An Overview of NIH Policies on Human Subjects

[Lyndi Lahl:]Hello. My name is Lyndi Lahl, and I'm the Human Subjects Officer in NIH's Office of Extramural Research, along with Pam Kearney, the Director of the Division of Human Subjects Research. We are going to be providing an overview of NIH policies on human subjects.

We have four different objectives that we are going to cover, so let's go ahead and start with the first objective. We will be talking about identifying NIH policies that pertain to research involving human subjects. NIH has many policies that pertain to human subjects research. During this session, we'll be introducing you to the ones that are displayed on this slide.

So it's an important question to ask, if you're conducting NIH-funded research activities, to know when the NIH Human Subjects Research applies. So, the first thing you need to know is the definition of research. Are you actually doing research, as defined by the revised Common Rule, and does that research activity involve human subjects? And that's also defined in the revised Common Rule. To note, some Human Subjects policies apply to clinical research, or medical research that would involve people, and then some of our Human Subjects policies apply only to a subset of those clinical trials. And NIH policies are complementary, or in addition to, the revised Common Rule.

NIH has developed a quick-decision tool that can assist you in determining if your research involves human subjects, if it's exempt from the federal regulations, or if your activity is not considered human research studies at all. Please note that this tool should not be used as the sole determination on whether your study is exempt from the regulations, the tool is available on the NIH Grants and Funding website.

So the first policy I'm going to talk about is the required education and the protection of human research participants. This has been an NIH requirement for over 20 years. All key personnel, who would include individuals responsible for the design and the conduct of the study, must have completed training in the protection of human subjects. This educational requirement also pertains to key personnel at alternate performance sites, including non-U.S. sites, as well as key personnel that begin after the award is funded. NIH expects that key personnel receive this required training before they are involved in the research, and this is a one-time training requirement.

So the next policy I'd like to talk about is the Certificates of Confidentiality policy, otherwise known as the CoC policy, and sometimes referred to as just the Certificate Policy. And basically, all NIH-funded research which falls within the scope of the NIH CoC policy is deemed to be issued a certificate. It's the responsibility of the recipient and their investigators to determine if their research is collecting or using covered information. I'm going to talk about covered information on the next slide.

So let me talk a little bit about the restrictions and protections now. So, any investigator or institution that is issued a certificate is not allowed to disclose or provide covered information in any federal, state, local, criminal, administrative, legislative or other proceeding, or to any other person not connected with the research. So this means that if you receive a subpoena to release research records, you would not be allowed to provide that information, because disclosure is only permitted when it is required by other federal state and local laws, such as for public health reporting of a communicable disease, such as someone who has been diagnosed with tuberculosis, or for child or elder abuse reporting. Another possibility for disclosing research data would be made with the consent of the subject, or if it's made for purposes of scientific research that's compliant with human subjects regulations.

So let's talk a little bit about what "covered information" means. Basically, covered information includes the names or any information, physical documents or biospecimens that contain identifiable, sensitive information that's related to a research participant. And in addition, if there is a very small risk that the information documents or biospecimens can be combined with another available data source in order to determine the identity of an individual, then that would also be protected by the certificate. Secondary researchers that receive information that's protected by a certificate are also required to uphold the protections of the certificate. So, all those disclosures that we talked about on the previous slide and the prohibitions for disclosing information would apply to secondary research. The certificate recipients need to inform any secondary researchers when information is going to be given to them that's protected by a certificate. And covered information is protected in perpetuity, so I would like to note that if you are going to continue to collect new data after your NIH funding ends, the newly-collected data would not be protected, because that NIH certificate would no longer apply, if you do not have NIH funding anymore. However, NIH can issue certificates for non-NIH-funded research. You would need to request a certificate in order to obtain protections of the certificate on any data that you will continue to collect after your NIH funding ends.

So the next policy I'm going to talk about is human fetal tissues. NIH's policy was implemented based on the HHS policy, which went into effect in 2019. And human fetal tissue research is defined as research involving the study, analysis or use of primary human fetal tissue, cells and derivatives, and human fetal primary cell cultures which are obtained from elective abortions. So if you are applying for research involving human fetal tissues, you'll need to provide sufficient details so NIH can evaluate this. You need to include all the information that's required, including a detailed budget. I'd like to note that if you're proposing research with human fetal tissues, you cannot use the PHS 398 Modular Budget Form; instead you'll need to use the R and R Budget Form. And I'd also like to note that you don't get additional room to be able to include these additional requirements. You'll have to stay within the applicable page limits. And if your application doesn't address all this information, it will be withdrawn, and will not be reviewed.

So the next two slides, I'm going to focus on inclusion. We actually have three policies that are applicable here. So the first policy is the inclusion of women and minorities in NIH research, and it is based on public law. And it requires that women and minorities are included in all NIH-funded clinical research studies, unless there is a compelling rational to exclude these potential participants. There are additional requirements, if you are doing an applicable NIH-defined phase III study, and you would need to do analysis by sex, gender, race and ethnicity for those studies.

So the two policies that are referred to on this slide, the first would be inclusion of children. It was revised in 2015, and it defines children as individuals under 18 years old. And then the second policy would be the inclusion across the lifespan policy, and its requirement is that individuals of all ages are included in NIH Human Subjects Research, unless there is a scientific or ethical reason not to include them. And this requires submission of individual-level data on participant age at enrollment, and in progress reports.

So now that you've heard about relevant NIH policies that apply to clinical research studies, I'm going to turn the presentation over to Pam, who's going to talk with you about clinical trials.

[Pam Kearney:]Thanks, Lyndi. Good afternoon, everyone. My name is Pam Kearney, I'm the Director of the Division of Human Subjects Research in NIH's Office of Extramural Research. And one of my other duties as assigned, I'm also the Clinical Trial Officer, and I'm going to talk to you today about the objective of helping you to determine whether or not the research that you're doing with human subjects is also a clinical trial.

So the first thing that we need to talk about is, exactly how does NIH define a "clinical trial"? Most people think of the classic clinical trial; you're doing a drug study, you're going to randomize people to use a placebo as a drug, you're going to measure the efficacy, you're going to measure the safety -- and that's very clear. That's what most people think of as a clinical trial. But what people don't understand sometimes is that a clinical trial can be many different types of studies. They can be exploratory. They could be pilot studies, or feasibility studies. They can be mechanistic or behavioral. They can even be basic science. There are types of studies called "basic experimental studies with humans," or BESH, that are both basic science and clinical trial. And the definition that we use is, a research study in which one or more human subjects are prospectively assigned to one or more interventions, which may or may not include a placebo or other control, and they will evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. So as you can see on this slide, the important points are highlighted in blue, and those are the ones we're going to concentrate on. And this definition is used to create four questions, which we'll see on the next slide here, that help one decide whether or not you're doing an NIH clinical trial. And you can find these questions on the Grants and Funding website. And when you answer these questions, it will help you determine whether or not you're doing a clinical trial.

So the first one is, does the study involve human participants? Well, this one is pretty easy. Most of the time you can determine whether or not human participants are involved. It's not always easy, but most of the time you can say, yes, I've got human people in my study. The second question is, are the participants prospectively assigned to an intervention? And there's two points here; first of all, is there an intervention? And is the participant prospectively assigned; meaning, do you decide in advance that you're going to assign people to undergo this intervention? In other words, this is not a retrospective study. The third question is, is the study designed to evaluate the effect of that intervention on the participant? And sometimes that's easier said than done, but we'll talk about that as well. And then the last one, is the effect that's going to be evaluated a health-related, biomedical behavior outcome? And in general, we say if the first three questions are yes, almost invariably the last question is also going to be yes. I'm never going to say always, but most of the time this is going to be yes, because you don't -- if you're applying NIH funding, do you really want to tell NIH that you're not looking for health-related, biomedical behavior outcomes? So most of the time that question is going to be answered yes.

And the answer to this question about whether or not you're actually doing a clinical trial is really important, because the answer to this is going to determine a number of things. First of all, it's going to determine which FOA type that you're going to apply for. There are several different types of FOAs, you've got a Clinical Trial-Required, there's Clinical Trial Optional, and then there's Clinical Trial Not Allowed. It also is going to determine certain requirements in the application, so the application form requirements -- what information you're going to have to fill out. If you were doing a clinical trial, you're going to have to fill out some specific information. It's also going to determine the criteria for evaluation for review, so the review criteria for clinical trials is specific, and your application will be reviewed based on clinical trial criteria. It also invokes a requirement for registration and reporting, and it also will invoke the requirement for GCP training, for the folks that are participating in the clinical trial in some way.

So if you answered yes to all of those questions, then you are doing a clinical trial. And we have a clinical trial decision tool on the Grants and Funding web page. And this will walk you through each of those four questions. And it will have some kind of helpful hints, links like case studies and FAQs, and that sort of thing, to kind of help you make that decision. Now the answer to the tool, of course, is dependent upon whether or not you answer these questions correctly, so utilize the other resources that are included in that tool to help you.

So I mentioned earlier the different types of FOAs. And you have to apply to the correct FOA, regarding whether or not you're doing a clinical trial. And the reason for this is that applications that are submitted to an incorrect FOA will be administratively withdrawn, and that would be unfortunate. So it's really important that you determine whether or not you're doing a clinical trial before you apply to the FOA, so that you can make sure that you apply to the correct one. And there's a number of reasons that this is done. First of all, tracking the clinical trials through the FOAs has improved NIH's ability to actually identify a proposed clinical trial, clinical trials that are proposed to us for us to fund. It also ensures that key pieces of trial-specific information are included with each application. So if you remember that I talked about that specific information that needs to come with the application, there are requirements that are invoked when you're doing a clinical trial, and that will guide you through the information that you need to provide for us. So it also helps with uniformly applying the trial-specific review criteria as well.

So you heard me mention earlier about basic experimental studies with human BESH -- I want to just touch on that briefly, because there are special types of FOAs called "BESH FOAs." And as you will remember, BESH studies meet the definition both for basic science, for basic research, and an NIH-defined clinical trial. And NIH extended the interim policy flexibilities for registration and reporting for studies coming through these BESH FOAs through September 24 of 2021. Now keep in mind that you still are required to register and report these studies, but there's a flexibility to use an alternative site, other than ClinicalTrials.gov. But these flexibilities only apply to BESH studies that are funded through BESH FOAs. So if you've applied to a regular Clinical Trial-Required FOA with a BESH study, that flexibility doesn't apply. So it only applies to trials that came in through BESH FOAs, so keep that in mind.

So the next thing we're going to -- while we're talking about registration and reporting, the policy -- we have a policy for the dissemination of NIH-funded clinical trial information. And this is the policy that requires the registration reporting of your clinical trial. And this policy requires, first of all, that you submit a plan in your application, which is going to outline how you're going to comply with this policy. And then number two, you have to register your clinical trial no more than 21 days after enrolling that very first participant. And then you have to report the summary result of your study no later than one year after your primary completion date. And you can check, as you may have noticed through this slide deck, that we have little blue boxes with Guide notices on there, and that will give you, if you go to those Guide notices, and those links there that we'll provide. We've got information at our booth and such, if you can't get to this through the online one, but we'll make sure that these are available to you. And you can click on those and get to the Guide notices and get more information.

And then if you are doing an NIH-defined clinical trial, another requirement that you have another policy is that everybody that is working on that clinical trial has to have good clinical practice training, GCP training. And basically, anybody who works at all on the clinical trial has to be trained in GCP. So I think they talk about those that design, conduct, do oversight management, et cetera -- basically, if you are working on a clinical trial, you need to have GCP training. It's a good idea anyway, even if you're just doing human subjects research. But the policy requires it for those that are working on clinical trials. And you can get this training through any number of ways. You can see here on the slide that you can take a class or a course, and you can do an academic training program. You can obtain a certification from a research organization, a professional research organization. But however you do it, you have to have that done, and the training needs to be repeated every three years. So you have to refresh every third year.

And then another policy that you need to keep in mind if you're doing a clinical trial, is that all clinical trials have to submit a Data and Safety Monitoring Plan. People often refer to it as the "DSMP." And this plan has to address the overall data and safety monitoring framework; this is how your study is going to monitor the safety and the data throughout the life of your study. The plan has to describe your procedures for reporting adverse events, and it also has to identify the monitor. And a monitor for study can range, depending on the risk of the study, if it's a very minor minimal risk study, the PI might be the monitor. You could have an independent safety monitor, an independent monitoring committee, or you can have a formal DSMB. Now a DSMB is generally required for NIH-defined Phase III trials.

So with that, I'm going to turn it back over to Lyndi, who's going to talk about considerations when applying for an NIH award for research that involves human subjects. Lyndi?

[Lyndi Lahl:]Okay, thanks, Pam. So the table that you see in front of you shows a consolidation of the PHS Human Subjects and Clinical Trials Information form, and this is where you would put all the information regarding human subjects, inclusion enrollment and clinical trials, all in one place. So you can see there's five different sections. And in addition, this also allows you to add study records and-or delayed onset studies, as applicable. So within each study record, you would add detailed information at the study level.

You can see from the slide that if you're proposing the clinical trial, there is additional required information, as opposed to if you are not doing a clinical trial. So we are going to go on and concentrate on section 3, which is the Protections and Monitoring Plans.

So applications that propose non-exempt human subjects must address four different factors, so we're going to talk about each of these factors in the next couple of slides. So the first factor that you need to discuss is risk. You'll need to talk about the study populations that you plan to include in the study, describe all planned research procedures, including interventions and interactions that would involve the participants. And for studies that are going to use previously collected biospecimens data or records, you'll need to describe the source of these materials, and whether this information can be linked to an individual, and if so, who would be able to link it? Is it somebody that's not involved in the study? You would also need to describe all potential risks to the subjects associated with each study intervention, procedure, or interaction, not just physical risk, but any other type of risk, and risk to privacy and-or confidentiality of the data.

So the second factor that you need to talk about within this form would be the adequacy of protection against risk. So you'll need to describe the process for obtaining informed consent, including any plans for obtaining consent from a legally authorized representative, if you plan to enroll adult subjects who are not able to consent for themselves. And if your research will involve children, you would want to describe the process for obtaining parental permission and child assent, if your IRB is going to need child assent. In addition, you would need to describe how you are going to protect against or minimize all potential risks that you've identified, and how you will protect the privacy of the participants and the confidentiality of the research data. This is also where you're going to describe plans for handling incidental findings, so that would be something that occurs that, within a study procedure or test that you've done that you weren't expecting to get. So you may see something on a research image or during screening tests, or you may even have a paternity test that comes back and you say, hmm, that wasn't expected. And if you're going to be enrolling any vulnerable populations in your study, you would want to provide a rational for involving these special, vulnerable populations, as well as any additional protections that you're going to provide for the participants.

So the third factor that you need to address is the potential benefits of the proposed research to research participants and others. So you want to describe the potential benefits of the research to research participants, and discuss why the research to subjects is reasonable in relation to the anticipated benefits to the participants. And please, don't put financial compensation as a benefit, because it's not.

The fourth factor that you will need to address is the importance of the knowledge to be gained. And in this section, you would discuss the importance of the knowledge to be gained as a result of the proposed research, as well as why the risk to subjects are reasonable in relation to the importance of the knowledge that is reasonably expected to be obtained as a result of this study. So you want to make sure that you're providing sufficient information in the application to address each of these factors.

Now on this slide, I've also listed some common human subjects' concerns that are identified when the peer review panel is looking at the application. So under Risks, it's often found that not all risks are addressed; an example of this would be including risk from a study product that will be administered during the study, but not including a risk associated with the two-week wash-out period that the participant will have to do before they actually start receiving the study product.

Another one would be inadequate protections for a vulnerable population. It would also include incidental findings that are not addressed, such as if a screen procedure with a chest x-ray shows there is a mass -- you need to have a plan on how you're going to address this.

So there are a few multi-site study considerations that I want you to be aware of. So all sites that are engaged in non-exempt human subjects research will need to have a Federal-Wide Assurance, otherwise known as an FWA, and they will also need IRB approval. So in general, this would include the funding recipient. If human subjects research is going to be done as part of their study, then they would be considered engaged in human subjects research. And that FWA that I mentioned is something that you would obtain from OHRP.

So under the revised Common Rule, sites located within the U.S. that are using the same protocol to conduct non-exempt human subjects research must rely on a single IRB to review the study. So any participating sites that are relying on this single IRB will need to sign a Reliance Agreement, and that Reliance Agreement clarifies the roles and responsibilities of the single IRB in the participating sites. And I would direct you to the OHRP website, which has more information of Reliance Agreements, on engagement, et cetera, and on the Federal-Wide Assurance.

And that takes us to our last objective, which is identifying resources for investigators conducting research involving human subjects. I have two different links on this slide; the first is to the NIH OER Human Subjects website. This has links to the policies that we've discussed to tools and to other FAQs and helpful information as well, so I would encourage you to look at this website. And then the second link is to the OHRP website, and this will provide you with the regulations that you would need to follow, OHRP has guidance documents, they also have FAQs and some tools as well.

And with that, I would like to thank you very much for your time. Pam and I are open to answering any questions that you might have. Thank you very much.