Dawn Corbett: So thank you for joining today's presentation, An Overview of NIH Policies on Human Subjects Research. My name is Dawn Corbett, and I am your moderator for the next 45 minutes. I'm pleased to present Dr. Pamela Kearney, Director of the Office of Human Subjects Research and the Office of Extramural Research and, Miss Lyndi Lahl, the NIH Human Subjects Officer. The format today includes a short pre-recorded presentation, followed by a Q&A with our presenters. While the presentation is playing, our presenters are available to answer questions in the Q&A box. So let's get started.

Lyndi Lahl: Hello, and welcome to an overview of NIH policies on human subject. My name is Lyndi Lahl. I'm the Human Subjects Officer with the Division of Human Subjects Research, and along with Dr. Pamela Kearney, who is the Director of the Division of Human Subjects Research, we welcome you and are glad that you are able to join us. So the objectives that we're going to cover in this session are identifying the NIH policies pertaining to research involving human subjects, determining when research involving human subjects is a clinical trial. Talk about considerations if you are applying for an NIH award that involves human subjects, and identify some resources when you are conducting human subjects research. So the first we're we're going to talk about is some of the policies involving human subject research. As you can see from this slide, NIH has a lot of policies pertaining to human subject research. We're going to be introducing these to you in the next slides. So an important question that you need to consider is, how do you know if you're conducting human subjects research? So we would refer you to the definition in the Common Rule for human subjects. And know that some of the human subject policies applied to clinical research and some of those human subject policies only apply to clinical trials. And that would be something like Data and Safety Monitoring in the Good Clinical Practice policy. And these policies are complementary, or in addition to what you would find in the regulations of the Common Rule. So NIH has a quick decision tool that will assist you in determining if your research involves human subjects, if it's exempt from the federal regulations, or if it's not considered human subjects research. And the link for this tool is available on this slide. Please note that you should not use this tool as a sole determination on determining whether your study is exempt from the regulations. So NIH has has a policy for education on the protection of human subject participants, and it's been a requirement for over 20 years. So the investigator and all key personnel who were involved in the research need to have human subjects training. This would also pertain to personnel at any other performance sites, not just the awardee site. And it also includes non-US sites as well. And please note that this is just a one-time training requirement, although we encourage you to get additional training. So next, I'll talk about the Certificate of Confidentiality policy. So all NIH-funded research which is within the scope of the NIH CoC policy is deemed issued a certificate. So NIH has placed the responsibility to the recipients and their investigators to determine if the research is collecting or using covered information, and would thus have to follow the CoC policy. So it's important that you know if you have CoC protections because you will need to disclose that to your participants, and you would also need to know that you can only disclose information that's identifiable and sensitive if it's only permitted when it's required by a federal, state or local law, such as child abuse or elder abuse or mandatory disease reporting, such as Tuberculosis, if it's with the participants' consent or for any other scientific research. So as I mentioned in the previous slide, the Certificate protects covered information. Covered information would be the name or any information, documents, or biospecimens that contain identifiable, sensitive information in relation to a research participant. And in addition, if there is at least a very small risk that the information documents or biospecimens can be combined with any other available data sources to determine the identity of a person, then they would also be protected by the certificate. Please note that the CoC also applies to copies of the data. So it's not just where the data is collected. It also applies to any copies that are given to other researchers, such as secondary researchers. And note that secondary researchers not only have this information that is protected via CoC, but they also must uphold the CoC protections. And then the last thing I want to tell you about Certificates are the protections last in perpetuity. So these protections go on forever, and you can't decide that you don't want to accept the CoC. It is an automatically deemed issued protection. So I just want to mention human fetal tissue does had a couple of guide notices and requirements associated with it. Human fetal tissue is defined as research that involves the study, analysis or use of primary human fetal tissue, cells, and derivatives. There are requirements that you would need to provide in your application if you're going to be using human fetal tissue. And, you're not going to get any additional pages to be providing this information, so I would encourage you to look at these guide notices to have a better understanding if you plan to do research with human fetal tissue. So inclusions are a big part of NIH protections. We have a couple of guide notices that talk about inclusions. I just want to highlight the inclusion of women and minorities in NIH research, and you would need to include women and minorities, and talk about that in your application in all NIH-funded clinical research, unless there's a compelling rational for excluding women and minorities. And note that if you're doing a Phase III clinical trial, you would need to do analysis by sex, gender, race, and ethnicity. And the second inclusion, by notice and policy requirements, would be inclusion across the life span. So this would require individuals of all ages to be included in NIH human subjects research unless there is a scientific or ethical reason to not include them. And please note that there is now a requirement for submission of individual level data on participant age and enrollment in the progress reports. You can learn a lot more about inclusions in the next session. I encourage you to stick around and listen to that if you're interested in learning more about inclusions. So there are two similar but separate requirements for use of a singe IRB. So the first is the NIH Single IRB Policy. It became effective in January of 2018. So it's been around for almost 4 years. Revised Common Rule Cooperative Research Provision Compliance Day was in January of 2020, so it's been around for almost 2 years as a requirement. And you can learn about these two requirements for single IRB use on the NIH single IRB for multi-site or cooperative research web page. And this site includes a link to all the relevant regulations and the several guide notices the NIH has published. And with that, I'm going to turn it over to Dr. Kearney to talk about clinical trials. Thank you.

Pamela Kearney: Thanks, Lyndi. Okay, the next part of our presentation, we're going to talk to you guys about determining when research involving human subjects is a clinical trial. Most of you have probably seen the NIH definition of a clinical trial, and it is a research study in which one or more human subjects are prospectively assigned to one or more interventions, and the study measures the effect of that intervention on the participant for health-related biomedical or behavioral outcomes. And NIH-defined clinical trials are actually quite broad. They can range anywhere from the type of clinical trials that we all think of, the pharmacologic efficacy type of trials, all the way to basic science studies, which are using a probe to expose a phenomenon in ... And as such, measuring biomedical outcomes on the participant. NIH has put together a clinical trial questionnaire, a set of four questions that are lifted directly out of the clinical trial definition. And as you go through each one of these questions, if you answer yes to all of them, this is a clinical trial. If you answer no to any one of them, it's not a clinical trial by definition. The answers to these questions are going to determine whether or not ... Are going to determine which FOA, or funding opportunity announcement, that you can apply to. It is going to determine the application form requirements that you will be under. It will also determine the criteria that reviewers are going to use to evaluate your application. And it's also going to determine whether or not you have to register your study on clinicaltrials.gov and report the results. It's going to determine the requirement for GCP training. On our website, there is a clinical trial decision tool, which takes you through each one of those four questions. The link to this will be on a resource page that you have with ... That will accompany this presentation. Now, I'm going to go through each one of those things that I talked about earlier, and the first one are the funding opportunity announcements, better known to some as FOAs. And the FOAs can come as a clinical trial required, clinical trial not allowed, or clinical trial optional. And you have to submit to the correct FOA. If you have a study that is a clinical trial and you submit to a clinical trial not allowed FOA, your application is considered misclassified as far as clinical trials. And applications that are misclassified to the incorrect FOA will be administratively withdrawn and they won't even be reviewed. So it's important that you get this correct. And the purpose of this policy is to improve NIH's ability to identify clinical trials, and that helps us stay compliant and helps you stay compliant as well with the regulations. And it ensures that key pieces of trial-specific information are submitted with the application. Again, this is a compliance issue. And it also allows NIH to uniformly apply the trial-specific review criteria to the applications. The next policy that we're going to touch base on briefly is the dissemination of NIH-funded clinical trial information. This policy requires clinical trials to be registered and have the results reported in clinicaltrials.gov. In order to be compliant, you'll have to submit a plan in your application, outlying how you're going to be compliant with the policy. You'll have to register your study no later than 21 days after enrolling the first participant. And the results, the summary results will have to be reported no later than 1 year after the primary completion date of the study. Now the next thing we need to briefly talk about is a special type of clinical trial called Basic Experimental Studies with Humans, or BESH. Now, BESH studies meet the definition for both basic research and an NIH clinical trial. We have a really great new website on the BESH studies. And if you do this type of research, I would really encourage you to check it out. It describes the four clinical trial questions that we talked about earlier, from the viewpoint of a BESH investigator. And it helps the BESH investigator kind of wrap their head around how they are also a clinical trial. And I would encourage you to take a look at that. And this is important to note, because certain BESH studies have some interim flexibilities. While they still have to register and report their results, they can do it in a platform other than clinicaltrial.gov. You can use an alternative platform. And these flexibilities are only for BESH studies that are responsive to a BESH FOA. So if the BESH studies come in under a regular clinical trial required FOA, they don't get these flexibilities. They only apply to those that are funded through BESH funds. Clinical trials also have a requirement that all of the investigators and staff that are involved in basically anything, design, conduct, oversight management, et cetera, have to be trained in GCP. And the GCP training requirement can be achieved through any number of things. It can be a class, it can be a training program or a certification from a recognized professional organization. But it has to be done by all of the staff, and the training has be refreshed every 3 years. Clinical trials also are required to submit a Data and Safety monitoring plan in their application. This plan has to address the overall data and safety monitoring framework for the study. It has to describe the procedures for adverse event reporting. It also has to identify a Data and Safety monitor, whoever that might be. It might be a PI for very minimal risk studies. It could be an independent safety monitory, or it could be a DSMB, or a Data and Safety Monitoring Board. And DSMBs are generally required for NIH-defined phase III trials. And with that, I'm going to turn it back over to Lyndi.

Lyndi Lahl: Okay, thanks, Pam. So, we're going to move on now to talk about considerations if you're applying for an NIH award that is going to involve human subjects. So the PHS Human Subjects and Clinical Trials Information Form has consolidated the information for human subjects inclusion and enrollment in clinical trials into a single form. So as you know, on this slide, you need to decide or determine whether or not your research is a clinical trial to know what information is going to ... You're going to have to include in this HSCT form. And I won't go into details of what all that will be because it's all listed on this form, or on this slide. So in your application, if you're proposing non-exempt human subjects research, you're going to need to address four different parts. A risk to the participants, the adequacy of the protections against the risks, potential benefits of the research to participants and others, and the importance of knowledge to be gained. So in terms of risk, you're going to want to talk about how the participants will be involved, their characteristics, the study design. You're going to want to mention all of the different planned research procedures, and any potential risk to the subjects associated with research study interventions, procedures, or interactions. This is not limited to physical risk. You also want to address psychological risk, social, cultural, financial, and legal risks. And then in terms of adequacy of protection against those risks, you'll certainly want to describe the informed consent process if you're getting informed consent. And if you have children, if you're going to be getting ascent, and then you're going to want to talk about the procedures that you're going to use to minimize the risks that you have identified. This would also include protecting the participants privacy and then there is a requirement that you have additional protections if you're going to involve any vulnerable populations. Vulnerable populations would including groups such as pregnant women, prisoners, institutional individuals, children, and any others who would be considered vulnerable. So the potential benefits of the proposed research, you're going to want to discuss what those potential benefits are, and then discuss why the risk to the subjects are reasonable in relation to what these anticipated benefits are for the participate and for others. Please note that financial compensation to a participant is not considered a benefit, so please don't put it down as such. And then the last thing, in terms of your application you want to discuss is the important of the knowledge to be gained. And you want to say what knowledge you think you will be gaining, and then in relation to the risks that are presented to the participants. So please note that the reviewers may not understand what you mean unless you give enough details in your application to be able to address each of these four sections. So you need to provide enough details for the reviewer to understand how, what, when, where, why and who, in terms of the risks and benefits and the knowledge to be gained. There are a few human subject concerns that are fairly often identified in peer review. The peer reviewers will often cite that the risks, whether it be physical, psychological or other, are not adequately addressed. Or maybe inadequate protections or no protections for any of the vulnerable populations that will be part of the research. You may not identify the source of the specimens and/or the data, and that can be especially important to know if the investigator was involved in the original data collection, or has direct identifiers associated with the source of the data. May not identify what you're going to do if there are any incidental findings, and there may be missing or inadequate Data and Safety Monitoring Plans. So these are some of the things that the reviewers find on a regular basis. So I wanted to take a moment to talk about multi-site study considerations, because you're going to need to indicate whether you're doing a multi-site study. The reason this is important is because all sites that are engaged in non-exempt human subjects research will need to have a Federalwide Assurance, or FWA for short, and have IRB approval. The Federalwide Assurance is something that would be obtained from OHRP. And please note that in general, if the funding recipient or the prime awardee is not doing research at their own site, they are still considered engaged in human subjects research. You can learn more about engaged on the OHRP website. They do have a guidance document that talks about that. And as I mentioned earlier, when it comes to single IRB, there is a requirement that if you have more that one US site that is going to be conducting the non-exempt human subjects research, you will need to rely on a single IRB to review the study. So when the single IRB is in effect, there will need to be a reliance agreement or authorization agreement between the relying site or sites and the single IRB that's going to be reviewing on behalf of that site. The OHRP has a sample authorization agreement on their website, and the link is here. So I'm going to take just a moment to talk about the resources that are available from NIH for conducting research involving human subjects. There are a few links on this page. The top link, NIH Human Subject Research home page, actually has links to pretty much all of the documents and resources that we've talked about this morning. I also want to call your attention to the Human Subject Protections Inclusion and Clinical Trial resource page, which is available and has a lot of additional details and links for it. So with that, I am going to stop and we'll open this up for questions. Thank you very much.

Dawn Corbett: Okay, hello, everyone. So if you have any questions, you can put those in the Q&A, using the Q&A button at the bottom of the screen. We'll go ahead and get started. It looks like we have some questions in there now. So the first question is for Pam. Do the CoCs have to be mentioned in any contract agreement between a primary site and its subawardee?

Pamela Kearney: Yeah, that's a good question, and I don't know if Lyndi, since Lyndi is actually one of the people who actually processes our CoCs, I'd be happy to send it to her. But the answer is yes. Every place for that data, if the data is covered by CoC, each person that gets that data has to honor that CoC. So that really should be in any agreements that the folks need to know about their responsibilities under the CoC. Lyndi, who don't I kick it over to you to see if you have anything to add?

Lyndi Lahl: Yeah, I think there's two different scenarios here. So you have a prime site and let's say the subawardees are also engaged in the research and they may be collecting information, that CoC that is issued to the primary awardee is also going to cover any of the subawardee sites. So it would be the responsibility of the prime awardee to make sure that the subawardees know that the data that they're going to be collecting, assuming that it's human subjects research, they have identifiable sensitive information, it would need to make sure that the subawardee knows that the CoC is covering any of the identifiable, sensitive information they are collecting. And they would need to disclose that to the participants generally through an informed consent. Thanks.

Dawn Corbett: All right, thank you. I have another question, and this one is about clinical trials and the definition. So for a human clinical trial, prospectively assigned does not mean randomized. What assignments would not be considered a trial?

Lyndi Lahl: Pam, you're muted.

Pamela Kearney: Now, sorry about that. That's a great question. Basically, prospectively assigned means that the design of the study has outlined how the folks will be assigned. So it is possible for prospective assignment to be patient-selected, for example. So if you have two interventions and you're going to go into a clinic and you're going to allow people to choose which ones, prospectively you have decided that. And they will come into the study not having had an assignment. You have written it out in your document how that will happen, and then the folks will be assigned. Something that would not be prospectively assigned, which is going to sound very obvious, is a retrospective study. So if you decide you're going to do a study, you're going to look at some records from your institution and you want to look at records of folks that had a certain intervention and didn't have a certain intervention, but that's already happened. And you go into the records and you are just pulling the records from the people that had the intervention and the records of people who didn't have the intervention. That even though you decided in advance you were going to do that, the intervention, it wasn't decided prior to the intervention. So prospectively assigned is simply that you are in advance deciding how the folks will have interventions that have not happened yet.

Dawn Corbett: Thank you, Pam. I have another question. This one is about single IRB, and the question is can you say a little more on the single IRB policy regarding multi-site studies and the IRB's responsibilities?

Lyndi Lahl: So, I'll go ahead and take that. And Pam, if want to add anything when I'm done, I'm more than happy to share the limelight here. So a single IRB is essentially taking the responsibility of that IRB review on behalf of all of those multi-site studies. Now, that doesn't mean that the institutions that are performing the research that are relying on an IRB external to their institution don't still have responsibilities. They generally are going to be looking for compliance, making sure that any of the other committee, such as a privacy board, all of things are satisfied. There is a reliance agreement that will need to be in place between the single IRB and the sites that are relying upon it. And that reliance agreement is going to really lay out what those responsibilities are for each of the parties. Pam, I don't know if you have anything to add.

Pamela Kearney: No, you did a great job.

Dawn Corbett: Great, we'll give people a minute to go ahead and put some questions in the Q&A box there. And while people are typing the questions, I do have one question, perhaps one of you could answer. And this is about the difference between exemption for research and research that does not involve human subjects. And so the person asking the question references the infographic that talks about exemption four, which involves the collection or study of data or specimens that are publicly available or recorded such that subjects cannot be identified. And, that in limited cases, they may be identifiable, and references the Common Rule. And the question is can you clarify, how is that different from research that is not human subjects research when using specimens that are secondary and not identifiable? Would you be able to answer that one?

Lyndi Lahl: Sure. Again, Pam, I'll start and if you have anything to add. So I think the real difference is under exemption four, the second one, it talks about information that is obtained, including from biospecimens, that was identifiable but then the investigator is recording in such a way that the participants cannot be identified. So it starts off identifiable, but when the investigator actually obtains that information, there are no identifiers associated with it. So it starts off as human subjects, and then to meet exception four and to protect the participants, it is de-identified. To meet the threshold of human subjects, it has to be something that's identifiable and obtained, studied, analyzed. I would refer you to the human subjects definition from the revised Common Rule for the specifics. So hopefully that helps the person understand. Pam, I don't know if you have anything else to add?

Pamela Kearney: Un-uh, no. Good.

Dawn Corbett: Okay, great. The next question is about reliance agreements and when they're required. And specifically, the question is can you establish a reliance agreement for exempt research? So research that would not require IRB approval or may require limited IRB approval, would you need to establish an reliance agreement for that, or could you?

Lyndi Lahl: Yeah, so general exempt human subjects research doesn't need IRB approval. Dawn, as you mentioned, there are a couple of those exempt categories that require a limited IRB approval, but that would generally be done at the institution where the research is being conducted. Now, if it is a multi-site study and everyone's doing the same exempt human subjects research, let's say exempt under category three, which is benign behavioral interventions, and they want to rely on one IRB to make sure that everybody is doing things the same, that would be acceptable that you would need to have a reliance agreement under that scenario if you're going to be relying on an IRB external to your institution. That is not a requirement, though, for the exempt research.

Dawn Corbett: Thanks. The next question that I have is about CoCs, and the question is when will the CoC be provided to funded investigators with clinical trials? So when do investigators get their CoC?

Lyndi Lahl: Well, that's a great question. So NIH ... For NIH-funded research, NIH automatically deems issued the CoC when the grant is awarded, or when the research is awarded. It is up to the investigator to figure out whether or not they have a CoC. I would refer you to the CoC pol and the CoC FAQs. It does a very nice job laying out the questions that you asked. Essentially, if you're doing human subjects research or if you're obtaining or collecting information that is identifiable and sensitive, you are most likely going to be deemed issued a CoC. I also want to say one more thing because we get a number of questions on this on a regular basis. NIH no longer issues paper or electronic certificates for the NIH-funded researchers. There is documentation that you would use to demonstrate that you had a CoC. That would include your notice of award, it would include the CoC policy. I think there's a couple of other things that you can use. But we not going to either confirm that you have a CoC because, again, it's the investigator's responsibility, and we are not going to issue you a paper or electronic certificate either.

Dawn Corbett: Thank you. So the next question is about SMART IRB. And the question is about the SMART IRB reliance agreements and single IRB. How is this related to the single IRB policy?

Pamela Kearney: Lyndi, do you want me to take it? You've been taking all of them.

Lyndi Lahl: Sure.

Pamela Kearney: Yeah, SMART IRB is not an NIH ... It's not out of NIH, although NIH is aware of it. We know about it. We have been to some of their meetings. So SMART IRB is not an IRB at all. It's actually an agreement. Institutions sign on to the SMART IRB, which means that they agree to the reliance agreements that they've ... In advance, they have agreed to the reliance agreement. So you can go ahead and sign onto these agreements without having to go through the legal wrangling of negotiating between the sites. It really doesn't have anything to do with the single IRB policy per se, except that it is a useful tool to help you be compliant with it. Lyndi, did I fill that okay?

Lyndi Lahl: Yeah, yeah. Yeah, it's just a tool. It just eases the ability to ... When the institutions that are involved in a specific research study, it helps to have everyone agree on what those requirements are going to be, who's going to be responsible for what. And NCATS, one of the NIH ICs, has been providing funding for SMART IRB. So we have a little bit of involvement in it. Thanks.

Dawn Corbett: We have a couple questions related to sites and how the single IRB policy relates to multiple sites. And so the question is can you clarify if the single IRB applies to multiple performance sites or one performance site with multiple recruitment locations? Can you explain how the single IRB policy applies to performance sites?

Lyndi Lahl: So I ... So before we get started, and it looks like Pam has something to say about this also, I want to remind everybody that we ... NIH has had a single IRB policy since 2018. The revised Common Rule came out with their single IRB requirements, and those went into effect in January of 2020. So it's not that they're competing, they actually are complementary to each other. So if your study had IRB review on or after January 20th of 2020, it is going to be ... And it's NIH-funded, it is going to be subject to the single IRB requirements both under the revised Common Rule and the NIH single IRB policy. We really rely on the revised Common Rule, but it kind of trumps when both policies apply. If it's an older study and it only applies to the NIH policy, then you don't have to worry about the revised Common Rule. And, sorry, now I forgot what the question was.

Dawn Corbett: I think that ... It's basically how the single IRB policy applies to sites. And so I think one of the things that we tell people is, right, are you using one IRB or two IRBs? That kind of answers your question. That if you're doing research in the US, you generally would need to use one IRB, unless you fall under one of the exceptions or it does not apply. Okay great. We have one more question here about the Common Rule. So this is related tot he elimination of IRB review of applications. And so the question is with the 2018 Common Rule and the elimination of IRB review of applications, is there a best practice? Should IRBs review the research award or what reviewer expertise by non-IRB personnel? So how ... Is there any expectation that IRBs verify the congruency of the application with the approved protocol?

Pamela Kearney: I'll jump in with that one. NIH no longer requires that IRBs review the application. And so at this point, it's really going to be up to the institution about how they wish to handle that. Some institutions will have a procedure by which they will make sure that the protocol and the application that resulted in the award are matching up so that the institution who is responsible for the terms and conditions of that award, to make sure that they are basically abiding by those terms and conditions. So I can't really speak to a best practice for the institutions, but it would be who the institution to makes sure that they are being compliant with the term conditions.

Dawn Corbett: Okay, so I'm going to ... I have one question here. What are my responsibilities if I have a CoC? Can one of you answer that?

Lyndi Lahl: I'd be happy to answer that. So first of all, you need to make sure that you have a CoC. Apparently you have already gone through and answer those questions, and you've determined that you do have one. So you need to make sure that the participants and the research know about the CoC protections, know about any limitations to those protections. So the old CoCs prior to the 21st Century Cures Act, it was the investigators decide whether or not they would ... They have the authority to be able to release data. And under the new CoC policy, they don't. They're prohibited from releasing data unless it is very specific circumstances. The participant has provided consent that they can release if it is for some kind of mandatory reporting, such as an infection disease or child abuse or elder abuse, if it is for other research. But if the institution receives a subpoena and asks for a biospecimen or asks for data or asks for an individuals name to confirm they were in study, they are not able to release that information. If they do release it, then they have violated the terms and conditions of their award.

Dawn Corbett: Okay, and I think this may be our last question. This is about single IRB exceptions. Who do I contact if I'm doing multi-site research and I want to request an exception to single IRB requirements. So if you are a great awardee, you would contact your program officer. If you are a contract recipient, you would contact your core. So it just depends on the award mechanism. And in general for the grants, they would submit an sIRB exception request just in time before that award is made. And then the program officer would shepherd that through.

Dawn Corbett: Okay, well I think that's all the time that we have for questions today. Thank you to everyone for attending. There are the slides posted where you went to join the presentation. You'll find the slides there. And there will also be a recording within 48 hours available. So thank you all.