't read, and it flashed by so fast. The answer is yes. Participants are prospectively assigned to participate in a workfulness, mindfulness program. Somebody says, "Mindfulness is an intervention." Yes, indeed, it is. The mindfulness program is the intervention, and they've decided in advance that people will be doing this. All right. Number three, is the study designed to evaluate the effect of the intervention on the participants? All right. I'm seeing a lot of yeses. Excellent, excellent, and the answer is yes. They're going to measure the effect of the mindfulness program on blood pressure, cortisol levels and stress levels. All right. All of those are effects that they're measuring. All right. And then the last one, is the effect a health-related biomedical behavioral outcome? Yes, pre and post. I'm seeing a lot of yeses. All right. And the answer, indeed, is yes. So blood pressure, cortisol level and stress levels are health-related biomedical and behavioral outcomes. I did see one comment that flashed back really super fast, what they're measuring, the effects pre and post. Now, keep in mind you wouldn't necessarily - To meet the definition, it may not be good science, but you don't have to do the pre. As long as you are measuring an effect, you are measuring the effect, okay? So if you're measuring the effect, it doesn't have to be before and after. All right. Now, here is the summary slide. We've answered yes to all four questions, so, yes, you guys got this right. This is an NIH-defined clinical trial. All right. Now, let's go back here. I think I jumped. All right. So now, what we're going to do with this is, we're going to shake it up. We're going to use this example, and we're having questions in the Q and A, but I do see somebody that says, "Poll questions." There are no poll questions. We're just putting answers in the chat, okay? So we're just doing this because there are so many of these questions, the polls would have taken too long. So now what we're going to do is, we're going to shake this example up, and we're going to play what if, okay? So are the participants prospectively assigned to an intervention? So, now, what if there was no randomization? Is the answer to question two still yes? Put your answers in the chat. Is it still yes? Oh, you guys are great. I love this. I haven't seen a single no. Yes, that is correct. It is still yes, and it is still a clinical trial. What if there was only one group? You don't have that not-group. Everybody is going to get the intervention. Is the answer to number two still yes? Yes, lots of yeses, yes. All right. Correct, it is still yes. It is still a clinical trial because the number of groups doesn't matter. All right? Now, what if participants chose their own group? You didn't randomize them. You came in, and they were able to just pick which one they wanted. They didn't really want to do the mindfulness program, but they wanted to be in it, thought it might be a fun exercise. Yes, you guys are great. Yes, it is still yes. All right. Now, number four, the mindfulness program is being conducted by the HR department, and it's going to happen regardless of whether or not the study happens. Is this answer still yes? I'm seeing a fair number of nos, a few yeses, a maybe, a lot of nos, yes because they're measuring effect. All right. So, no, this is not a study intervention, okay? So the HR department is going to do this regardless of whether the investigators come in and do measurements on it. They are not doing this. It's not a research intervention. It's just something the HR department is doing. The investigators are just taking advantage of said thing, and they're observing what's going on. This is an observational study. It is not a clinical trial. So the answer to this would be no. This is not a study intervention if the researchers aren't doing the intervention. This going to happen regardless of whether the research happens or not. All right. Very good. Most of you got that right. All right. Now, let's go to question number three and do some what-ifs. So we're looking at evaluating the effect. What if the investigators are only measuring feasibility or usability of the mindfulness program only to see if it's possible to set it up? But we have more mixed answers. All right, a fair number of nos. Okay. So, no, it would not be. If they are truly only measuring the feasibility or usability of implementing a mindfulness program at this office, and they're not measuring any effect on the participants, they're just seeing, "Can it be done?" they're not measuring any effect on participants. So the answer to number three would be no, and therefore it would not be a clinical trial, because all four questions wouldn't be no. No. They're testing the usability and feasibility, and their surveys include questions about stress level. Is the answer to number three still yes? I'm just watching the scrolling, a lot of yeses, a few nos, a couple more nos. All right. The answer to this is yes. It is still yes because what they've done, and this is why you have to be so very careful with these feasibility studies, whenever somebody gives you one of these to review, you have to be careful about what they're actually measuring. If they are only measuring feasibility and usability, it is not a clinical trial. But if they go into this pilot effectiveness stuff, and it just seems like you investigators just can't help themselves, they've got to find out, could it possibly be working? Is it worth a bigger study? And they throw in some of these effectiveness studies, and if they start asking questions about stress levels to see whether or not that was something g on there, then you've now moved into clinical trial territory. And I see this somewhat frequently with investigators who go in, but it's a feasibility study, but, yes, you did a pilot effectiveness study on it, so it's still a clinical. That part is a clinical trial. If any one part is a clinical trial, the whole project is a clinical trial. So when you're designing these, or if your administrative and your investigators are designing these, make sure you point out because it would be very easy for them to do that in another study or something like that. But be careful you don't bump yourself unintentionally. Now, if you intend to do it, great, but if you're not intending to do that, don't unintentionally bump yourself into clinical trial territory. So now, what if they're testing the effectiveness of the mindfulness program, and there is a tiny, minor aim? We're still in an otherwise very large study that's not a clinical trial. So this particular study is aim six, and would the project still be designed to measure the effectiveness of the mindfulness program? And you guys are nailing this one. You're hitting it out of the park. Yeah. Yes, the answer to this is still yes, and it would still be a clinical trial. So now, let's do some what-ifs on question number four. What if they were only measuring the employees' learning and knowledge of the potential health benefits of mindfulness activities? They're not going to do the blood pressure. They're not going to do blood draws. They're not going to measure stress levels. They're just going to measure before and after their knowledge about the health benefits. You guys are great. I'm so encouraged. This is so amazing. Yeah. You guys are really hitting this out of the park. Exactly, the answer to this is still yes, okay? All right. Now, what if they were measuring the intent to go forth and engage in healthy activities? Is the answer to four still yes? Awesome. Awesome. I'm seeing an awful lot of yeses, and you guys are 100 percent right. It is still yes, therefore it's still a clinical trial. All right. All right. Now, that was great, guys. I'm really pleased. You guys did an amazing job. Now, what we're going to do is we're going to go into an example that is a little less obviously straightforward, okay? So this one also is a fictional study. It's adapted from our case study number 42 off of the clinical trial website. In this study, you've got a group of young, healthy adults that are going to perform a go, no-go task while undergoing MRI. The purpose of the study is to characterize the pattern of neural activation in the frontal cortex during response inhibition. So we're going to look at, is this one an NIH-defined clinical trial? All right. I'm seeing some mixed answers, so let's take a look. Let's go, again, question by question. Does the study involve human participants? This one is easy. I won't spend a lot of time. Yes, they're looking at young, healthy adults. All right. Let's look at question number two. Are the participants prospectively assigned to an intervention? All right. Is every some yeses, one or two nos, a few nos. All right. All right. More yeses, but a few scattered nos. All right. So the answer to this is yes. The intervention here is the go, no-go task. Okay, and it's decided in advance that these people will undergo the go, no-go task. The go, no-go task is a probe. It's a manipulation, okay? They are probing. All right? So this is an intervention. This is an NIH-defined intervention, the go, no-go task in this particular study. All right? All right. No, this is definitely an intervention, the go, no-go task in this study. They are probing something to get an answer here. All right? So is the study designed to evaluate the effect of the intervention on these participants? Right, this one, yeah. We're getting a lot of yeses. I won't wait any longer on that yes. They're going to measure the effect of the response inhibition on neural activation in the frontal cortex, so they're looking at the effect of neural activation of that response inhibition. All right. So lastly, is the effect that will be evaluated a health-related biomedical or behavioral outcome? And the answer is, yes. A pattern of neural activation in the frontal cortex is a health-related biomedical outcome. So with this example of the go, no-go task in the MRI scanner, they're probing the participants, and they're exploring a phenomenon. They're looking at the pattern in neural activation. Is this an NIH-defined clinical trial? And the answer is, yes. This would be an NIH-defined clinical trial. All right. As I can see, I expected the answers to be a little bit less definitive on this one because this one is not as classic. The other one was more classic. This one is an example of a BESH. It's a clinical trial that is also basic science, so this is an example of BESH that we've talked about. These are both NIH-defined clinical trials and basic research, and they're exploring understanding of fundamental aspects without any process or product in mind. And just to go back, and I would refer you also to the BESH web page that we have where we talk about measurement versus intervention, and they have a really nice little paragraph there. But now that we've established that this is a BESH, what type of FOAs can this BESH be responsive to? Now, it can respond to a designated BESH FOA. All right? It is a clinical trial, so it could respond to a clinical-trial-required FOA as long as that FOA allowed for it. Now, there are some FOAs that will specify that they won't take basic science or have some other reason why it wouldn't be able to come in. But theoretically it is a clinical trial, and it could respond to a clinical-trial-required FOA that will allow it in. Again, same difference, it can go into a clinical-trial-optional FOA as long as that FOA did not say that BESH could not. All right? So, all right. I'm not sure why my answers are showing up on that next slide. My animations got ... All right. All right. So this is unfortunate. My slide ... The animations got taken away. But what we'll do is, we'll talk about it anyway. So the answer is, will this study be required to register and report results? And the bottom line is, yes, it is a clinical trial, so it has to register and report results. Okay. So does it have to register and report in clinicaltrials.gov? And the answer would pop up, and I was going to ask you guys, would it have to? And the bottom line, that's a trick question because it depends, okay? It depends on what FOA it was responsive to. If it's responsive to a clinical-trial-required or optional FOA, and it's not a designated BESH FOA, if it's clinical-trial-required, then, yes, it will have to register and report in clinicaltrials.gov. There's no flexibility for BESH that come into those type of FOAs. Now, if it goes into a designated BESH FOA, these studies, these BESH, can use a platform other than clinicaltrials.gov through September of 2024, and I hope the rest of my animations are okay. No. All right. Well, it's okay. So the bottom line here, kind of spoiler alert, the answers are all up here. But talking about all of the rest of the clinical trial requirements, will the investigators on this BESH need GCP training? Yes. It's a clinical trial. They have to follow all of the clinical trial requirements, okay? The flexibilities are only for the registration and results reporting, and they still have to do that, but they can do it on different platforms through 2024. They have to submit and follow a data safety and monitoring plan because they are a clinical trial. You see the theme going on here. Will they have to upload the consent form in clinicaltrials.gov or regulations.gov? And the answer is, yes. They are a clinical trial, so they have to upload the consent like all of the other clinical trial requirements. So for more information, this is the BESH web page that I told you about. This is a screenshot of it. It's really nice in that it goes through each of the clinical trial questions, one through four, from a basic scientist's eye, from a basic scientist's point of view, and kind of explains it. I actually find it very helpful just in regular clinical trial determinations. And now, just going through some of the resources, we've put together a seminar resource document, which will be with all of the rest of the resources from this presentation, and that will have a fair number of the links on it. But the next four slides here, I just kind of did it by policy. This one has the definitions and the policy and the web pages and the podcast and that sort of thing. The next one has the FOA policies and GCP links on it. The next one talks about the data and safety monitoring requirements and the registration and results reporting links that we had. And then the last one has some links to the common rule and some instructions for posting the consent in clinicaltrials.gov and that regulations.gov docket. And then the last one are some of the Human Subjects ones, as well, and the link to the matchmaker on reporter. So now, you have become an expert in clinical trial policies at NIH. You have reviewed and practiced how to make a clinical trial determination, and you have reviewed some clinical trial resources. So I hope this was helpful for you, and at this point, we will be able to take a few questions.

Lyndi Lahl: Hey, Pam. There have been a lot of questions. NIH staff have been responding to a few of them, but we still have a lot more left. So there were a number of questions on DSMBs. One of those questions is, would a DSMB be required for a phase I multisite clinical trial?

Dr. Pamela Kearney: Yes.

Lyndi Lahl: Okay. That was ...

Dr. Pamela Kearney: Yes, because it's multisite. It's a multisite NIH study. It is, yes ...

Lyndi Lahl: Okay.

Dr. Pamela Kearney: ... because of the multisite part.

Lyndi Lahl: Okay, very good. Can you give an example of the difference between an intervention and a measurement? I think this came in a little while ago. I think it was when you were talking about BESH.

Dr. Pamela Kearney: Right. Yes, this actually ... Interventions in measurements are pretty easy to determine if you're doing a classic applied clinical study, a drug study. The measurements are your X-rays and your hemoglobins and your glucoses and that sort of thing. And the intervention is going to be the drug that you give. Now, it gets a little bit more nuanced when you start crossing into basic science. I like to think of a measurement in order for an intervention to be a measurement. Now, let; me give you a good example of where you have kind of this intervention that is an actual measurement, a known measurement. Think of a glucose tolerance test. A glucose tolerance test is a recognized way to help diagnose diabetes. A patient, not a participant, a patient, is given a bolus of glucose, and then they measure the glucose levels over time over 4 hours. And then they do that. But that is characterized. It's in the literature. It is a true measurement even though if you're kind of overthinking it, you could say, "Wait a second. The glucose is an intervention." Okay, but that is a well-characterized, well-studied measurement. Now, it is possible that you could have some research measurements that are so well-characterized in the literature that you would have to be using it to literally measure something. So I'm going to get myself in trouble here trying to do the science because this is not my area of science, but I'll try. So if you're doing a study in a flashing checkerboard, I understand that the effects of a flashing checkerboard in MRI is very well-known, and it's very well-characterized. So if you're going to use that, and you've got another intervention, so you're going to do something, and I'm just going to pick something out of the air, that you've got an agent that you're going to give the folks, and you're trying to explore some basic science things, and then you're going to put people on the scanner, use the flashing checkerboard, and you're going to measure with the flashing checkerboard and the MRI scanner the effect of that other agent, the other agent is the intervention. The flashing checkerboard FMRI is the measurement. Now, those, I understand, are quite extremely rare. Most of the time, the researchers are using the task as a probe. And if you're using that task as a probe, and you're using the MRI to measure the effect of that probe, then the probe is an intervention, not a measurement. So unfortunately this is not my area of science, so I hope I got that right. I'm channeling some of the BESH POs that I worked with on that. But in order for it to be a measurement, it would have to be very well- characterized as a measurement, and you're using it to measure the effect of something else. If you are using it, and you are just using it as a probe, if it's a probe, then it's the intervention. I hope that didn't make it clear as mud there.

Lyndi Lahl: No, that's great. Thank you. So someone asked the question, can you provide some more examples of what constitutes an intervention? Because it sounds very broad, meaning any manipulation of the person or the environment, regardless of the duration of that intervention, or is it invasiveness that makes it an intervention?

Dr. Pamela Kearney: No, you're absolutely right. It is broad. And, no, it does not have to be invasive. You can do the Zen effects of gardening. You can put them through a gardening intervention and measure the Zen effects. That's the clinical trial. It can be anything. It can be using a computer application. It can be any sort of probe. You can show people emotional faces, and you're looking at a particular response in a particular part of the brain. You're exploring that. That can be an intervention. So, no, it does not have to be invasive. It can be very, very benign. Like we mentioned earlier, you can even have interventions that are so benign that they're exempt from IRB review. Think of Exemption 3, those benign behavioral interventions. It is possible for those to be a clinical trial, which, by the way, is the only exception to that multisite DSMB requirement. So if you're doing an Exemption 3 study, and it's multisite, you don't have to have a DSMB. You can have a more appropriate, lesser monitoring. But, yes, interventions can be quite benign. It just has to be a probe or a manipulation of the participant or their environment.

Lyndi Lahl: Okay, great. So can you explain? How do you know if it is an effect?

Dr. Pamela Kearney: I ...

Lyndi Lahl: Yeah, that's all that they said. I think it was when you were going through the four clinical trial questions. How do you know if there's an effect?

Dr. Pamela Kearney: Well, the effect is what you're measuring. The effect is what you're measuring, so when you're thinking about the study, you do an intervention, and you're looking for the outcome. So the outcome really is the effect that you're measuring. So the effect, it can be just about anything. You could have a program that you're putting forth in the community to increase vaccine uptake for a particular illness, and you have this community program, so you are manipulating the environment of people. And then you're going to measure folks' change in their intent to get a vaccine. Does seeing these billboards, did that change your intent to get the vaccine? Are you more likely or less likely to get it? That would be the intent, would be the effect, of that campaign. So the effects can be quite broad. I hope that answered sufficiently.

Lyndi Lahl: Yeah, I think that there was a little bit of confusion if you don't have a pre and post test or a pre-lab and a post-lab that you're looking at baseline versus what happens afterwards. How can you say there is an effect?

Dr. Pamela Kearney: Well, I didn't say it would be good science. But again, for example, let's go back to that vaccine, the vaccine campaign where you've put out billboard and signs and radio ads and TV ads and that sort of thing around a particular event in a community. And you're going to enroll people who stop by the booth and ask them about the effect of that campaign that they had. You will not have a before. You're just going to be asking them. There was no way you could have asked them, what is your intent now? You can only ask them, before you saw it, what did you see? What did you think? And now that you saw it, what do you think and that sort of thing so that you would be measuring the effect there, and there would be no pre? So, yes, you don't have to have a pre-post. And, again, make sure that whatever you're doing, that the science is sound because you won't get funded if it's not. But, yes, it is possible to not have the pre-set and still be measuring an effect.

Lyndi Lahl: Okay, yeah. Thank you. I think that that is helpful to our audience. That seems to be what they were asking about.

Dr. Pamela Kearney: Mm-hmm.

Lyndi Lahl: So somebody asked a question. Does NIH awards dictate if the research study with human subjects is a clinical trial?

Dr. Pamela Kearney: Say that again. I'm sorry.

Lyndi Lahl: Does the NIH award dictate if the research study with human subjects is a clinical trial?

Dr. Pamela Kearney: Well, when you apply, when you submit your application, you have to indicate whether or not you're doing the clinical trial. And so that is what's going to determine it unless someone at NIH sees that you've misclassified it. So you can't really say, I guess, that it depends on the definition of NIH saying it, but if you are going to put it in your application, and then when it comes to NIH, they'll determine if it was misclassified or not.

Lyndi Lahl: Okay, thank you. So there's a question. If we do a trial to test whether navigation increases clinical trial participation, they're assigning people to be navigated or not. Are there any ethical problems in not offering navigation to a group?

Dr. Pamela Kearney: All right. I don't know what you mean by navigation.

Lyndi Lahl: Well, they didn't really explain that.

Dr. Pamela Kearney: Mm-hmm.

Lyndi Lahl: Yeah, I'm assuming that there are people in the community that are helping to get people into different services, and possibly a clinical trial is one of them, and ...

Dr. Pamela Kearney: So, well, I guess rather than looking at the specifics of it, your clinical trials all have to be IRB-approved, so you need to make sure that whatever you're proposing, that it is ethical and that the IRB agrees that it is.

Lyndi Lahl: Okay, excellent. Thank you. So there were a few questions as you were going through the scenarios. So in the scenario, or we can just say a scenario, that only one aim of the proposed research is a clinical trial and that the only aim required to meet clinical trial requirements including registration and reporting ... Wait. Wait a minute. In the scenario that only one aim of the proposal is a clinical trial, that is the only aim required to meet clinical trial requirements including registration and reporting. Is that correct?

Dr. Pamela Kearney: Correct, and I can have Dawn jump in here, too. But what will happen is, that application, the project code will be clinical trial, so the whole project is going to be flagged as clinical trial. But when you actually start ... I'm sorry. The study level codes will be different, so, Dawn, can you jump in with the coding, with the whole ... The whole project has to be clinical trial, but then each of the studies will be coded differently.

Dawn Corbett: Right.

Dr. Pamela Kearney: And only the study will have to meet the registration reporting and that sort of thing.

Dawn Corbett: That's right, and so depending on the kind of grant, application that you're submitting, you may have one or more studies in that grant. Some of them may be trials, and some of them won't. So you're entire project will include in the notice of award terms and conditions, which indicate whether or not a trial is included, and you'll need to meet those terms and conditions. But in terms of registration and reporting, it would only be for those studies that were designated as clinical trials.

Dr. Pamela Kearney: Oh, and, Lyndi, just jumping back to the question that we had previously about the effect, something that I forgot to mention is that if you're trying to figure out what your effect is, it's helpful to think of the effects as the dependent variables that are going to be tested and measured. So I'll just kind of throw that out there, as well.

Lyndi Lahl: Okay, thank you. So I just want to mention we have 5 minutes left in this session. Oh, actually, 1:25 p.m., are we supposed to be done right now, Cynthia?

Cynthia: I think we're out of time.

Lyndi Lahl: Yeah, I was thinking that it was 1:30, but I have a note to myself saying it was 1:25. We are done. I am so sorry. I missed the 5-minute warning.

Cynthia: We could go on all afternoon. Let's keep going, so .. .

Lyndi Lahl: Okay. Well, because we are done, we're going to stop the Q and A for now. Remember, at 3:15 we are going to have another opportunity to be answering your questions. So thank you, Pam, for sharing your expertise on clinical trials, Dawn, for jumping in on that last question, and to everyone who joined us for today. Now, remember, the PowerPoint and related resources are located in two locations, one on the NIH Grants Conference website and the second inside the virtual NIH Grants Conference Center. And Pam's slides are going to be uploaded later today, is my understanding. So look for the Human Subjects Research Pre-Con Event page, and you'll be able to find them there. So I'd like you to take a moment to stretch, refresh or even check out our exhibit hall resources. We'll be returning in about 5 minutes for our presentation on diverse populations in NIH clinical research. Thank you very much.

Dr. Rebecca Favor: Hello, everyone. Thank you for joining today's presentation focused on including diverse populations in NIH clinical research. During the next 45 minutes, our presenter will be highlighting some important information related to diversity and inclusion in your clinical research followed by the opportunity to get your questions answered during our Q and A portion. My name is Dr. Becca Favor, and I'll be the moderator for today's presentation. I serve as the NIH Human Subjects and Inclusion Policy Analyst in the NIH Office of Extramural Research. Now, let me introduce your NIH expert on the topic. Dawn Corbett is the NIH Inclusion Policy Officer within the Division of Human Subjects Research in the Office of Extramural Research here at NIH. Dawn, take it away.

Dawn Corbett: Thanks so much, Rebecca. So today, I want to talk to you about including diverse populations in NIH-funded clinical research. And to start out in our discussion, I first want to discuss NIH's longstanding commitment to ensuring the inclusion of diverse participants in our research. This commitment goes all the back to 1986, when NIH first established a policy encouraging the inclusion of women in clinical research studies, which was largely developed out of concern that women of child-bearing age were routinely excluded from clinical research studies. In 1994, it became a requirement that NIH include women and members of racial and ethnic minority groups in all clinical research studies, and this was based on the NIH Revitalization Act, which became law in 1993. In 1998, requirements for inclusion extended to children, and when we found there were similar concerns about the inclusion of children in clinical research studies, we made a small change in 2015 to change the definition of a child to an individual under 18. It had previously been an individual under the age of 21. And then in 2017, we had some new changes in response to the 21st-Century Cures Act, which was passed in 2016. We had new requirements for reporting of NIH-defined phase III clinical trials, which I'll talk about a bit later. And then in 2019, most recently, we started requiring inclusion of individuals of all ages in any research. So I'm going to talk about those requirements in depth in this presentation, but I do want to acknowledge that despite all of these efforts over the years, we are still not where we want to be, and this is where you all come in. So while we'll be talking about requirements and forms and things that you need to fill out, what we're really looking for here is a paradigm shift, and we need all of you for that paradigm shift. I think this was illustrated quite nicely in a recent report from the National Academies of Science, Engineering and Medicine. This was published earlier this year. There were a number of recommendations for NIH and others involved in inclusion, but among the insights was that without a paradigm shift that looks beyond tactics and process-oriented changes, disparities in research access and inclusion will persist at the expense of minority population subgroups and the nation's public health. So I want to keep in mind that what we are trying to achieve is we're trying to achieve science that answers the question for all of those with a condition that's generalizable and that's asking the right questions when needed. So with that, let me go into talk a little bit about what our policies are. So NIH has two inclusion policies, and the first is the Policy on the Inclusion of Women and Members of Racial and Ethnic Groups. And this requires that women and members of racial and ethnic groups must be included in all NIH-funded clinical research studies unless there is a compelling rationale for their exclusion. So what does this mean? This means that women and members of ethnic and racial minority groups must be included unless there is a good reason for not including them. What is a compelling rationale? So usually this should be based on the science. So, for example, if you are doing a study on prostate cancer, and you are not including individuals whose sex at birth is female, that's probably okay because the condition does not occur in that group. However, if maybe you're doing a study, and you want to exclude women because it's too expensive to do pregnancy tests on everyone, this would not be acceptable. In fact, the law specifically says that cost is not an acceptable reason to exclude groups. I would extend that and say, to NIH, convenience is not an acceptable reason to exclude these groups in research. If you're doing a NIH-defined Phase III clinical trials which these are these broadly-based prospective studies that compare two or more interventions, and for FDA-regulated studies, these are often the last step before approval. If you're doing these, they have some additional requirements that you have to do analysis of the primary outcome by sex or gender, race and ethnicity, and the progress of these analyses needs to be stated in your progress report, and you also need to report the results of those analyses in your RPPR project outcomes which is a section of your progress report that is made public and is available on the NIH report site. If you're doing a NIH-defined Phase III clinical trial that also happens to be an applicable clinical trial which means, generally, it's a drug or device, an FDA-regulated drug or device study, you also need to report results of those analyses in clinicaltrials.gov. So in addition to you other study results, you need to report the results of the analyses of your primary outcome by sex or gender, race and ethnicity in clinicaltrials.gov, and that's due at the same time as all the rest of your results, within 1 year of the primary completion date.

So our next inclusion policy is our Inclusion Across the Lifespan policy, and this policy requires that individuals of all ages must be included in NIH human subjects research unless there are scientific or ethical reasons not to do so. So this was an expansion of our inclusion of children policy, and the requirement now has extended to older adults and to the entire population, but if you're going to exclude people based on age, you need to have a reason based on science or an ethical or safety concern for them not to be included in that study. Again, for example, if you're studying pediatric cancer, and you don't have older adults in the study, that's okay. The condition does not occur in that group. And I also want to emphasize that if there are specific groups that are at higher risk, there's a scientific reason to study a specific group, that's okay, but you do need to justify it, and that justification needs to be based on the science or ethics. I have had an investigator say, "I don't work with children. I don't know anything about them, so I'm not going to include them in my study. Is that okay?" The answer is no. That sounds a lot to me like convenience, so I need something else to know that children should not be in your study. We would expect in that case that you would reach out perhaps to pediatricians or other groups and make sure that you have the study expertise to work with children, unless there was some other reason that children should not be in that study. There's some additional progress report requirements under the Inclusion Across the Lifespan policy. I should mention this applies to applications that were submitted for due dates January 25th, 2019 or later. So if you submitted an application, and it's been funded after that date, this applies to you, that in your progress report, you need to submit individual-level participant data on sex or gender, race, ethnicity and age at enrollment. So this is your Inclusion Enrollment Report that you will submit. I'll show you what it looks like a bit later.

But before we move on, I want to do a quick knowledge check. So DeRon, if you can, bring up our first poll. I'd like to ask the audience to respond, and the first question is, cost is an acceptable reason to exclude women from an NIH clinical research study, true or false? And go ahead and answer there in the poll. Okay, why don't we go ahead and pull up the results? Great! Almost all of you got this right, okay? Cost is not an acceptable reason to exclude individuals from a study. In fact, the law specifically says that women and members of racial and ethnic minority groups cannot be excluded from a clinical research study due to cost. Very good, thank you. Okay, so moving on, let's do one other quick knowledge check to make sure you understand our policies. Children may be excluded from a study on Alzheimer's disease because the condition does not occur in children, true or false? What do you think? And for this one, I'm going to ask that you use the chat. I think our poll is not quite working for this. You can just put it in the chat. Okay. All right. Very good, I see a lot of trues in there, and you are correct. The answer is true. If the condition does not occur in that group, the Inclusion Across the Lifespan policy specifically mentions this as one reason why you can do a study in a specific group.

So I mentioned earlier that this is really a paradigm shift in that we want you to be thinking about inclusion throughout the entire course of your study, from the time you're developing an application until you get to close out. We want to make sure that inclusion is a part of your study. In terms of the specific requirements for NIH, there's requirements at the time of your grant application or proposal. You'll need to submit inclusion plans and an Inclusion Enrollment Report. That information will undergo peer review and be considered in review. If you're doing a research project grant, that's considered under both approach and additional review criteria, and then for Just-in-Time, if you need to submit any information to NIH, we may request additional information on inclusion. And then finally, when we get to your study monitoring and progress report, you'll need to update us on your cumulative enrollment progress and also any progress that you've made on your analyses by sex or gender, race and ethnicity if you're doing an NIH-defined Phase III clinical trial. Let's talk about these a little bit more in depth.

Okay. All right. So what's required when applying for funding? So if you're developing an application, you're going to need to include plans for inclusion of women and racial and ethnic minorities and plans for individuals across the lifespan. You'll also need to include the minimum and maximum age limits of participants in your study and an Inclusion Enrollment Report. So let's talk about those. So all of this information will be provided on the PHS Human Subjects and Clinical Trials Information form. The relevant information on inclusion is in section two on study population characteristics, and you can see there are questions for the different plans, for the Inclusion Enrollment Report, and you'll also specify your minimum and maximum age limits there. So in your inclusion of women and minorities plan, you'll need to include a description of the plan distribution by sex or gender, race and ethnicity, and you also need to provide a rationale for the selection. Why does the population look the way that it looks? How did you decide what the demographics of your sample should look like? And you'll also need to justify any exclusions in this section. So for example, if you are not including women in your study, you would explain why you're not including women here. You also should describe any proposed outreach programs for recruitment. So if you're working with community advisory boards, or for example, if you have certain methods of recruitment that you're using, you should provide those there. It's also helpful to provide data if you have them in terms of why you're using certain methods and how you expect to be able to reach out to various groups using those methods. And then if you're doing an NIH-defined Phase III clinical trial, you will need to include plans for analyses by sex or gender, race and ethnicity. You'll include a separate Inclusion Across the Lifespan plan, and in that plan you'll need to provide similarly a rationale for the age distribution, so describe the age of your participants. Why did you choose participants of that age group? Explain how it will contribute to the analysis and again justify any exclusions. So if your age limits are, say 16 to 40, why did you choose those age limits? Why is it important to the science that you have participants of those age groups? You'll also want to provide a description of the study team expertise and the appropriateness of the facilities for included age groups. So the purpose of the policy is not simply to include people and try to put them into a study that isn't designed for them, but you want to make sure that you have the right study team expertise to deal with these populations and also make sure that you have the appropriate facilities.

So also in your application, I mentioned, you'll provide an Inclusion Enrollment Report. So the Inclusion Enrollment Report includes both the section with specific fields and some data tables. You have a few required fields. You'll need to provide an Inclusion Enrollment Report title and indicate if you're using the existing dataset or resource, so this is, for example, if you're doing a secondary analysis study or maybe you're using a repository. This is an example of an existing dataset or resource, and so you would answer yes to that question. If you're doing a prospective study, you'll probably answer no. You indicate whether enrollment is domestic or foreign. If you are including participants both within the U.S. and outside the U.S., you'll need to provide that separate tables for those populations. Then you'll include data tables both planned and actual data tables for your planned enrollment which is usually what you provide in an application, but if you do have actual enrollment, for example, if you are working with an existing dataset, you can provide that as well.

All right. So let's do another quick knowledge check. In the justification section of my inclusion of women and minorities plan, I should explain that the distribution of participants is based on local demographics. So what do you think, true or false? Okay, while we're answering, you're answering that, I will address, I'm sure, Polly's question. In a hospital setting that doesn't treat children, does the study still need to include children through collaboration? So, yes, if your scientific question is not limited to adults, so it really depends on the question that you're asking. All right. Let's look at the results of the poll. Okay, most of you got this right. Well, actually most of you maybe got it right. This was a bit of a trick question. So most of you said true, so my answer was a little different, tricking you guys a bit, which is false unless additional information is provided. So again, it's a bit of a trick question. You can explain the local demographics, but what we're looking for here is, what is the population that's appropriate to your study? And so this is something that we often see, and reviewers often comment on it, that the plans don't really include the rationale for the population that they're including. So in some cases, your local demographics may not be the appropriate population for your study, and you may need collaboration with other sites to be able to get the appropriate population, so keep in mind we usually expect participants to look like the people with the condition. If your local demographics don't necessarily support that, you may need collaboration plans. So unless you gave me some additional information, again, I would still need to know why did you just choose people based on your local demographics? How do we know that's okay? And you might give me something like prevalence or incidence and some evidence that people of your local demographics will actually participate in the study.

All right. So I'm going to move on. So the information that you submit in the application, as I mentioned, will all go to peer review. We have guidelines published on our website which indicates what peer reviewers are looking for when they're looking at your inclusion plans. Inclusion is considered in the score. It's reviewed both under approach and additional review of criteria for research project grants. For training and other awards, it may just need an additional review criteria. So review, besides including considering it in the score, will also consider whether each application is acceptable or unacceptable, and they do this through a series of codes that appear on your summary statement which are, as you can see here, at the bottom of the summary statement, there's codes for gender, minority and age. Each one of those will get a code. The first number just describes the population, but the second on describes whether it's acceptable or unacceptable. So you'll get an A if acceptable, a U if it's unacceptable. If you receive a U code from peer review, that application cannot be funded until any concerns are resolved, so that's something to keep in mind if you see a U code. You will likely have to provide some additional information to NIH before your study could be funded.

So let's do a quick knowledge check. For my RO1 application, peer review will consider my inclusion plans under approach and additional review criteria. True or false? All right. DeRon, can you show us the results? Good! So you all did very well, much better on this one. Most of you answered true, so yes. For an RO1 application, inclusion plans are considered under both approach and additional review criteria, and they are factored into your overall score.

Okay, so let's talk about Just-in-Time. So you made it through peer review. Now your application has - We've asked you for some additional information because it scored above a certain threshold generally. So some things to consider in Just-in-Time, for most of you, you will not need to submit anything during Just-in-Time, if you've provided all of the required information. However, if you did get an unacceptable code in peer review because they found your plan was not acceptable, you have to resolve those concerns prior to funding, so your Institute and Centers staff will likely be reaching out to you to discuss those concerns. And then if any information that you submitted maybe was changed either due to review or programmatic concerns or adjustments or maybe something was missing, the IC may reach out to you to ask or provide that information as well.

And then, now we've gotten to the NIH award. Congratulations. So once you've been awarded, now what do you need to provide? Well, every year in your progress report, you will need to provide cumulative actual enrollment data. So you'll provide us Inclusion Enrollment Report, and you'll tell us who you've enrolled over the life of your grant, and then for some situations, there are some additional requirements. So if you're doing an NIH-defined Phase III clinical trial, you will also need to report on the status or the results of analyses by sex or gender, race and ethnicity. And as I mentioned earlier on, if you're also in an NIH-defined Phase III clinical trial and an applicable clinical trial, then you'll also need to report those results on clinicaltrials.gov within 1 year of the study's primary completion date.

And the next special situation is delayed onset studies. So these are studies where they can't be described at the time of application, so you don't have full information on them. Often you'll have a restriction on your award for delayed onset studies, and you can't start them until you get approval. So once you can describe a delayed onset study, you'll need to provide all of the information you would provide for any other study. You need to provide the full PHS Human Subjects and Clinical Trials Information form once the study can be described, and that will include all of the inclusion information I mentioned earlier. In progress reports, if you come under the Inclusion Across the Lifespan policy which means you submitted your application January 25th, 2019 or later and you were funded, you will need to provide individual-level participant data. As I mentioned, those data are on race, ethnicity, sex or gender, age at enrollment. So it looks a lot like this, like a spreadsheet. It's submitted in a CSV file and uploaded into our system which Rebecca will tell you a little bit about in the next session.

Okay, let's do another quick knowledge check. Which of the following participant characteristics does NIH require to be reported in progress reports? Select all that apply. So your options are A: sex or gender, B: disability status, C: race, D: ethnicity, E: primary language and F: age at enrollment. So again, you'll select all that apply here. Oh, it only allows one answer, Daniel? Oh, okay. Well, thanks. All right. Well, you know what? You can put it in the chat if you want. I know it's quite a bit. All right. So why don't I just move to the answer then? DeRon, you can close out the poll. Thank you. So you need to include sex or gender, race, ethnicity and age at enrollment, not quite all of the above, Rosie. These two here, disability status and primary language, you do not need to provide for the purposes of the inclusion policy, but you do need to include sex or gender, race, ethnicity and age at enrollment. Okay. All right. So thanks, all of you. All right. Let's do another. Let's test your knowledge again, this time with a case study. I'm going to ask you to put on the hat of an NIH peer reviewer, and you tell me what you think about these situations, if you're a thumbs up or a thumbs down, I think, in your poll. Your answers will be yes or no. So if it's thumbs up, you can put out a yes. If it's a no, you can put a thumbs down. So our first case study, a research proposes a study investigating risk factors for eating disorders that will exclude males because the prevalence of eating disorders is lower in males than females. Yes or no, what do you think? If only peer review were this simple, I know, but we're simplifying it for today. And feel free to comment in the chat if you have a maybe answer. Okay, no. Okay, very good, right? So I like, Daniel, how you put it, "Lower does not mean nonexistent, and reporting is really bad in males, so it's probably underrepresented." Something that I keep in mind when I'm thinking about inclusion is, who's going to benefit ultimately from this information, and will there be gaps, right? So yes, the prevalence of eating disorders in lower in males, but that doesn't mean that it doesn't exist, and so I would need some kind of stronger justification than just this if I were going to exclude males from a study. And, Alex, you said, "What if, in this case, the justification has to do with something other than prevalence, different age of onset?" So this is an important point, Alex, and one of the conditions in which you can exclude populations is if a separate study is preferable and warranted. So the investigator may be able to make a case that a separate study in males is preferable and warranted because maybe the age of onset is different. Maybe the symptoms are different in severity. I don't know eating disorders, isn't my field. Yes, so absolutely the investigator can make that case. They haven't done it here, but they could make this better. Okay, let's try another one. Okay, so I give that one a thumbs down. Let's go to case study two. All right, DeRon. You can put this one up. So in case study two, a researcher proposes a study for a new drug that will exclude individuals over 60 because of the likelihood of hypertension in this age group. Yes or no, what do you think as our peer reviewer? And I will say don't assume any other information in these, just what's provided. Okay, this one is evenly split, yes or no, and I'm not surprised to see that. So I will say if I just saw this, I'm going to say no. Know why? So is hypertension a reason to exclude someone from a study? Well, certainly there are many studies for which it's appropriate, if there's a safety concern. The problem here is we're making an assumption that every individual over 60 has hypertension, right? What else could you do? Can anyone think of something else you could do besides excluding everyone over 60? How else could you think about this? Maybe you could exclude people with a certain blood pressure, right? You could do screening, exactly. So this is something to think about, and there may be cases where this would be appropriate, but I would suggest, based on this information, my preference would be that you do some screening of individuals. Not everyone over 60 has hypertension, and there are certainly people under 60 who do. So think about the people that you really do need to exclude and try to make your criteria as close to that as possible rather than using age or something else as a proxy. Okay, so great job on that one. Okay, now let's go to our last case study, and, DeRon, you can put up our last poll. A researcher proposes a study of glycemic control in adolescents and young adults 13 to 24. Other ages will be excluded because the study will target individuals at a unique developmental stage with higher risk of poor glycemic control than other age groups. What do you think, as the peer reviewer? Is including only individuals 13 to 24 appropriate here, yes or no? Okay, great! I'm very happy to see almost all of you got this right. Yes. What's different? Why? Why is this one okay and the other one wasn't? In this case, because a separate, right, they've provided a justification that a separate study is preferable and warranted in this group, and they've given us some information based on the science of why we need a study in this specific group. So they provided a justification where in others' cases, they haven't. I will say sometimes we think reviewers can just assume that a study may be appropriate or not, or they'll understand. Don't make assumptions, write your justification down in your inclusion plan. You don't have a page limit there so spell it out, so that they understand why you're including the groups that you're including.

Okay, so let's move on then from the case studies. I did want to make - Before we go to Q&A, I did want to give you all some resources when you're writing your inclusion plans and some things to think about. We had an Inclusion Across the Lifespan Two workshop back on September 2nd, 2020, and in that workshop we identified a number of recurrent themes of, kind of common sticking points for inclusion and things that could make inclusion better, and these are things that I think are helpful to think about as you're writing your inclusion plans. First is limiting inclusion and exclusion criteria are often a barrier to inclusion. So as we gave the example, instead of excluding individuals over 60, maybe you need to exclude individuals with hypertension or with certain measurements. So that's something to think about and also thinking about weighing the risks of exclusion versus participation. Yes, children are considered a vulnerable population. We need to make sure that we have protections in place when we include children. However, we also need to consider that if we don't include children, we're not going to understand how our knowledge applies to that group and eventually how treatments work in that group if they're not included, and so we need to make sure this is considered. Also, when you're designing your study, think about maybe your participants' experience in that study and caregivers' experience and thinking about minimizing participant and caregiver burden. It can be hard, as someone who's been a clinical trial participant and a caregiver of a participant, when you have multiple study visits, multiple procedures. These are the kinds of things we need to think about in terms of, how can we minimize the burden to the participant and to their caregivers? Also consider there's diversity within populations, and so groups are not a monolith. It's really important to have relationships with your local community and understand their individual needs and assessing and adjusting your recruitment and retention. So I would highly encourage you all to make sure that you're monitoring enrollment over the course of your study, not just once a year but regularly taking a look at it and thinking about, is this okay? Do we need to make adjustments or change course? And then finally they recommended researcher training and resources which today is one example of that. I also want to point you to our NIH inclusion data. So we take all the data that you provide us every year, and we aggregate it all, and we provide it for the public and for Congress on our NIH report site. We also provide this by research disease or condition. So I encourage you all to take a look at it if you're interested, and you can see who's included in NIH research. Finally, I want to point you to some resources before we get into the Q&A. Please take a look at our website. We have links to training, many resource documents. One document I want to point, in particular if you're developing an application, is on resources on the recruitment and retention of women, racial and ethnic minorities and individuals across the lifespan, where we've taken a number of resources across NIH that are available to investigators to help you think about these issues. Thank you.

Rebecca Favor: All right. Thank you very much, Dawn, for that very informative presentation. So we have quite a few questions in the chat or in the Q&A box. So I'll go ahead and read some of those so we can get started. The first question is, how do you determine who falls into the racial and ethnic minority group category?

Dawn Corbett: Yeah, so for NIH, we use the OMB categories which are mandated by the Office of Management and Budget for all federal agencies to use. So in terms of what you report to us, the categories that are considered racial and ethnic minority categories are American Indian or Alaskan Native, Black or African-American, Native Hawaiian or other Pacific Islander and Asian. So those are the categories provided. I will say that depending on the context that you're working, those may not be the most relevant categories to you, and it's always fine to collect more granular data as long as you aggregate those into our categories, and you can use fragmented subpopulations with which you may be working in your Inclusion Enrollment Report comment.

Rebecca Favor: Okay, great.

Dawn Corbett: I should also mention the categories are currently under review by the OMB. So there may be some updates, so stay tuned.

Rebecca Favor: That's good to know. Thank you, Dawn. All right. The next question is, how do you report or what do you report - Do you report sex at birth or do you report gender identity or both in your Inclusion Enrollment Report?

Dawn Corbett: So our policy gives you a lot of flexibility to report the information that's most important in the context of your study. So you're actually - You can report either sex or gender, and in terms of the time point at which you report that, that's really up to you. We don't specify it has to be gender at enrollment or that kind of thing. So you can set that based on the needs of your study and report it to us in the categories that we provide.

Rebecca Favor: Thank you. Along the same lines, there were a few questions related to more gender-inclusive definitions, and so for example, people who are nonbinary, both how they should report that and also kind of just what NIH's thoughts are at the moment.

Dawn Corbett: All right. And so we certainly have been hearing a lot of feedback about this, and there's been feedback across federal agencies. I know NSF has been working on this as well, and so we've been working with our federal partners in thinking about the best way that we can answer, we can ask these questions and get the information that we need. For now, if you are nonbinary, if an individual identifies as nonbinary, there's a couple of different ways that investigators usually use to report those individuals on our forms. One is if you're collecting sex assigned at birth, for example, you can report the sex assigned at birth of that individual. If you're reporting gender, and that individual does not identify with the female or male categories, you can include those in the unknown or not reported for now.

Rebecca Favor: Okay, thank you. And what you mentioned about having the IER comment there, that might be another way for them to specify, if they expect that there's a large number of people that identified that way, so thank you. The next set of questions, generally there were several questions about kind of what to do if your local population is not particularly diverse. So what would be something that researchers can do in that situation?

Dawn Corbett: So if your local population is not very diverse, or the clinic that you're working at or the university medical center does not have a diverse population, you're probably going to need to establish plans for collaboration. There are a lot of different ways to look at this. It kind of boils down to tapping into community leaders, either in your local geographic area or elsewhere, and you - that may mean partnering, for example, with another university. It may be partnering with a clinic somewhere else. So it kind of depends, but I encourage you to reach out to individuals within your institution to get a sense of who you might partner with and also to your NIH program officer. This is something that you can talk to them about as well. In addition to that, I'll mention we do have a number of resources on our website which you can take a look at which might give you some ideas about how to go about doing that outreach.

Rebecca Favor: Okay, great. Thank you, Dawn. All right. We have another question that asks, does NIH envision that in specific situations, researchers are encouraged to include prisoners?

Dawn Corbett: So I think certainly NIH supports research on prisoners, and I think there are study questions that are unique to prison populations. That being said, there are special protections in place for prisoners, and you need to make sure that those are followed. So, yes, there's no reason not to include prisoners in your study unless there was a concern, but you do need to keep in mind that there's special permission needed. There's special protections that are going to apply.

Rebecca Favor: Okay, great. Thank you.

Dawn Corbett: Sure. I will just use that question just to plug that because special protections apply to a population is not necessarily reason to exclude that population. We generally, for example, in excluding children, maybe it's a little harder to get consent, but there are ways to do that, and again, we have some resources on our website to help. Individuals, for example, with mental illness, there are ways to consent individuals with mental illness, and so I would really encourage you, before excluding groups of people because they have special protections, to look into see if your study can address those special protections.

Rebecca Favor: Okay, great. Thank you for that addition. So we had a few questions about studies that involve cohorts. This particular question is that if a cohort is an established cohort from a previously funded NIH study, but only part of that cohort is being included in a proposed study, is that an existing dataset or resource, or is that considered not to be?

Dawn Corbett: Yeah, they can get pretty complicated. I don't want to give you kind of a one pat answer here during the talk because I need to look at your study and if you're following up with people again and that kind of thing, but often if you're just doing a type two, and it's the same cohort, it's usually not an existing dataset or resource, but again, we'd have to look at particulars there.

Rebecca Favor: Okay, thanks. And so in that case, would it be best for them to just contact their program officer for additional information? Okay.

Dawn Corbett: Yeah, yes, please talk to your program officer, and we can look at the specific case.

Rebecca Favor: Okay, sounds good. All right. So we have a question here that is about multiple studies. So the person said, "As an administrator, how do you determine if you need a study record for each of the studies versus having a new Inclusion Enrollment Report?"

Dawn Corbett: Well, I think Rebecca might be touching on this a bit in our next talk, but what I will say is you can have multiple Inclusion Enrollment Reports on a single study. We may see this, for example, in a study that involves mothers and children. You may want to monitor them separately, and so you have one table for mothers and one for children. I always tell people, "Can you fill out the form completely and accurately?" And when you get to the point that you can't do that, that's probably a good indication you need a new study record. So if it really is a truly separate study, and you can't provide accurate information on the form because you can't fill out all those fields in the same way for both studies, then you'll probably need another study record.

Rebecca Favor: Okay, great. Thank you. So one more question here, this is actually similar to one of the local population questions, but this is a little different. So what is the policy if risk is far less in one group versus another, and so there's difficulty in enrolling participants in one group versus another on a study that's already occurring?

Dawn Corbett: So I - It's a pretty broad question, so I'm not sure how well I can address that. What I will say is your IRB will - I think I would talk to your IRB if there's concerns about risk to your participants, but risk may or may not be a barrier to participation, and I think one thing that we always want investigators to do is to be minimizing that risk. But I'm not sure if I understand the question. Rebecca, feel free to chime in, if you think there's something that I missed.

Rebecca Favor: Sure. I think that the person might be kind of alluding to what to do if they have low enrollment in a particular group during - while a study is occurring because they're not meeting their enrollment targets as they should.

Dawn Corbett: I see. So if one - if a certain - If you're not meeting your enrollment targets in a certain group, what can you do?

Rebecca Favor: Right.

Dawn Corbett: So if you're not meeting your enrollment targets in a certain group, I think ideally this is something that is addressed during study design. It's a lot easier to address it at that point. However, there are times that the best-laid plans of mice and men don't always go the way that we think. I would encourage you to reach out to your program officer to talk about what you could do. You also want to make sure that you're working with your IRB if you're going to be, for example, adding sites or new cohorts or that kind of thing, but again, at that time, there's a couple things that I've seen. One is you may need to establish a new collaboration if you're not able to recruit the population you need with the population that you had anticipated recruiting from. Another - Sometimes people will hire consultants, and those can often be very helpful, to help them strategize and come up with ideas or execute programs for outreach to diverse populations.

Rebecca Favor: Okay, thank you. So I think we have time for maybe one more question, and so we had a couple of people ask about consequences for not meeting your enrollment targets. Is there a way that researchers are held accountable?

Dawn Corbett: Yes, so your enrollment targets are part of your terms and conditions of award, and as I mentioned, in your progress report every year, you'll need to report your actual enrollment. While different ICs have different policies and ways of looking at this, the bottom line is absolutely if you're not meeting your enrollment targets, NIH can take a number of enforcement actions. Usually the first action will be talking to you and finding out what's going on, maybe seeing what we can do to change things, but for continued or serious problems, it can get as serious, for example, suspension of an award or funding.

Rebecca Favor: Okay, thanks. And then I think we have time for one more final quick question. Is there any flexibility related to the policies when it comes to feasibility or pilot studies?

Dawn Corbett: Well, there's not flexibility in the sense that the policy applies to everyone, right, and so I think your program officer is always going to be looking at your population, and peer review will be looking at your population in the context of the scientific question that you are asking, and so the context is going to be different perhaps for a pilot study or a feasibility study than an NIH-defined Phase III clinical trial. So that will be part of the consideration, but the bottom line is it needs to be justified in the context of the science, and that requirement is the same for all studies.

Rebecca Favor: Okay. Thank you very much, Dawn, and thank you to everyone for participating in this presentation. Remember that the PowerPoint and the related resources are available in two locations for you. The first is on the Grants NIH Conference website and then also inside the Virtual NIH Grants Conference Center. You can look for the Human Subjects Research Pre-Con event page for that. So now we're going to take a 15-minute break which will allow you to stretch, refresh or visit the Human Subjects Research booth along with others from all of our other awarding institutes and centers. That'll be in the Virtual Exhibit Hall, and there's also some available resources and helpful information that you can add and save to your swag bag. Thanks, everyone.

Dawn Corbett: Okay, welcome back from the break, everyone, and thanks for joining today's presentation which is focused on using the ERA Human Subjects System. During the next 45 minutes, our presenter will be highlighting some important information on this system and answering your questions. My name is Dawn Corbett. I'm your moderator for today's presentation, and I'm also the NIH Inclusion Policy Officer in the Division of Human Subjects Research within the NIH Office of Extramural Research. So now let me introduce to you our NIH expert on this topic, Dr. Rebecca Favor, NIH Human Subjects and Inclusion Policy Analyst, who is also within the Office of Extramural Research at NIH. Rebecca?

Rebecca Favor: Thank you, Dawn. So let's talk about the Human Subjects System. So the goals for today's session are to help you understand basically what the Human Subjects System is, or HSS, as we will be calling it for short just because the Human Subjects System is kind of a long name. So I want you to be able to understand what HSS is and describe the methods for navigating HSS. There is specific information that's required to be provided to us in the system if you have a study that is human subjects research that's not a clinical trial versus a clinical trial, and we'll go over that information, so you can understand those requirements as well as understand how to provide information and updates in HSS as well.

So to start off, let's talk about what's required pre-award for studies that involve human subjects research. So when you're filling out your initial grant application, there is a PHS Human Subjects and Clinical Trial Information form that needs to be completed for human subjects research studies. That form has five sections in it, and the sections that you complete are based on the type of study that you are proposing. So let's take a look at this table. The table outlines what's required for studies that do not meet the definition of a clinical research per NIH definition and those that do, and if you recall, the clinical trial designation is based on the response to four questions that are at the beginning of the PHS Human Subjects and Clinical Trial Information form. This is in section one, and if you answer yes to all four of those questions, your study is designated as a clinical trial. If the response to any of those questions is no, then your study is not designated as a clinical trial. Excuse me. So if your study is not a clinical trial, you're required to complete section one. You're generally also required to complete section two as well, except for some fields that are optional if your study meets the criteria for the exemption four. Section three is also generally required as well, and then there are a few fields that are not depending on the type of human subjects research that you're doing. On the other hand, if your study meets the criteria for a clinical trial, you're required to complete sections one through four and then also section five in some cases. This is only if the specific Funding Opportunity Announcement that you're responding requests information in that section. Otherwise, that section should not be completed.

So let's now fast-forward to the post-submission environment, or in other words, once you're submitted your research, and you are in the Just-in-Time process. You've learned that you're going to get your NIH funding. Once you're in that stage, then you will be required to provide updates to your information as you go through your study. The information that you provided in your initial application is then pulled into the Human Subjects System, and that's where you're able to edit it, make updates to your studies and that sort of thing. The Human Subjects System, or HSS, mimics Assist. So if you used Assist to complete your initial grant application, the screens and the functionality will seem pretty familiar to you. It's important to note that there are also specific permissions that are required in HSS, just as there are in Assist, to help you or allow you to be able to update information. So you'll need to get with your signing official to make sure that the correct role was assigned to you for you to be able to provide the updates that you need. As a note, updates in HSS to your study records can be made at any time, even though at certain periods you'll be required, for example, annually to provide updates to your records, so that we know what's happening at the time of your progress report.

This diagram outlines how the Human Subjects System interacts with other modules and other application types that we have. So again, for example, at your initial grant application, you fill out the PHS Human Subjects and Clinical Trial Information form, and eventually that information is pulled into the Human Subjects System, so that you can then make updates. You can access this information during the time of your RPPR through the RPPR module or, as I mentioned, anytime by directly going to the eRA commons to make updates that way, and I'll show you the way that you access those systems, so that you can make the updates at those times. In addition, our Human Subjects System also interacts with clinicaltrials.gov, and this happens in two ways. So first, the information in HSS can be used to initiate your clinicaltrials.gov registration if your study is a clinical trial because there are some fields in your study record that are mapped or is the same as study fields in clinicaltrials.gov. Additionally, clinicaltrials.gov information that you update after you've registered can be used to update fields in HSS. That way you can make sure that the information that we have in your study record is the same and is up to date with your clinicaltrials.gov information. I'll talk a little bit more about exactly how you do that a little bit further in the presentation.

So first let's talk about how to access HSS. So the first way that you can get into the system is by going into the RPPR module. So if you've completed an RPPR before, there is a section, Section G4, that is designated for human subjects. Within that section, there is a human subjects link, and when you click on that link, you'll be taken into HSS. The page that you land on is the application information page, and this is within HSS and the summary tab. There's some general information about your grant there. So it'll list the grant number, for example, the name of the PI, your organization name and the application status. So that's the landing page that you access when you first get into HSS that way.

The other method is to go in through eRA commons, and you go in through the status tab. So once you've searched for the list of projects that you have, you can access HSS through a human subjects link as well. For signing officials, it may look a little bit different than it does for PIs. So for example, for signing officials, you would click on the meatball icon, as we call it, or the dot, dot, dot that's next to the application ID, and you'll see a drop-down with some options for the human subjects link and a couple of other things. So you click on the human subjects link to go into HSS that way. For PIs, the human subjects link may be under available actions that'll be in the listing for your application or your award ID instead. Either of those will take you into the same application information page that I showed you on the previous slide.

So let's pause there really quickly to do our first knowledge check. So let's say that Dr. Cox has an RPPR that's due soon and needs to update the study record. What methods can Dr. Cox use to access the record, A: access to RPPR module and then click on the human subjects link, B: use the common status tab to search for the project and then go in that way or C: either is fine, D: neither is fine? I'll give everyone a couple of seconds to put their answer in the poll. All right. Looks like we have responses, and it looks like most people said C: either is fine, and that is correct. So even though Dr. Cox does need to update the RPPR, it's perfectly fine to first go in through the commons status tab and to search for the information that way or to go ahead and access the RPPR module and then go into section G4. Good job, everyone.

So now that we know how to access the system, let's talk about updating the information in the system itself. So the first thing that you'll want to do, once you land on the application information page and you need to make edits, is check the status that's listed on that page. So in the example here on the slide, the status is in Submitted status. When you're in submitted status, you're unable to make any edits, so you'll need to change that status to Work in Progress which is what is needed to make edits and to be able to go into edit mode itself. To do that, you'll click on the Update Submission Status button that's available under Actions under the panel on the left. It'll be on the left side of the screen. When you click on this button, a message box will open up that has a drop-down menu, and you can choose Work in Progress from there. Once you do that, you can click on the hyperlink text that says Continue Without Adding a Comment, or you can go ahead and add a comment, so you can note the reason that you're making updates, if you like, if that's important to you and your study team. Click Add Comment, and you'll save the information, and you'll save the status that you've changed it to.

So now that we've changed the status to Work in Progress, what information do you need to update? So for all studies, you'll need to update the inclusion enrollment data if you've begun enrollment on your study. You may also need to update the recruitment status or any other information that's required by funding IC or that's requested by a program officer. For clinical trials, you'll need to update the same information, but you'll also need to provide your NCT once you register your study in clinicaltrials.gov. You'll also need to update the clinical trial milestones which are available in section six that are required starting at your first RPPR.

So to edit your study and provide the information that we just mentioned, you click on the HSCT post-submission tab that's available on that first application information page that you land on in HSS. When you do that, it'll open up a page that lists the study records that are available on your project. Then there are two ways to start making edits. So first you can click on the Edit button that's at the top of that screen. It'll then populate an Edit button in the listing for each study record, so you can click on Edit on the study record that you want to see, or you can click on View to view a particular study record that you're interested in first and then click on the Edit button that opens up when that study record opens. Either way is fine. There's more information about how to go ahead and edit your study record in the HSS online help chapter How Do I Edit Studies?, if you need more information.

So we've learned how to access HSS, and we now know how to update the submission status and begin to edit information. So let's talk specifically about updating the inclusion information in your study. To update the inclusion information, you'll need to access your Inclusion Enrollment Report. This is found at the end of section two within your study record. So if you scroll down to section two, you'll see an Enrollment Report section where it lists each of the Inclusion Enrollment Reports that you have. There's also an Add a New Inclusion Enrollment Report button. So this button is there, and it should only be used if you need to actually add a new Inclusion Enrollment Report to describe a population you hadn't described in your study before or to provide something new. You don't want to click that button if you just need to provide edits or provide updates for an already existing Enrollment Report. To do that, there will be an Edit button that's in the listing of the Inclusion Enrollment Reports for each of those that you have on your study. So click on the Edit button for the particular Inclusion Enrollment Report, and it'll open the report for you. Once the report opens, you'll see the listing for the different fields. So the study - the Inclusion Enrollment Report title, you'll see the buttons for whether or not it's an inclusion, describes an existing dataset or resource, whether or not it's a foreign or domestic study and that sort of thing. So all of those attributes will be there. You'll also see the planned enrollment table and the cumulative enrollment table for that particular Inclusion Enrollment Report.

Now, because of the Inclusion Across the Lifespan policy, all research that came in on applications January 25th, 2019, or later are required to provide individual-level or participant-level data. The way that this is provided to NIH is by completing a spreadsheet that we have available as a template for you to use to provide a line item describing each of the participants. So as you can see in this screenshot of the template, there's a column for race, ethnicity, sex or gender, age and then the age unit. In the template, there's some sample data provided, just as it is in this screenshot, that provides an example of how the information can be entered on the template. There are a couple of things to note about the template itself. First, the location, so you can access this template from several different locations, including in your Inclusion Enrollment Report itself. There's a button that's located at the end of your Inclusion Enrollment Report that allows you to download the template. The template is also available from the inclusion policy websites and then also from the eRA HSS training web page. All these resources are listed at the end of the presentation. Secondly, the template is a CSV file, and it's very important for it to remain a CSV file when you complete the information. That way the system is able to recognize the file and upload it appropriately. If the file type is changed, you may receive an error when you attempt to upload your spreadsheet. Secondly, it's important for you to maintain the columns that are listed and not change the order around and make other format changes. Again, if that's done, then the information will not be uploaded correctly in the system, and you'll get an error when you attempt to upload. We have a tip sheet that's available to provide some of this information and also details about how you provide the race information, what variables or what names to use, what units you can provide for the age units and that sort of thing, and a tip sheet on several websites as well. This is also available at the end of this presentation as a resource for you. So it will be advantageous, or I would encourage you to open that tip sheet at the time that you're completing the spreadsheet, for the first time especially, so that you can make sure that you're entering the information in a way that the system will be able to recognize. Of note, you can manually list out each of the participants and type them in individually, or you can copy and then paste the information from another source into the spreadsheet, provided that you paste the information as values only, so that you don't copy any formulas or other formatting into this spreadsheet.

So once you've done all of that and you've gone through and made sure that the information is in there correctly and you've saved it, you can return to your Inclusion Enrollment Report and upload the attachment. There's an Upload Attachment button that's located at the bottom of the cumulative enrollment table. When you click on this, it'll open up an option for you to be able to choose the file from your computer and then upload the report. If the report uploads correctly, what will happen is that the cumulative enrollment table will populate aggregate information for what you've provided in the spreadsheet. If the upload does not go through, you will get an error message letting you know that it did not work, and it will also include some tips about things you'll want to check to see what exactly is causing the error within your spreadsheet.

Of note, you can also download the participant-level data once you've provided it initially to us. That way you can have a copy of what you provided to us and in case you need to go back and confirm all the information that was provided. Since this is cumulative enrollment data that you're providing to us, please note that you should make sure that you add participants as you enroll them to your spreadsheet, rather than only providing new participants to us each year. That will replace the previous participants instead of providing a cumulative list which is what you actually need to provide.

All right. So let's do another knowledge check. What items do you need to submit an Inclusion Enrollment update for your study, A: permission from your program officer, B: the participant-level data template, C: editing access in the Human Subjects System or D: graph paper. I'll give you a few seconds to answer the poll. All right. Just a few more seconds, and the poll is closed. Let's see what your responses were. All right. So most people got this correct. So the two correct items are the participant-level data template but then also access in the Human Subjects System which is something that I mentioned at the beginning of the presentation. You want to make sure that you have the correct roles to be able to edit information in HSS in order to make your inclusion updates. Sometimes this comes up with PIs as they're beginning to work on their RPPR, and they have research assistants and others that are helping. You need to have access in HSS in order to provide the edits and information that you need.

All right. So let's move on to talk about the clinical trial information that you'll need to provide. So again, first, if you have a clinical trial, you'll need to register the trial in clinicaltrials.gov. Now in this presentation I won't go over the process for that, but there is helpful information on the clinicaltrials.gov website for you to look at if you are the responsible party and will need to be the one who is doing the registration. Here I have a screenshot of the How to Register Your Study page and then also the Protocol Registration and Result System log-in that would be needed to go ahead and log in and register your study.

So with that being said, if you recall, at the beginning of the presentation I mentioned that you can use your Human Subjects System information, particularly your study record data, to provide some of the initial information that you need for your clinicaltrials.gov registration. There are two ways for you to able to do this. So the first way is by going into HSS and, within your line item for any study record that's a clinical trial, there's an Export XML button. When you click on this button, it'll open up an option for you to add your PRS organization name and to create a unique protocol ID for that particular study. Once you do that, you click the Export button, and a file will be downloaded to your computer that you can then use to upload into clinicaltrials.gov to begin your registration. On the other hand, if you're a signing official, there's an additional option for you. So what you can do is access the same way and click on the Export XML button, and when you fill out the initial information at the top of that box that opens up, you can then click on the Upload Directly to clinicaltrials.gov check box. You'll then receive an additional set of fields where you can enter your PRS username and password. You'll have a button there that says Upload to clinicaltrials.gov, and when you hit that, then that'll go ahead and do the upload for you directly into the system. You'll receive a message to let you know if the upload is successful or unsuccessful. If you need more information about this particular process, there is information available in the HSS Online Help for External Users, where there's a specific chapter that walks through this process.

So before we go on, since we're talking about clinical trials, I did want to mention the fields that we have in HSS that also map to clinicaltrials.gov or our shared fields. The fields listed here are specific fields that we, as NIH, check for congruence with the information that's in clinicaltrials.gov. These are fields that we want to make sure are the same so that we can make sure that we have updated information about your study and to confirm that we have the same information that clinicaltrials.gov does for compliance. Some of these fields include age limits and the recruitment status, also includes the study primary completion date and the enrollment of your first participant, so it's important to remember some of these fields, that you're aware and because sometimes if these fields are not the same, you may receive errors as you are completing or attempting to submit your information in HSS, and I'll talk a little bit more about that in a few more slides.

So now that we have registered our study, let's say, and we are now ready to enter the NCT into the Human Subjects System record that you have for that particular study, so you will enter the NCT in section one, where there's an item specifically for that, a field that you can provide that. Once you enter the NCT, you can use the Populate button that's located next to it to pull the information from clinicaltrials.gov into HSS for the specific fields that I mentioned in the previous slide, and here they are again. So once you click that Populate button, what will happen is the HSS fields that map will populate with the updated information from clinicaltrials.gov. The second thing that you may need to update would be the information in section two. Now, we've talked about how to update your Inclusion Enrollment information, but I want to note that you may also need to update your recruitment status. Now, this is one of the fields that maps to clinicaltrials.gov. So if your study is a clinical trial, this information will populate from clinicaltrials.gov, if you've used the Populate button to refresh the information in HSS with your clinicaltrials.gov information. And then lastly, let's talk about section six which includes the clinical trial milestones. So this entire section is dedicated to kind of key dates and information for your clinical trial. Importantly, there is a date that you provide in your initial application which is the enrollment of first participant date, what you anticipate that to be. Post-submission, that date moves down here to section six, so can be grouped along with all the other dates that you have that are important. So for each date that you have, you can set the date to Anticipated to describe when you anticipate that that particular milestone will be met, and then once it's met, you can update the date with the actual date that it occurred and set that date to Actual. One really important thing to note is that for the enrollment of first participant date and for the study primary completion date, once those dates are set to Actual and that particular change is saved, recipients are not able to make any edits to that date. Part of the reason is for compliance purposes. So if you make an error, if you set the date to Actual accidentally, and you note that it's incorrect, you'll want to check your clinicaltrials.gov information, and if that information is correct in clinicaltrials.gov, you can use the Populate button to refresh HSS and provide the actual information that you want to provide in that field. If not or if, for example, you haven't registered your study yet or your study hasn't begun, and you have to provide an anticipated date instead of an actual date, you'll want to contact your program officer to let them know about the situation, and they can provide additional guidance about what to do next.

So now that we've talked about all of the ways that you edit the information, let's talk about really important thing which is saving your changes, right? So at the bottom of each page in HSS, there are three buttons that will be available to you. There's a Save and Keep Lock button which you want to use if you're saving the data but continuing to make changes on your records. Then there's also a Save and Release Lock button. So that one you want to use once you've done making all of your changes, and you are getting ready to exit the study, not make any more changes or even close out of the program completely. If you don't release the lock, then if you - Say one of your colleagues is going in to make some other edits. They won't be able to do so because the system will still be locked in on your account. So it's important to release the lock once you're done with the information that you're changing and you've saved those changes. Lastly, there is always going to be a Cancel and Release Lock button. So if you started making changes, and you realize that you've made an error, you can cancel and release the editing block, so you'll no longer be in editing mode. You can also use that if you've already saved information. You enter the page, and you don't need to make any edits. You can hit Cancel and Release Lock to get out of the edit mode that way as well. All right. So we've gone over kind of all of the basic information for editing your information in HSS and providing the updates. So there are some key things that you want to remember that need to be updated. Now of course, first is updating the Inclusion Enrollment information for all studies. Secondly, for clinical trials, you want to remember to register your trial and then provide the NCT in your study record in section one and then use the Populate button to provide updates to your HSS record from clinicaltrials.gov to make sure that we have the correct and most up-to-date information.

So I wanted to talk about a couple of recommendations when it comes to filling out information for your RPPR. The first is that if you have any challenges or significant issues on a particular study, it's important to provide these updates in the narrative of your RPPR. Sometimes we get questions about where that information can be provided in HSS within the study record, and the answer is that the study record generally has the structured fields where you're providing specific information to us, whereas if you want to describe a particular thing about your study and about the progress to NIH and so that your program officer can take a look at it, you'll want to do that in the narrative of your RPPR. The second thing is that when you're making updates for your RPPR, you want to make sure that you go into HSS, complete your updates and then submit your updates before you submit your RPPR. The RPPR image will include your study records, but it will only include the last submitted version of the study records that we have. So if you've made updates in HSS but haven't submitted them, the RPPR will not recognize them and won't include that updated version of your study in your RPPR image, so make sure that you submit your HSS changes first before your RPPR.

So let's talk a little bit about troubleshooting. So I know that often people will encounter warnings and errors in the system, and generally there are questions about what the errors and warnings mean. I want to encourage you to take a look at each of the errors and warnings when you receive them and read the text information that's provided in each of the warnings or errors. Often they'll mention exactly what the problem is with the information that's been provided, and they'll give you some cues about how to address the error or the warning to resolve it. One example would be the clinicaltrials.gov and HSS mismatch error that sometimes comes up for our users. That particular warning includes the particular study record title and also the field or fields that do not match between the two systems. That way you can go to that study record and take a look directly at just those fields and see where you need to make your changes. Another important thing is to always check submission status when you enter HSS if you would like to make edits. Sometimes users will go into HSS to view information, and then they'll realize there's something that they need to change and then try to make edits without first going back and updating the submission status first. So you'll want to remember to update the submission status first in order to make your edits. Here's a list of some of the common warnings and errors that we receive questions about, and in this table I have a column that has a question about what you might want to look at that might help you resolve that warning or error. So for example, with the first listing, "Inclusion monitoring is required but no IER exists," so the question that you'll want to ask yourself is, "Has an Inclusion Enrollment Report been provided?" If it hasn't, then you'll want to go ahead and provide one. That will address the error that is existing at that point. Another one is "Participant-level data, including age at enrollment, is required." When you see that warning, what you'll want to do is make sure that you've uploaded the participant-level data using the template as required for research that came in on an application January 25th, 2019 or later. There are additional system warnings and errors that you may see. Some of them are related to policy compliance, then others are system validations to make sure that the information that's entered in kind of makes sense overall. So for example, some other policy compliance warnings or errors that you may see have to do with clinicaltrials.gov registration and reporting. As you may know, you must register your clinical trial within 21 days of the enrollment of the first participant and then report results within 12 months of the end of the primary completion date. You may also see policy compliance warnings if there are fields that are required that haven't been completed. Some examples of system validations that you may see instead have to do with, for example, a date that's in the past that you attempt to set as anticipated. Since that date passed, you are unable to set it as an anticipated date. So the system will ask you to either update the date or provide an actual date for that particular field. You may also see system validations for items that are completed for a clinical trial, for example, when your study is not a trial, and the system will ask you to remove that information since it's not required for your study.

So here I have the list of resources that I mentioned earlier that may be helpful to you. They include the ERA HSS Online Help and the HSS Training page that includes videos, the tip sheet that I mentioned, the participant-level data template and other information that will be helpful to you. I also have a direct link to the data tip sheet here along with the RPPR Online Help and the inclusion websites and FAQs, as those will give you more information about the way to provide your Inclusion Enrollment information. All right. So let's take some questions.

Dawn Corbett: Thank you, Rebecca. So we have quite a few questions in the Q&A. Let me start with the first question which is, can you leave sections of the HSS blank if your funding was awarded in 2016, your application was submitted in 2015, prior to the expansion of HSS?

Rebecca Favor: If your application came in - That's a good question. So if your application came in before the implementation of Forms E, so that was later in 2018, then there are fields that you are not required to fill out. However, with that being said, the fields are still there for you to complete, and if you re-compete, then you will then be required to provide that information.

Dawn Corbett: Thanks, Rebecca. The next question Laurie Roman has actually volunteered to answer, so you get a little break. Laurie Roman is from ERA, so we're very fortunate to have her here. The question is, "Is there a guide to HSS like there is for the study record? I recently was told to edit my submitted study record, and now there's a section six in my study record. This is not the pre-award study record guide."

Laurie Roman: There's actually two places to find information. One is online help available through Assist, and I can put that link in the chat or the questions, and also, as Rebecca alluded to, there's a lot of other helpful information for completing the post- submission information in the RPPR manual.

Dawn Corbett: Great. Thank you, Laurie. Okay, the next question is, to confirm, during the RPPR we do not need to update the protocol design or any of the inclusion documents, timeline, study team, et cetera?

Rebecca Favor: Generally speaking, no, you would not have to update this unless you've been asked to provide some additional information by your program officer. There might be a situation in which that may be required, but generally speaking you're required to provide your inclusion information updates at least annually, so that would be in your RPPR.

Dawn Corbett: Great. So this question is along similar lines. What if you don't have any changes or updates to make? Then what do you do?

Rebecca Favor: That's a good question. So if you don't have any updates, if let's say you haven't started enrollment. That's your first RPPR. That's perfectly fine. There's nothing for you to update, so you don't have to do anything.

Dawn Corbett: Okay, great. For the individual-level participant data template, is it possible to save a copy to update and share?

Rebecca Favor: Yes, it is. So when you - The copy that you create to upload to us, of course that file you can keep, and then you can also download a version of what you provided to us from within your IER so that way you can have, you can download a copy from that, and then you can add to your spreadsheet and then upload a new version of it each year.

Dawn Corbett: Okay, great. Another question, if there are no changes in enrollment, I think we did that. If there are no changes in enrollment since the previous RPPR, do we have to upload the participant-level data again? I think you touched on this, but this is specific to the participant-level data.

Rebecca Favor: Sure. The answer is no, so it would be the same. If there are no updates, then you don't have to upload a new participant-level data sheet.

Dawn Corbett: Great. Okay, another question, for a subawardee, who is responsible to report enrollment of participants in clinicaltrials.gov and all related compliance reporting requirements? And let me know if you'd like me to jump in on this one, Rebecca.

Rebecca Favor: Sure. Actually, Dawn, I'll let you take that one.

Dawn Corbett: Okay, great. So if you're a subawardee, NIH, our relationship is with the primary and not with the subawardees, so you would need to coordinate with them. In terms of who's responsible for reporting to clinicaltrials.gov, the responsible party is the person who's responsible for that reporting. However, NIH expects the NIH recipient to coordinate with the responsible party to make sure that happens, so I would talk to the NIH recipient and figure out who's responsible for that. Okay, next question, "There are many times when I update the Inclusion Enrollment Report, and when I save as a PDF draft, the updates do not show. I can see the updates in Assist. However, they do not reflect in the PDF version. Is there something I can do to ensure they match?" Do we know about this situation, or maybe this is news to us?

Rebecca Favor: Yeah, this one is new. Did someone from eRA want to take that?

Adam Levy: Hey, this is Adam, Develop Manager for Assist. I am thinking that this has to do with that age data question that you guys talked to us about, where we're not putting the age data in the image, right, yet, and we're not planning on it. So that's my guess.

Dawn Corbett: So that's a good point, Adam. So right now we don't display the age data to the recipient, so even if you upload, you won't see age. However, you should be able to see the sex or gender and the race and ethnicity of your participants. If you're not, please report that to the help desk, and that will get back to us, and we can investigate if there's some other issue going on. Okay, next question, "Are we not able to just update the cumulative enrollment table manually in the Inclusion Enrollment Report? Do we have to use the template?"

Rebecca Favor: That is a good question. So if your research came in after January 25th, 2019, then yes, you do have to use the template because you're required to provide the age data, and the use of the template is the way that these data can be provided to us. In addition, the participant- level information itself is part of what's required for the 21st Century CARES Act, so we do need all of that information that way.

Dawn Corbett: Okay. This question, Laurie, I may ask your help with, but I will pose this. If the PI delegates an assistant on their RPPR, do they have access to HSS for the grant to update Inclusion Enrollment? So the PI delegates an assistant, I guess. So they've delegated an assistant for their RPPR, and I guess the question is, would that PI delegate have access to HSS to update Inclusion Enrollment?

Laurie Roman: Adam can correct me if I say something heretical, but I do believe we follow the delegation established in commons.

Adam Levy: Correct.

Dawn Corbett: Thank you. And this is similar and a similar question about, how do we apply to get HSS access if we are not the PI, but we're in charge of entering information in clinicaltrials.gov? I would just delineate there, Rebecca, that those are two different sets of permissions. So, Rebecca, perhaps you can speak to how they can get access to HSS or ERA can help with that and then clinicaltrials.gov, which I'm also happy to help address?

Rebecca Favor: Sure. So for HSS access, they would need to talk to their signing official because that individual is the one who assigns the roles. For clinicaltrials.gov, that may also depend on who the individual is in their institution who's responsible for that, and so they would need to talk to them about access.

Dawn Corbett: And you can look up your PRS coordinator on the clinicaltrials.gov website, so that would be separate from HSS access. Okay, great. The next question is, so should we not change either date - and I think they're referring to the enrollment of first participant or primary completion date - to actual until after enrollment is finished?

Rebecca Favor: No, so you'll want to change the dates to reflect when actual enrollment begins. You shouldn't wait until after you've completed your study. The thing that I mentioned about the date locking is just to confirm that the information in there is correct, and that way we know when to anticipate the time by which you should, for example, have registered your clinical trial, but you won't want to wait until after you've completed your study completely to provide the actual dates to us.

Dawn Corbett: Great, and I love how people are helping each other out in the chat.

Rebecca Favor: Yeah.

Dawn Corbett: That's great to see, so keep it up. All right. The next question is, do clinicaltrials.gov and HSS only need to be filled out for NIH-funded studies or all research at U.S. institutions?

Rebecca Favor: So HSS is only used for NIH-funded research, so you wouldn't want to use it for all U.S.-related research. Clinicaltrials.gov, on the other hand, is open to research in general, so that is a different, it's a separate platform that's available as a resource for clinical trial-related information.

Dawn Corbett: Great. The next question is, "If you're completing an RPPR and the enrollment table was completed and final the prior year, how do you complete the human subjects section? If we don't update something, we will receive a warning or error."

Rebecca Favor: Yeah, so that's a good question. The warning that you receive in the RPPR related to not updating your inclusion information is there to remind recipients to update information if it's needed. That particular warning is a warning, so you can see it, and if you don't need to address it, you're still able to go ahead and submit your RPPR because you know that you don't actually need to make any updates.

Dawn Corbett: Okay, we have time for one or two more questions. This one is, "Is there a way to see if a particular grant needs to report age in the Inclusion Enrollment Report? A few of the grants I manage were awarded right around that date you mentioned, so I'm not sure they're applicable to the age-reporting requirement."

Rebecca Favor: That's a good question. So one of the ways that you can take a look at that is the date that the initial application was submitted to see if it falls into that January 25th, 2019 or later application due date phase or time frame. The other thing that you want to do is contact your program officer and ask them to assist you in kind of figuring out if your research or if those projects fall in the Inclusion Across the Lifespan policy.

Dawn Corbett: Okay. The next question is, "It was mentioned that if you have accidentally entered an actual study start date, you can update on clinicaltrials.gov if the correct information is there. However, that would bring all the data back from clinicaltrials.gov. Is that correct?"

Rebecca Favor: That is correct, yes. So it will refresh the information for that date and then the other fields that map.

Dawn Corbett: Okay. So I think we are running short on time. We do have a question about, "Will the presentation be available as a recording?" So, yes, all of this will be available, but I do want to take this opportunity to thank Dr. Favor and all of you for attending the session today. It's been very informative, and the PowerPoint and related resources are located - There's two locations, on the NIH Grants Conference website and inside the Virtual NIH Grants Conference Center. Look for the Human Subjects Research Pre-Con event page. Okay, so we're going to take a few seconds now to bring together all of our HHS and NIH presenters from this 2-day event, and we're going to transition into our extended Q&A, so just give us a few seconds, and we'll shift into our Q&A. Thank you.

Deysi Duque: Okay. Good afternoon, everyone. Welcome to continuing the conversation with a Q&A with the NIH and HHS human subjects experts. We're so pleased to have you join us for this 45-minute Q&A with our experienced panel of human subjects experts. They will be addressing your questions from previous presentations as well as addressing them live from the Q&A box. My name is Deysi Duque, your moderator for today's presentation. I'm a Human Subjects and Clinical Trials Specialist in the Division of Human Subjects Research within the NIH Office of Extramural Research. I know you're anxious to get started, so let me introduce you to the experts for today's panel. From the Department of Health and Human Services Office for Human Research Protections, OHRP, we have Dr. Yvonne Lau, Director of the Division of Education and Development, and we have Marianna Azar, Public Health Program Specialist also from OHRP's Division of Education and Development. From the NIH Division of Human Subjects Research located in the Office of Extramural Research Office of the Director, I would like to introduce Dr. Pamela Kearney, Director of the Division of Human Subjects Research; Dawn Corbett, NIH Inclusion Policy Officer; Dr. Rebecca Favor, NIH Human Subjects and Inclusion Policy Analyst; and Lyndi Lahl, NIH Human Subjects Officer. So let's get started. We're going to be monitoring the Q&A box, so if you can, enter your questions in the box. We'll be reading those to the panel, and please, we will be taking different topics from the sessions from yesterday afternoon and this afternoon, so anything related to the Common Rule, human subjects protections, Certificate of Confidentiality, single IRB, clinical trials and inclusion. So we're starting to get some really great questions in the NIH box. So I have one that has to do with data and specimens, and I will just direct this question to our experts from OHRP. So I'll direct this to Marianna or Dr. Yvonne Lau. So we have, "If data or specimens are obtained from living individuals, and those individuals are later deceased, when the data or specimens are used for secondary research with identifiers, is that still considered human subjects research?" And there's a second part to that question. "There are identifiers, but at the time of the secondary research, the individuals are deceased."

Marianna Azar: Yeah, so if you're conducting research using biospecimens or data that belong to deceased individuals, the definition of a human subject is not satisfied. So it is only at the time that the individuals are living that you are conducting human subjects research.

Deysi Duque: Okay, thank you, Marianna. That's a really good question, and I think it was related to a question that I noticed in the Q&A session yesterday related to secondary research. I don't believe it was answered, but it's really just asking us this other part of the question. For human subjects involved in secondary research, do investigators need to obtain informed consent? And I think what they were trying to say is that for the primary research, so the initial research, they had consent of participants, and the participants had consented to the use of data for future use. Do they still have the consent, investigators, for the secondary research?

Marianna Azar: So it would depend. So recall that if the research otherwise qualifies for exemption from the Common Rule regulatory requirements, that includes the requirements for informed consent. So if it is secondary research that's conducted under, let's say exempt category number four, then informed consent requirements would not be applicable. Yvonne, did you want to add to that?

Yvonne Lau: That is a really complicated question to actually respond to because it depends on many things. In theory, if you are a researcher and you are obtaining data, private data or biospecimens for your research and that it's - Was it identifiable, did we say, or was it not identifiable?

Deysi Duque: They did not specify if it was identifiable, but I believe it was.

Yvonne Lau: Ah, okay. So from the point of view, the Common Rule basically applies from the perspective of the investigators who are proposing the research project. So if you are the investigator proposing a research project, and it is a secondary research, in other words, you are making use of data and biospecimens that have been collected for another research or for things other than research, right, so clinical care or other reasons that the data were collected. That's secondary research. In theory, when you receive those materials for your research, and they come to you without any identifiable information, that is considered not human subjects research, and basically, based on our interpretation, therefore it doesn't come under the Common Rule jurisdiction, and therefore you don't need to have informed consent, correct? However, there is the other part that is interesting, right, because if - going back to how the specimens or how the materials were originally collected, right? Because many people would think, "Well, if we were doing a research, we collect specimens and information, and then we plan that at some point in time, they could be used in subsequent secondary research," right? At the time of collecting those materials, even though those materials are being collected as part of the primary research, and we're not collecting more than necessary, and it's only whatever that's remaining, right, especially in terms of specimens, right, since data will always be there. So whatever that's remaining from the specimens, and we plan to use it subsequently. Now, in the revised Common Rule, there is now a requirement that as you are getting informed consent for your research at the primary stage, you need to include a notification, right, to the participants as to whether there is any intention to use the materials for future secondary research, even if it's without associated identifiable information. You see how it's really complicated to explain that, right? And then the other thing, of course, is the additional requirement that, of course if you're thinking already specifically that you will potentially use the material for future secondary research in an identifiable way, right, there is a possibility for you to get the consent at that time, when you do the primary research, right, and that is a different matter as well, how much you need to - how much information you need to provide. Is it going to be called primary consent, or is it going to be - What consent that becomes a really difficult thing to explain in this short period of time. I think that it's better to - OHRP is planning on doing a webinar, two sets of webinar actually on the use of data and biospecimens in research because of all the different complicated issues. We plan to do that and open it to the public sometime in early next year, and we'll announce about that at the beginning of the year. So join our LISTSERV, the OHRP LISTSERV. You can find it, the information for joining our LISTSERV on our website very easily, so that you get the first-hand information when that comes out, and it's going to be virtual, and participation is free.

Deysi Duque: Very nice, thank you, Dr. Yvonne Lau. That's very helpful. So I think we're going to move on to another question, a different topic, and it's single IRB-related. So I'll direct this to Lyndi, and it has to be with the dates. So they're asking when the single IRB is required, so for multi-site nonexempt human subjects research, and the PO asks for the date, and they're saying specifically the full IRB approval to remove restrictions in the Notice of Award. Does this mean the IRB approval date for the single IRB protocol, the primary site, or is this the date when all the sites participating in the study listed in the grant have obtained IRB approval? What is that date that the PO is requesting?

Lyndi Lahl: Okay, so this was a restricted award, and now they want the single IRB date so - And I know how it works with these cooperative research projects. They generally have a protocol that is reviewed, and then they look at each of the sites independently to make sure local research context is - and it's approved for each site - And, Dawn, please jump in and correct me if I'm wrong. I think that the date is going to be the date of initial IRB approval for probably the prime recipient site, who they're reviewing for, because I don't think approval of the protocol itself without actually approving for a site would be able to lift the restriction. So, Dawn, do you have anything to add?

Dawn Corbett: Yeah, so you are supposed to date that the last protocol was approved to the IC, but I will say that ICs have different procedures, so it's going to be really important to get in contact with a grants specialist and make sure you're providing documentation that they ask for.

Deysi Duque: That's great. Thank you, Dawn, and thank you, Lyndi, for that. I'm going to ask another question that's IRB-related. So from one of the Q&A here in the box, is IRB review required for research conducted outside of the U.S.? And I'm going to direct this to Yvonne or Marianna. So the question is, is IRB review required for sites conducting research outside of the U.S.?

Yvonne Lau: Well, okay, so for any HHS-funded and support nonexempt human subjects research, in other words, it's human subjects research that do not fall within an exemption category mentioned in the Common Rule. You would require full IRB, you would require proper IRB review whether you are outside of the United States or within the United States. What may be slightly different is the single IRB cooperative research mandate. So if this research, the international site is doing this as part of a cooperative research project with some other institutions involved, and they may be in the United States, that international site has the option of not complying with the single IRB review mandate. In other words, there is the option that the international site, if they are also considered engaged in human subjects activities that they have their IRB, their local IRB, to review the research, and they do not have to rely on the single IRB that was designated for the cooperative research project. Does that make any sense?

Deysi Duque: Yes, that's ...

Yvonne Lau: Okay, so they have that option, but then they also have the option to defer that and rely - defer that review and rely on the single IRB as well, so they can choose either or for international site, but just by the fact that they're international, they - If they're receiving HHS funding for nonexempt human subjects research projects, they still have to comply with the regulations like everybody else. There's no exception.

Deysi Duque: Great. Thank you, Dr. Yvonne. So I'm going to move on to some questions related to clinical trials, and I believe we got some of those in the earlier sessions this afternoon, and it has to do with observational studies. So I'm going to direct this question to Dr. Pamela Kearney, and it had to do with the applicant proposing observational studies. Are those considered clinical trials? Pam, I believe we cannot hear you.

Pamela Kearney: All right. Sorry about that. I was muted. By definition, an observational study is not a clinical trial. A clinical trial has human subjects. It has a prospectively assigned intervention. It measures the effects of that intervention on the participants, and those effects are biomedical or behavioral outcomes. An observational study is simply gathering information about something that's going on. You're not intervening in any way. You're observing, and so without an intervention, it can't be a clinical trial.

Deysi Duque: Great, thank you. There was another related question in terms of an applicant proposing a study and whether randomization would make it a clinical trial. Does randomization matter when an applicant is trying to determine if a study meets the clinical trial definition?

Pamela Kearney: Randomization makes absolutely no difference. There's nothing about randomization in the NIH definition of clinical trial. It just has to be prospectively assigned. Randomization doesn't matter. The type of intervention doesn't matter. The method of assigning doesn't matter. The participants can choose their own group. The physicians can assign the group based on what they feel is the best fit for that patient. As long as the investigator has determined in advance how that assignment will be done, it prospectively assigned. So randomization makes no difference.

Yvonne Lau: But, Pamela ...

Deysi Duque: Thank you.

Yvonne Lau: This is Yvonne. Wouldn't you agree that by nature of the fact that they are planning to randomize, so randomly assign people to a group, that makes it already - That would make it fall into the clinical trial definition?

Pamela Kearney: There has to be an intervention, and they have to be measuring the effects of that intervention.

Yvonne Lau: That's true.

Pamela Kearney: And those effects have to be biomedical or behavioral outcomes. So the fact that it is not randomized - And that's usually the question we get. An investigator will come to me and say, "I can't be doing the clinical trial. It's not randomized." That doesn't matter. The NIH definition does not include randomization.

Deysi Duque: Great, thank you, Dr. Pamela Kearney. We also received a question, and I think it was asking about examples of that prospective assignment to interventions when those will not be clinical trials, if I understand the question correctly. So, Pamela Kearney, if you can help us with some examples when a study with human subjects does not include prospective assignment to an intervention and is not a clinical trial?

Pamela Kearney: Sure. So these would be, I guess we're doing the opposite. We're asking for examples of things that are not clinical trials, and I can think of a few types of studies that would fall into that category. You can think of any retrospective study that you would do a chart review with identifiable information, an observational study, like we talked about before, where the folks decide that a city has put out a particular vaccine advertising campaign, and investigators want to find out the effect of that. They're just observing what the city is doing. They're not, It's not a research intervention because they're not doing it. They're just observing something else. Another one might be a longitudinal study for disease natural history, where investigators had a disease where they're just gathering certain information every year, every 6 months on people with a particular disorder. They're not intervening in any way. They're not doing anything. They're not measuring the effect of a drug or a treatment. They just want to know what happens during this disease. So those are a few examples of clinical studies that are not clinical trials.

Deysi Duque: Great, thank you. There was a related question to, I think it was observational studies, and we could just kind of go over this, and I think they were using a watch. Give me just a moment.

Pamela Kearney: I think I see that one. "I plan to conduct an observational study that includes" ...

Deysi Duque: Correct.

Pamela Kearney: Yeah, and ...

Deysi Duque: Correct.

Pamela Kearney: I'm very reluctant to give specific clinical trial determinations because like I mentioned in my presentation, the devil is in the details. I can talk in generalities, but I want to express the caveat that this should not be considered an official clinical trial determination for your study that would be on the actual application that is submitted, all of the many pages and all of the many parts that might have a paragraph or two that might say something different. But if you are doing a study where you're having people wear those smartwatches that's going to collect data on the sleep and physical activities, it depends on what the purpose of that study is. If you are just looking to see whether or not people like wearing this, whether or not it's feasible to have people do this, whether or not the smartwatches work, that sort of thing, those are things where you're not measuring the effect of the intervention on the participants. Now, if your study is designed to have people wear these smartwatches, and you want to see if their behavior changes, whether their sleep activity changes or their physical activity levels change because now they're aware of how much they're doing or not doing or sleeping or not sleeping, if you're looking at the effect of wearing that smartwatch, you could be doing a clinical trial. But if you're just having people wear the smartwatch because you're trying to develop said smartwatch, and you want to see if it actually collects the data you want it to collect or whether or not people like it, is this something that people would want to use, that would not necessarily be a clinical trial because you're not measuring the effect of wearing that smartwatch. You're just looking at whether or not the smartwatch works or people like it. Does that make sense?

Deysi Duque: It does. Thank you, Dr. Kearney. I'm going to jump to another human subjects-related question, and it's about HIPAA authorization. So they're asking if we can provide more information about the waiver of the HIPAA authorization and types of exempt research it would typically cover. So I will direct this to Dr. Yvonne Lau or Marianna Azar.

Marianna Azar: Yvonne, if you don't mind, I'll jump in. So we cannot address HIPAA-related questions because HIPAA is not under the jurisdiction of OHRP. It is under the jurisdiction of the HHS Office for Civil Rights. So any HIPAA-related questions, we would defer to them.

Yvonne Lau: We can answer though, Marianna, with regards to exemption category four ...

Marianna Azar: 4iii?

Yvonne Lau: ... three little i's. So if you can, maybe just say a little bit more about that to clarify?

Marianna Azar: So the exemption at 4iii is an exemption that can be used for research involving data at a HIPAA-covered entity. So if you are conducting secondary research, and that secondary research involves identifiable data at a HIPAA-covered entity, the HIPAA exemption or exemption for category 4iii may be applicable. Did you want to add to that, Yvonne?

Yvonne Lau: Yeah, and it just means that if that exemption is applicable, so you follow what the conditions of that exemption require, and if it applies, it means that you just have to follow what the HIPAA rules require you to do, and you don't have to worry about the Common Rule. So it's an exemption, exempt from the oversight of the Common Rule, and you then just have to follow what HIPAA requires you to do, and with regards to the details of when you can waive informed consent or not, you have to follow the HIPAA regulations, and like Marianna said, we don't really want to comment on the regulations under another jurisdiction.

Deysi Duque: Thank you, Dr. Yvonne Lau and Marianna. I'm going to ask another question about single IRB, and I'll direct this to Lyndi. They're asking about specific types of funding mechanisms and specific types of studies. The question is specifically asking on the single IRB requirements in the context of collaborative UL1 pilot studies. Are the single IRB requirements the same or different depending on the type of funding mechanism or the type of studies involved in nonexempt human subjects research, or is it just the same single IRB requirements?

Lyndi Lahl: So it could be the NIH policy, single IRB policy applies. Most likely it would depending on when the application was submitted, January 25th of 2018. It could be that the revised Common Rule single IRB requirement would apply depending on when the initial IRB approval is. If it's on or after January 20th of 2020, it would apply. If the pilot study is being done by a subawardee, your prime recipient is considered involved in the research, and so they and the subawardee who is actually conducting the nonexempt human subjects research would both be considered involved and single IRB requirements would apply, again depending on the dates. Funding mechanism does not matter, at least for the revised Common Rule, and the U award would fall underneath the single IRB requirements. Thanks.

Deysi Duque: Thank you. Thank you, Lyndi. Another single IRB-related question, "The NIH application states that studies using this same protocol to conduct nonexempt human subjects research at more than one domestic site are subject or expected to use a single IRB. Does the site need a domestic collaborating institution or organization involved in the research? Sometimes we think of a site as a field site from which data is being collected." So, Lyndi, can you help us with this question?

Lyndi Lahl: So I guess when it- So, well, first of all, let's go back. We're talking about domestic sites only that would fall under either of the single IRB requirements. So if it's being done in an international setting, the single IRB requirements would not apply. If the field site is - If that research is being conducted underneath the, let's say the prime recipient's federalwide assurance, their IRB is reviewing on their behalf. It's their investigators that are going, let's say to the local school to conduct the research, and that's the only activity that's involved, just the research activities from the prime recipient. It's their employees or agents that are conducting the research. They're at this field site, then single IRB would not apply.

Deysi Duque: Thank you, Lyndi.

Lyndi Lahl: Mm-hmm.

Deysi Duque: I'll jump to the inclusion topic, and so I'll direct this to Dawn. We have a question about planned enrollment. Does planned enrollment need to be updated in the IER, and that's the Inclusion Enrollment Report, if plan enrollment numbers change during the study? Can this be updated in HSS. And I think this will be a part maybe for Rebecca, who just presented about HSS. Can this be updated in HSS at any time and submitted to NIH, or do we have to wait until the time of RPPR submission to update this information?

Dawn Corbett: So, yes, you can go into HSS at any time to update your planned enrollment. I will throw some caution out there that a change to planned enrollment may require prior approval depending on exactly what you're changing about that planned enrollment. Your PO will receive a notification if you put that in HSS. That tells you that they've made a study change, but if there's some significant change, it's also, I think, a good idea to shoot your PO an email and let them know what that change is and whether or not you'll need prior approval for that. And, Rebecca, I don't know if you want to speak to the HSS piece at all.

Rebecca Favor: No, I think that you've hit the nail on the hammer, as they say. You're able to go into HSS and make edits if you need to.

Deysi Duque: Great. Thank you, Rebecca and Dawn, for your answers. I'm going to jump to the clinical trial-related questions. We got one, and they're asking about a few examples of BESH. What's BESH? Can you give us an example of BESH studies? So I'll direct this to Dr. Pamela Kearney.

Pamela Kearney: Okay, that's a good question, and it's very broad. It's like saying, "Give me an example of a clinical trial." A BESH, or basic experimental study with humans, is any study that meets the definition of an NIH-defined clinical trial and is basic research. So we see BESH most frequently kind of in the kind of behavioral study world and also in the neuro fields. A lot of fMRI studies turn out to be BESH, where the functional task is being used as a probe to get some information about what happens in certain parts of the brain, where does the blood flow increase with particular tasks and that sort of thing. Those would be example of BESH. So that's probably a good example.

Deysi Duque: Thank you, Pamela Kearney. So that's really helpful. We have some questions that are following on, I believe HIPAA. So I'm not sure that we will have the answer for this information, for this question, but they're asking about, is it appropriate to use the HIPAA Safe Harbor standard to determine whether information included in an IRB protocol, whether primary or secondary, are identifiable? And I believe one of our panelists mentioned that they would not ...

Yvonne Lau: Yeah, but this is not exactly directly about HIPAA. It's about the definition of identifiability. It's under the Common Rule. So under the Common Rule, if you are trying to apply the regulations, we always ask you to go back to the definition. So go to the definition in the Common Rule about what is identifiable, and the definition, you'll notice that it's much more subjective. The HIPAA indices are very objective. They are clearly, okay, names, date of birth, et cetera, et cetera, right? If you don't have these, it's considered nonidentifiable. In the Common Rule, the definition is much more - There's a level of subjectivity. So let's just give an example. So sometimes if a researcher is going to be doing research on a rare disease, and there are just that many people involved, that many people who have this kind of rare diseases in their locale let's say in the United States, and the investigator is kind of the expert in that area, right? If you have a situation like that, likelihood is that that investigator would probably know all the people who are involved, right, because it's just such a small community. So even though you might say you have a dataset where everything is stripped, right, you don't have any of the detailed information, but you have enough of things like description of the presentations, the symptoms, the signs, right, and they could vary a little person to person, even though it's the same rare disease, but that could be sufficient for the investigator and to know and to identify the specific individual, right? This is an extreme example, but it illustrates to you how, by that analysis, this could potentially be considered as identifiable under the Common Rule and definitely not under the HIPAA Safe Harbor situation, right? So in a way, you can say potentially the Common Rule has a broader implication in that sense, but at the same time, there are more flexibilities. So sometimes if you turn it around, sometimes you can have a few indices of the HIPAA or Safe Harbor indices in there, in your dataset, but from the point of view of the Common Rule ... because you cannot meet that criteria of readily ascertainable by the investigator. So let's say you are an investigator. You are looking at 10,000 sets of data, and yes, the data may have the zip code or a couple more other factors, right? In this day and age, with the technology and those people who can use the technology, they're going to tell you, "Yeah, that's identifiable," but from this investigator's situation, this is an investigator who looks at some molecular functioning, and they don't really ... It's not an IT project, right? So for all intents and purposes, one could say, "Well, having these few indices, this investigator is not considered readily ascertainable." The individual identity of the subject would not be readily ascertainable by this investigator, and therefore, by definition under the Common Rule, it will be considered as nonidentifiable. So there are more subjective interpretations, right, and it really kind of calls for having some sort of objective person to do that determination, and that's why usually we would recommend that investigators don't only make their own determination for these sort of things and have their HRPP or IRB office to help with doing these sort of determinations. And at the end of the day, it's always a good idea because if you gone through a third party like the HRPP or IRB office, when journals eventually ask you, "Did you go through IRB review of some sort or an independent review of some sort?" as you're about ready to publish your data, then you have a clear answer. Yes, I went through the IRB office or the HRPP, and they told me this, right? Then you don't have to go back and suddenly realize, "Oh, I haven't done this, and I have to go back," and then somebody says, "Well, I'm not so sure."

Deysi Duque: Thank you, Yvonne. I'm going to ask a question about IRB exemptions in the .. . proposed in the application or included in the application. So I'll ask this question to Lyndi. If an applicant claims an IRB exemption, so one of the categories, at the time of application submission and later learns that the exemption should not have been claimed, what should the applicant do if the application is still under peer review? Can they change the exemption, wait for the peer review to be completed, during, after? What does the applicant have to do to update that information?

Lyndi Lahl: So Dawn is my resident expert when it comes to the peer review questions. So I'm going to attempt to answer, and then, Dawn, I'll let you jump in. I believe that the application should go to peer review and be reviewed. The peer reviewers are going to look to see if the exempt category, if they've provided justification that this should be exempt, and then they'll flag it if there are any human subject concerns. So after it goes through peer review, it goes to council. Let's say it gets a good funding score, and now the PO reaches out and asks for Just-in-Time information. I believe that would be when they would need to say that, "Oh, oops, we made a mistake." The PO is going to be asking ... Well, at that point, they would need to provide the IRB approval date, and then it would be able to be coded properly. Dawn?

Dawn Corbett: Yeah, I agree with you, Lyndi. So those kinds of things will generally be worked out Just-in-Time, so either if the reviewer had concerns, and they may note that they felt the human subjects code was wrong or if they didn't have concerns, but your IRB has determined that another exemption applies or it's not exempt, all of that documentation will be provided during the Just-in-Time period.

Deysi Duque: Thank you, Dawn and Lyndi. We have a question related to the IRB for international sites, so I'll ask this question to Yvonne or Marianna. An international IRB has their own standards and regulations. How could they defer to a U.S. IRB?

Yvonne Lau: So I guess in that case they don't. They don't, and they are also - They don't have to comply even if they were involved in a cooperative research project with the U.S. Institutions. The single IRB mandate does not apply to the international site. However, I want to remind people in the international sites that yes, you may have your own requirements and laws to satisfy and so on, and so therefore it makes sense for your IRB to review the projects as it's going to be conducted in your locale, but don't forget also that whatever your IRB does ... If you're getting HHS money or, for that matter, other Common Rule agencies' money for to conduct that research, your IRB will also need to be able to comply with the regulatory requirements stipulated in the HHS regulations at 45 CRF 46, and it's not just the Common Rule, right? If it's HHS, it's also Subpart B, C and D if they apply. So on top of making sure that your local laws are complied with, you still need to make sure that the regulations, the HHS regulations at 45 CFR 46 are complied with as well for human subjects protections.

Deysi Duque: Great, thank you, Yvonne. There's a question about Inclusion Policy Exemption Requests. I'll direct this to Dawn. Can you comment on the Inclusion Policy Exemption Request and its uses and if it can override an IRB decision?

Dawn Corbett: Sure, so regarding the inclusion policy, an important point that I didn't make earlier is that the inclusion policy does not apply to studies that are considered to be Exemption 4 research. So if you designate Exemption 4 on your form, you won't be asked to provide all relevant inclusion documents. However, there's no actual inclusion exemption. We do have some rare exceptions to the inclusion policy when inclusion isn't appropriate with respect to the health of the subjects, for the purpose of the research. We have a handful of those that we deal with each year, and those have to be requested by your PO to our office, so they're quite rare. They're usually for things like program evaluations where the collection of inclusion data might not be appropriate, so the inclusion requirements would apply. The IRB, as far as I know, would not determine whether or not NIH inclusion policies apply unless their determination of whether the research was human subjects research or exempt or nonexempt or Exemption 4, and we would defer to the IRB in terms of what the appropriate exemption would be - I should say we would defer to the institution which may defer to the IRB.

Deysi Duque: Great, thank you. I think we may have time for maybe one more question, and I'm going to ask this question that has to do with single IRB as well. So I'll direct this to Lyndi. If an investigator is applying to be a study site on an NIH-funded collaborative cohort study where the program itself has an overarching protocol, and it is designated single IRB, does this change the level of detail expected of them in the PHS Human Subjects sections, like data and safety monitoring plan?

Lyndi Lahl: So the data and safety monitoring plan is going to be required if it's a clinical trial, so it just depends on what they're doing in the research, and Pam talked about the four questions to make that determination of whether or not the research is a clinical trial. So the collaborator cohort study, if it's observational and all they're doing is following people over time and doing periodic lab work and looking at surveys, et cetera, then it likely is not going to need a DSMB or any kind of data safety monitoring plan.

Deysi Duque: Great, thank you, Lyndi. So thank you to our expert panel from both NIH and HHS, as well as to all of you joining for this very informative Q&A session. Related resources can be found in two locations, on the NIH Grants Conference website and inside the Virtual 2022 and 2023 NIH Grants Conference Center. Look for the NIH subjects research pre-con event page, and before you leave today, please take a moment to complete the quick survey which will be populated and let us know how we did. We strive to improve our events, and your feedback is very valuable. Also, do not forget to mark your calendar for the highly anticipated 2-day NIH Grants Conference. This will be occurring on February 1st and 2nd, and it will include 25 live sessions and opportunities to meet with experts during the 20-minute private chats. If you have not visited the Virtual NIH Exhibit Hall, you may need to stop by, and although it's not staffed until after the conference, all NIH-awarded Institutes and centers along with numerous NIH officers are offering valuable documents, videos and resources that can be downloaded and emailed to yourself. So if you have any questions about our 2-day human subjects research event or February's conference, please reach out to us at the NIH Grants Events at nih.gov. Thank you and have a great day.