Human Subjects Research: What SBIR & STTR Applicants Need to Know Webinar Transcript

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Stephanie Fertig: Good afternoon, everyone, and welcome to today's webinar focused on human subjects research and what SBIR and STTR applicants need to know. I am joined .. . My name is Stephanie Fertig. I'm the HHS Small Business Program Lead, and I am joined today by a wonderful team from our Office of Extramural Research Division of Human Subjects, and my wonderful panelists will be talking and answering some of your questions around human subjects research. I'm going to provide a brief overview of the SBIR STTR program just to make sure everyone is on the same page, but then we're going to talk about some human subjects research basics by Lyndi Lahl, who is the Human Subjects Officer within the Division of Human Subjects research within the Office of Extramural Research.

Then we're going to talk about clinical trials requirements from Pamela Kearney, who is the director of the Division of Human Subjects Research in the NIH Office of Extramural Research, and that office, that specific division oversees the implementation of human subjects, clinical trials and inclusion policies and regulations for all of extramural NIH, and so that you're hearing it directly from the people who really know these policies and rules today. And then finally, you're going to be hearing from Dawn Corbett, and Dawn is the NIH Inclusion Policy Officer within the Division of Human Subjects Research in the Office of Extramural Research, and she specifically helps coordinate and, again, provide trans-NIH leadership around ensuring the inclusion of women, racially and ethnic minorities and individuals across the lifespan in NIH-defined clinical research.

So today we're .. . And then we're going to have some questions and answers because I can assume that you guys will have a few questions after those presentations. So let's get started. Let's talk about SBIR STTR. We're going to go through a number of .. . We're going to quickly kind of overview the SBIR and STTR today, so I encourage you to check out our website for more information. If you have specific questions about SBIR STTR program, our website is a great resource for you. Now, we really utilize the small business program to meet our mission,

which can be summarized as turning discoveries into health. So we take those great innovations that are all across the country and help individuals get those innovations into the hands of the patients, clinicians, caregivers and researchers that need them, and often, that may involve human subjects research, and that's why today's webinar is so important.

When we talk about the small business programs, you also might know them as America's SEED Fund, we're thinking about the SBIR and STTR. Now the SBIR and STTR have similar scope. You can get clinical trials in both in SBIR or in STTR. Really the difference between the two is that the SBIR allows for partnering while the STTR requires it. Now, there are some differences in policies. We're not going to get into those today. Again, I encourage you to go to our website, but clinical trials can occur in either of those programs. Now, NIH funding is one of the largest sources of early stage capital for life sciences in the United States, and we really do fit within that space of you've done the basic research and discovery and you're really moving into proof of concept and further research and development to hopefully move you to a point where you are able to de-risk the technology to the point where an angel investor, venture capital or strategic partner will take over and help provide capital or license the technology or transition ... and help you transition it out to the market.

This is non-dilutive funding, and oftentimes, awardees do leverage funding to attract those investors and partners. And, again, many times some of that de-risking may involve human subjects research, and it may be something that investors are looking for. We've had a number of companies that have successfully taken these great innovations and turned them into products, and so we have those online, and I encourage you to take a look at those different success stories. They really show the breadth of the kinds of technology that we support. We support companies all across the country. We support them in a wide variety of different technologies from diagnostics to therapeutics, both drugs, biologic devices as well as research tools, so we support kind of a wide variety of things that fall within the NIH mission.

Now, the SBIR STTR programs are phased programs, and with regards to clinical trials, there is some difficulty in the nomenclature for SBIR and STTR. So we do have two phases in the program, a Phase I, which is a feasibility study, and Phase II, which is full research and development. Now, an SBIR Phase I and an SBIR Phase II, they're not clinical trials phases.

They're not related to the phases of a clinical trial. It is an unfortunate similarity in the nomenclature. So we'll try to make sure to keep that straight and make sure you're aware of which one we're referring to, but obviously you can always ask us questions, but the SBIR and STTR Phase I versus the SBIR STTR Phase II are not related to the clinical trials phases there. I will often get the question of whether or not a clinical trial can be in an SBIR or STTR Phase I, and, again, it is possible, but it's also important to note that not all institutes and centers allow for clinical trials within their SBIR and STTR, so that's why it's so important to reach out and talk with us well in advance of applying, particularly if you're doing anything with regards to human subjects research.

Now, I did provide information on the budget guidelines, and we do have waivers to exceed these budget guidelines from the Small Business Administration, and, again, human subjects research is often one of the topic areas that we do have some flexibility to provide some additional funding or time, and so, again, it's very important to reach out and talk with us in advance of applying because different institutions and centers, again, do participate and do have different budget guidelines for human subjects research. Now, the majority of our funding does go through investigator initiated grant applications. We do have standard receipt dates. The next one is January 5, and you can find all of our open funding opportunities online, but I think it's important to note .. . And I put the general grant omnibus solicitations here. It's important to note that we do have separate clinical trials not allowed and then clinical trials required, so you do need to know whether or not you're doing a clinical trial to determine whether or not .. . which one of these program announcements you should come in under. And, again, individual institutes and centers may not accept clinical trials, and so it's important to know whether or not a specific institute or center that you're likely to be assigned to would accept your human subjects research proposal, and so read the program descriptions and research topics section very quickly.

Targeted solicitations may or may not allow clinical trials, and so, again, important to know. We have a lot of information about preparing an application including application instructions, annotated form sets, and, again, there are programs for applicants, applicant assistance programs if you are new to the SBIR and STTR programs. Those application instructions and the

detailed information, if you're doing human subjects research, there are specific instructions around human subjects research and clinical trials, and we're going to get into some of that today, but, again, it's important to make sure you review and read that information carefully. But, again, the most important information is to talk to us. Talk to a program officer well in advance of applying. The program officer can be a real help .. . a real benefit to understanding whether or not you fit within the program at a specific institute or center, particularly with regards to clinical trials since there, again, is some variation across the national institutes of health as to whether or not we will accept them.

So, again, please reach out to us and talk with us. If you're not sure who to contact, you can look at a list of small business program managers. We do have the RePORT tool online where you can look and see what similar .. . what things within your topic area, where they've generally been assigned and who they've been assigned to, and finally, if you're not sure who to contact, you can always reach out to our office, seedinfo@nih.gov. So I'm going to leave it there. That was a fast, fast version of the SBIR and STTR programs. We do have webinars online. You can .. . If you're interested a more in-depth conversation or an in-depth webinar on the SBIR and STTR programs, you can find those online, including transcripts and recordings and slide decks. But with that, I am going to .. . Hopefully, this will work, and we'll turn it over to Lyndi.

Lyndi Lahl: Excellent. Thanks, Stephanie. Well, good afternoon, everyone. I am really happy to be here with you today, and I'll be talking about human subjects protections and the requirements associated if you're going to be human subjects research. And remember, you can put questions in the Q and A, and we're going to have a lot of time at the end to be able to answer those questions. So let's go ahead and get started on considerations when proposing research involving human subjects. So the regulations at 45 CFR 46, otherwise known as the Common Rule, harmonize the protection of human subjects research when that research is conducted or supported by any of the 26 U.S. Federal departments and agencies that are signatories on the Common Rule.

Now, some of these departments and agencies include the Department of Defense, the Department of Veterans' Affairs, Department of Education, National Science Foundation and, of

course, Department of Health and Human Services, under which NIH is. So when a recipient is conducting non-exempt human subjects research with NIH funds, the regulations 45 CFR 46 apply. Now, there's also four subparts that go along with the Common Rule, and these provide additional protections for vulnerable persons and apply when NIH-funded research involves pregnant women, fetuses, children and prisoners.

Now, I'm not going to talk about the fifth subpart, which is IRB registration because it really isn't applicable for this talk. So a lot of my presentation is going to be devoted to how you determine if your proposed activity is non-exempt human subjects research. And to make this determination, you need to ask three questions, and it should be in the following order. One, is the activity research? Two, does the research activity involve human subjects? And three, is the human subjects research exempt? So I'm going to through each of these questions so you'll have a better understanding of how to answer the questions.

I do want to note that most institutions that routinely conduct NIH-funded human subjects research have a process in place for making this determination, if the activity is research, if the research involves human subjects and if the research is exempt. In general, this is going to be done by somebody that's not involved in performing the research activities, such as someone in the IRB office, maybe a staff member, maybe an IRB member. It doesn't have to be that, but it really should be done by somebody that's not involved in the research activities themselves, and the reason for this is the persons performing the activities are conflicted, and they may not make the correct determination, so I would recommend that if you're in that position and you need to have a determination, if you have an IRB office within your institution or you're otherwise affiliated with one, you would want to contact your IRB office or Office of Sponsored Programs or another entity within the institution so you get an unbiased answer.

And we do have some decision tools that would help, and we'll talk about that a little bit more later, but it's not like you are just left on your own, so there's that as well. Okay. So .. . Whoops. Okay. So let's talk about the first question, determining if the activity is research, and to do that, I'm going to think about the Common Rule and how the Common Rule defines research, and it's defined as a systematic investigation including research development, testing and

evaluation designed to develop or contribute to generalizable knowledge, and it's the bolded words that I'm going to focus on in the next slide.

So let's dive a little deeper. Is the activity a systematic investigation? Are there plans to use some kind of method in the approach? Is there a hypothesis? Is there a research? Are there plans to systematically collect and analyze the data? Now, once you have thought about is this a systematic investigation and you've decided yes, it is, you need to think about the second part of the definition. Is the activity designed to develop or contribute to generalizable knowledge? So you need to think about will the activity add information and contribute to generalizable knowledge? And regardless of what the activity is, the questions on this slide can help you in the determination if the activity is research. And remember, NIH funds research. We general .. . We do some training, grants and fellowships, but mostly what we do is we fund research. Okay. So let's go on to the next slide. So we've answered question one. We've decided an activity is research.

So now the next thing you do is determine if the research activity involves human subjects, and, again, I'll go back to the Common Rule, which provides the definition for human subjects, and they are defined as a living individual about whom an investigator conducting research either obtains information or biospecimens through intervention or interaction with the individual and uses, studies or analyzes the information or biospecimens or obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens. So let's consider question two, and the following questions are going to be relevant if you're determining if human subjects are involved.

So you need to think about who is the subject. A human subject is the person that the information is about or from whom the specimen was taken. Now, note that this means if you're talking with a parent and soliciting information about their child's health, the child is the subject, not the parent. However, keep in mind that the parent may also be a subject in the research if you're also soliciting information from the parent about themselves, and we see this a lot in research that is done, let's say in a clinic setting, and you're asking health care providers about their experience of treating, let's say disease X, and you are also looking at the

participants or the medical .. . the patients in that medical clinic who we call human subjects or participants.

So you can have several different groups that are human subjects within your activity. So after you identify who is the subject, then you need to think about is there an intervention or an interaction, or does the investigator have identifiable private information about the subject or identifiable biospecimens? And I do want to note that an investigator does not have to directly interact with a subject or perform interventions with the subject for the person to be a subject if the investigator is obtaining private identifiable information about the subject or obtaining identifiable biospecimens. Okay. So let's say we've identified it is research and it involves human subjects.

Now, the third question to ask is determining if the human subjects research activity is exempt, so I want to talk for a moment about what it means to be exempt so you have a better understanding of this. So research activities that meet the conditions for one or more exempt categories are exempt from the typical requirements of the Common Rule which would be things like have IRB review and approval or obtaining informed consent. Now, remember, if the proposed human subjects research activity is exempt under one or more of the exempt categories, then the activity is not non- exempt human subjects research. So I want to look at the different exempt categories of research now. So there are eight different categories of exempt research, and I want to talk about one in particular and then just kind of give you some broad notes on a few of the others.

So category four is secondary come here involving the use of identifiable private information or identifiable biospecimens, but it needs to meet certain criteria, and there's four different criteria that it might meet in order to qualify for this. So the most common one that we most often see is that it's when the information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, that the investigator does not contact the subjects and agrees that they will not re-identify the subject.

Now, please note that this category does not apply to studies that involve research interventions or interactions with participants since it's only for secondary research. It's only secondary use of specimens or data. So some of the categories will require limited IRB review, and it's under categories two, three, seven and eight, and depending .. . Again, there's some qualifiers under each of those, so it may or may not need limited IRB review. Some exempt research may involve a clinical trial, so this would be categories one, three, five or six.

Now, it doesn't mean that if you are doing exempt research under one of those categories that it's a clinical trial. You would need to decide if it's a clinical trial or not, and Pam is going to talk about clinical trials and the four questions that you need to consider when determining if your research is a clinical trial or not. I also want to spend just a moment talking about exemption five because that particular exemption is often confused with research that's reviewed by an IRB under category five using an expedited review procedure, so two completely separate things, and I do want to mention that today, NIH has not funded any research activities that are exempt under category five, so likely that is not a category that you will ever use.

Now, NIH has a quick decision tool that can assist you in determining if the research involves human subjects, if it may be exempt from the federal regulations and if the activity is not considered human subjects research. Please note that we do not expect you to use this as the sole determination on whether your study is exempt from the regulations, but it is, like I said, a helpful tool. Okay. So we've gone through the three questions, so let's figure out where we are now. So when you answer the first two questions yes and you answer the third question no, that means that you have now determined that you're activity is non-exempt human subjects research, and it will require IRB review and approval.

So let's talk a little bit about what that would mean for you. So per the Common Rule regulations, institutions engaged in HHS and NIH conducted or supported non-exempt human subjects research have to provide written assurance that their institution will comply with the regulatory requirements, and this is done through the institution obtaining an OHRP-approved Federal-wide Assurance, or abbreviated FWA. That's what most of us call it, and the institution needs to certify to NIH that the research was reviewed and approved by an IRB and that the research will be subject to continuing review by an IRB. And I want to note that the IRB that is

reviewing on behalf of the institution that's holding the approved FWA must be registered with OHRP.

Now, I'm going to concentrate on the first key term that I have bolded on the slide, and that's engagement. I'm not going to talk about FWAs and certification of IRB approval, but I do want to note that the resource document that will be available later on, well, it does include references for this information. Now, in general, institutions are considered engaged in an NIH conducted or supported non-exempt human subjects research project when the institution's employees or agents obtain for research purposes data about the human subjects through an intervention or interaction or they obtain identifiable private information about the subjects or they obtain informed consent from the subjects.

I do want to note that if you are a prime recipient of an NIH award, this could be for a grant, contract or cooperative agreement, if the award is going to involve non-exempt human subjects research, the primary recipient is also considered engaged in the research project even when all activities involving human subjects are carried out by employees or agents of another institution. So in other words, if you received that award from NIH but you really don't have the capacity to do the human subjects research, so you do a subaward to another entity that's going to conduct the research, as the primary recipient, you are still considered engaged in the research. Okay.

So the next three slides, and that's going to then be it for my presentation, are about select NIH policies that pertain to investigators and their institutions when they are conducting NIH-funded human subjects research. Now, NIH has a requirement for education on the protection of human subjects research for investigators and all key personnel. This includes key personnel that are at a consortium, institution or performance site, and this is when the sites are participating in research involving human subjects. Now, this is just a one-time training requirement, and NIH does not require that a specific course be taken or say that there is specific required content in that, and so institutions determine what is appropriate. I do want to tell you though, even though it is a one-time training, NIH recommends that refresher training be done every few years for both investigators and key personnel because it's an appropriate thing to do. Okay.

The next policy that I'm going to highlight is the NIH Certificate of Confidentiality policy, or CoC policy as we commonly refer to it. So all NIH-funded research within the scope of the NIH CoC policy is deemed to be issued a certificate. Now, it's the responsibility of recipients and their investigators to determine if research is collecting or using covered information. Well, what is covered information, you might ask. Certificates protect covered information. This includes the name or any information, physical document or biospecimen that contains identifiable sensitive information that's related to a research participant.

Now, the reason that certificates are so important in the protection of participants is that the certificate prohibits any investigator or institution who is issued a certificate from disclosing or providing the name or information, documents or biospecimens containing identifiable sensitive information in any federal, state or local civil, criminal, administrative, legislative or other proceeding to any other person not connected with the research or for any other purpose, and there are a few exceptions in there. So think about if you get a subpoena that asks you to disclose the name of your .. . the participants or asks you to provide a specimen. The certificate will prohibit you. You don't have an option here. It prohibits you from providing that if you are covered by the certificate. Now, like I mentioned, there are some exceptions to this disclosure. Disclosure is permitted only under certificate circumstances.

When it is required by other federal, state or local laws, such as for public health reporting of communicable disease or child or elder abuse reporting, if it is made with the consent of the participant or if it's made for purposes of scientific research that is compliant with human subjects regulations, and only under those circumstances may you disclose that information or biospecimen or the name of the participant. I do want to mention that the protections of the certificate last in perpetuity, and when you have the NIH funding and you have determined that, yes, you fall under the scope of the CoC policy, all of the data that is collected under the certificate will continue to be covered by .. . will be covered by the CoC until your NIH funding ends. But remember, even after the NIH funding ends, all that data that was collected during the time you had funding is protected forever, and there's a lot of information on the NIH CoC website, and I also want to mention, if you're ever doing non-NIH-funded research and are interested in getting a certificate, we do have .. . We can issue certificates for non-NIH-funded

research as well, and, again, I would have you go to the CoC website, which talks about that as well. Okay. Let's talk about the two Single IRB requirements.

So the NIH Single IRB policy has been around for a number of years. It first started in 2018 and applies to domestic sites of a multisite study when those sites are conducting the same non-exempt research protocol .. . human-subjects research protocol, which means that the domestic institutions are required to use a single IRB. Now, there is another single IRB requirement, and this one is in the Common Rule, and it's the Cooperative Research Single IRB requirement, and it applies to any institution located in the United States that is engaged in cooperative research. The institutions must rely upon approval by a single IRB for that portion of the research that is conducted in the United States.

Now, when a single IRB requirement applies, there needs to be a written agreement between all of the sites that are relying on the single IRB and the actual reviewing single IRB and links to the NIH single IRB guide notice and the regulatory citation under the Common Rule for that cooperative research single IRB requirement are on this slide, but in addition, NIH has a lot of information on single IRB for multisite or cooperative research available online, and that would be a place that I would suggest that you also look for more information, and that concludes my portion of the slides. I'm going to go ahead and turn it over to Pam. Thanks.

Dr. Pamela Kearney: Okay. Now I think you can .. . I think you can hear me now. Welcome, everybody. Thanks so much for being here. My portion of the talk is about clinical-trial requirements and what small business applicants need to know. Quite frankly .. . let me see if I can .. . there. What you need to know about clinical-trial requirements, truth be told, is really the same as anybody who's doing a clinical trial, and I'm going to try to go over some of these requirements today. The goals are for you to understand the NIH definition of a clinical trial. We're going to review how do you decide if your study is a clinical trial. I often hear a lot of folks who are surprised when they find out that the study that they're doing, which is not a classic drug study .. . They're surprised to find out that NIH considers them to be doing a clinical trial and that they're covered under all of the regulations.

We're going to do a very high level overview of the clinical trial policies and regulations. Unfortunately, we only have about 20, 25 minutes to do this. We could probably do an entire 1/2-day seminar on these, so my goal is to kind of go over each of these policies and regulations and give you some relevant resources where you can go and do a deeper dive and look into them. So my goal is to give you enough information to know what you need to know so that you can go and dig out the details when you need to. We're also going to go over a bunch of resources. As Lyndi mentioned earlier, we have put together an entire list of resources, links and websites and tools and that sort of thing that will be included when they post the slides in about 7 days. They're also going to post that resource.

Also, in my slides, I always take the links and such that I use, and I put them in slides at the end so that if you're going through the slides and you're trying to find something and you're looking for the link, you can just go right to the end and pull the links out that you need. So the very first thing is what exactly is a clinical trial, and at some point in time, you have probably seen any number of these words associated with clinical trials, and it's actually quite broad. The NIH definition encompasses a large number of types of studies that are considered to be clinical trials. There can be mechanistic studies. There can be feasibility studies can be clinical trials. Basic science can be a clinical trial. So there's a wide range of things that meet the definition of clinical trial. The policy came out in 2015. The link is here.

People refer to it as the new definition. As you can see, it's really not so new anymore, but the definition is a research study in which, one, human subjects are prospectively assigned .. . Number two, they're prospectively assigned to one or more interventions. Number three, those .. . the study is designed to measure the effect of that intervention, and number four, those effects are health-related or biomedical outcomes. And when you go and fill out your application, you will actually see four questions, and these will look very familiar from the last slide. The questions are pulled directly out of the definition, and if you answer these four questions, all of them .. . If you answer them all yes, then you are doing an NIH-defined clinical trial. And I've highlighted and bolded the most important parts of these questions, and we want to make a couple of notes.

Folks can sometimes get confused about what some of those definitions mean. When you go on to our website and you look at our website, it will actually link you to all of the definitions, but I want to point out some common misconceptions just from the very beginning. When we refer to prospective, that they're prospectively assigned to an intervention, prospective only means assignment of the intervention is arranged in advance. So it's not a retrospective study. You have decided in advance that X people at X time will undergo X intervention or manipulation. It's arranged in advance. When it's assigned .. . People think it has to be randomized to be a clinical trial. This absolutely is not true. You do not have to randomly assign your participants to undergo a particular intervention. It simply means that you are assigning them in advance. You can decide that participants at X place will come in, and they will choose their own group. Participants can choose their own group. The physician can choose. Just doesn't have to be random.

They think that this person would do better in this group. They're getting put in that group. You have decided that in advance that this is the way that they will be assigned. There also can just be one group. You can just have one group, one intervention. The people will all get the same thing. That is still assigned in advance that they will get it. And also, interventions don't have to be classic drugs. These can be a manipulation. If any of you are familiar with functional MRI, very often the task in the functional MRI, the f part of fMRI, is an intervention. You can have a flashing checkerboard, or you can show people emotional faces and see what happens in certain parts of their brain. So that is a manipulation. That can be considered an intervention. So it doesn't have to be a classic drug study.

Also, biomedical outcomes can be as simple as an increase in health knowledge. So if you are doing an intervention where you are educating a group of students about the mercury in their diet so that they can avoid the dire consequences of consuming mercury, and you test them before and after, and you have increased their knowledge about mercury consumption, then you have demonstrated a biomedical outcome and change of knowledge. Same thing with intent to change behavior. You don't have to necessarily document said behavior. You can just document an intent to change behavior.

So just keep in mind that these definitions may not be exactly what you think they are in the classic drug study sense. So just one quick word about a special type of clinical trials that you guys may not run into that much because you're one step further, these are studies that are clinical trials but they're also basic research, and a basic research studio is a systematic study that is directed at getting greater knowledge or understanding of a phenomenon and observable facts without specific applications in mind. Since you guys often have specific applications in mind, it doesn't always fit, but if you're doing one step before you get to this part, you might be doing a BESH, and there are certain flexibilities that might be given to BESH. So .. .

But just keep in mind that these are studies that are both basic research, and they also are a NIH-defined clinical trial, so that's just something to keep in the back of your mind. All right. What I want to do is I want to give you an example, just so you can start wrapping your head around what a clinical trial might look like that is not a classic drug study, and keep in mind this is a very, very fictional case. This is completely made up. Don't look at the science part of this. Don't pick apart the different things. This is simply for demonstration purposes. So we're looking at a study where some investigators that are interested in narcolepsy .. . And they're going to test the concept that electronic signals delivered to the skin can affect alpha waves of early sleep.

So what they're going to do is, they're going to take healthy volunteers. They're going to deliver these electric signals to the wrists of people who are starting to drift off to sleep, and they're going to use EEG to measure what happens to the alpha waves. So when we look at this, what I want you to think about is going question by question. This is what you're going to do for your own study. First of all, does the study involve human participants? I don't know if we can have people throw things in the chat or not. I don't know if that'll work. We can try. It may or not. Anyway, with this particular one, I think this one is pretty easy. Yes, this one absolutely involves healthy volunteers. We've got human subjects here. Now, the next question, are these participants prospectively assigned to an intervention?

She just said that the chat is open, so if you want to throw things into the chat to answer this question, then you can. Do you think that these folks are prospectively assigned? And I'm

seeing a number of yeses here, and those that said yes can pat themselves on the back. Absolutely. Congratulations. There are electronic signals being delivered to the wrists of these human subjects. And then let's take a look at the third one. Is this study designed to evaluate the effect of the intervention on the participant? And just throw that in. So lots and lots of yeses, and I'm very happy because, yes, this study is going to use an EEG, and they are going to measure the effect of those electrical signals on alpha brain waves. And then who thinks that the alpha brain waves are biomedical or behavioral outcomes? Four. We've got four yes. Yes. Some yeses. There's one no. Yes. Unclear. Yes. Well, so when we think about this, somebody once joked to me, "Do you really want to apply to NIH for money, the National Institutes of Health, and say that you're not looking at health-related biomedical or behavioral outcomes?"

It was said in jest, and we all kind of laughed when they said it, but it rings rather true. And I have to tell you, I .. . It is very, very rare .. . I think I have seen it one time where somebody answered yes to the first three questions and then answered truthfully or correctly no to the last one. And, yes, the change in alpha brain waves, NIH would consider to be a biomedical outcome. So yes, we would consider this one a biomedical outcome and that this example, as fictional as it is, would be an NIH-defined clinical trial. So let's move on. So what happens?

Now you're completely confused because you thought that it had to be a drug study. What do you do now? Well, there are a couple of things that you can do. NIH has a clinical trial interactive decision tree on our website, and you can go through that. Now, granted, when you go through it, the definitions are going to come up, what is prospectively assigned, what is an intervention and that sort of thing. So you're going to have those definitions, so just keep in mind that those are the definitions that you'll see, but it can be very helpful to kind of help you think it through as you go through.

Another thing you can do, and I would really encourage you to do this is talk to your program official or your contract officer. These are folks who can help you .. . point you in the right direction, point you to the right funding opportunity announcement that you need to go to, and if you don't have one, NIH has this nice tool that is called the NIH Matchmaker. I have a link to it here. You can put in some text of the study that you're doing, the types of subjects that you're doing, and it will give you a list of program officials who have those kinds of studies in their

portfolios so you can reach out. And just keep in mind, it's very important that you remember that NIH-defined clinical trials often don't look like a randomized drug study. And you can really consult the resources on our Grants Clinical Trial website. It's got all of this information and more, and I would encourage you to go there and take a look at it. And so why do we even care that we're doing a clinical trial or not?

Well, for a lot of reasons, as you probably have already guessed the answer to that. First of all, NIH has specific FOAs. They have clinical trial required, clinical trial not allowed, clinical trial optional, and you have to apply to the correct one. So you have to know if you're doing a clinical trial or not. And if it's misclassified, your study might even just be withdrawn, and it can be withdrawn before it's even reviewed, so it's really very important that you get this right to minimize the chance that your study will be administratively withdrawn.

Now, there are a whole lot of clinical-trial-specific requirements. There are regulations, and there are NIH policies. There are specific clinical trial review criteria, so reviewers, when they go in and look at studies and they're reviewing a study, if it's a clinical trial, they have specific criteria they have to review that application under. There is a requirement to register and report summer results, and the clinical trials stack up. There are requirements for Good Clinical Practice training. There is a requirement that you post a consent of clinical trials, and that's out of the Common Rule actually.

There are specific clinical trial monitoring. You have to include a data and safety monitoring plan in your application, and there are certain studies that NIH expects to have the highest level of monitoring, which is a Data and Safety Monitoring Board, or DSMB, multisite studies, Phase III studies, et cetera. I'm going to quickly go through these. Like I said, we don't have a whole lot of time to go into a lot of detail, but we will take a look. And your clinical trials have to be compliant to all of these. Now, it's going to be part of the terms and conditions of your award. The disadvantage that some of you guys may have over a large academic institution is that a lot of you don't have an entire clinical trial office or a full-time employee that's dedicated to nothing more than making sure that you get all your stuff in right.

So this is going to fall .. . For this group, it'll fall more on you than in some of the other instances, in the other cases. So it's very important that you be familiar with the requirements, reach out and get help if you need it, and I would just encourage you to be as organized as you can. In advance, know what you need to do. Have your spreadsheets. Get your calendar. Put on the reminders when do you have to register the study, when do you have to report the study and have all of these different things marked with reminders and that sort of thing, and that will kind of help you to keep you compliant so you don't inadvertently run afoul of any of these. So let's talk about some of the policies.

The first one we talked about was the funding opportunity announcement, or we call it FOA policy. And applications have to .. . involving clinical trials have to be submitted to the correct FOA. And as I mentioned earlier, it's a big risk .. . is that if it's submitted to the incorrect FOA, it can be administratively withdrawn, and so it won't even go to review, and that's a lot of work not to go to review. So it's very important that you get it right. And the purpose of this was to really help NIH in their tracking and identifying of clinical trials and making sure that clinical trials are reviewed correctly with the correct information and that clinical trial specific criteria are uniformly applied across the board. Another important one is the Good Clinical Practice Training. Lyndi mentioned training for human subjects protections. You do also have to do .. . We call it GCP, GCP training, and GCP training has to done for done for NIH-funded studies for basically anybody who touches the clinical trial, anybody involved in the design, conduct, oversight, management, anything, needs to be trained in GCP, and the GCP, there is no specific training that is required. There are a number of different trainings that would suffice. It can be a class, a course. It can be an academic. It can be a certification. On the website, there are a couple of places that you can see and go to, and it's required that training be refreshed every 3 years, and while you don't have to send it to me, you do need to make sure that you have this documented.

If somebody asks you for the documentation of your training, you should be able to provide that. So make sure .. . This is one of those organization things that .. . Know who is involved in your study and make sure they get the training and make sure that it's documented somewhere that they've done this. Data and safety monitoring, this is a very important part of doing clinical

trials just in general. Your IRB will make .. . will review your protocol and determine what level of monitoring that you need to have. The Data and Safety Monitoring Policy requires that clinical trials have to submit a data and safety monitoring plan in the application, which is going to address the overall data and safety monitoring framework. You have to describe the procedures that you have if there is an adverse event in your clinical trial, how are you going to report that. You need to identify the monitor.

For minimal risk studies, it may just be the PI. If it's .. . Marching up the risk scale, you could have an independent monitor. You may have a monitoring committee, or you may have a full formal DSMB. And NIH actually requires a DSMB under certain circumstances. For example, multisite clinical trials generally have to have DSMB. NIH-defined Phase III clinical trials generally have to have a DSMB as well, and as per usual, I've got some links to some of the websites here that you can go and read all about it. Here's one that's been in the news a lot recently, the dissemination of NIH-funded clinical trial information. This policy requires that you register and report your study in clinicaltrials.gov if you are doing an NIH-defined clinical trial. So now, it's also required under FDA for applicable clinical trials if you're doing an FDA-regulated study.

But NIH requires it for NIH-defined clinical trials. You will have to submit a plan in your application outlining how you're going to be compliant with this policy. You need to register your clinical trials no later than 21 days after you enroll that first participant, and then you have to report the summary results on clinicaltrials.gov no more than 1 year after the primary completion date, and this is very important. This is one that you really need to pay attention to. You have to pay attention to all of them, but this one is getting a lot of attention, so put a big star by this one. Also, here's one that people .. . I'm finding that people are less familiar with, but this one is actually required by the revised Common Rule. You have to post a copy of a consent that was used during the study on a designated federal public website, and this is required. Here's the length to the part of the Common Rule where it's required, and NIH has a policy about it, which you can get to from our website here, and there are two different places that you can post these.

There's also some specific timing around this one that makes it a little bit more challenging. You cannot post it during the study. You have to wait until recruitment closes. This is just what the Common Rule put in. So this has to be posted after you close your recruitment and then no later than 60 days after that last study visit by any one participant. So there's a timing window to be compliant for this, and there's more information here on the website. So now you are familiar with the definition of clinical trial. You've looked at an example in order to kind of think beyond the classic clinical trial definition. We've done a big fast flyover of the different clinical trial policies and regulations, and we've gone over some resources that you can use to go for help.

And as promised, I put a whole bunch of these, all the ones that I put in my presentation, I've done on these last four slides. So the first two are websites. So these are some websites that .. . The BESH website, even though you may not be doing BESH, is often very useful to look at because it has what's the difference between a measurement and an intervention, what does .. . how can interventions be manipulations and so forth, so it's very useful to kind of peruse through that. Here are some more websites talking about the GCP training and the informed consent posting and so forth. I won't go through .. . I won't read all of these. You can read it as well. And here's some links and resources. We talked about Matchmaker, and there is that interactive decision tool, Clinical Trial Decision Tool, that I talked about. Something I didn't talk about earlier, and it's not specifically related to clinical trials but you might find useful, is there's some information about protocol writing, and there's an e-Protocol Writing Tool that our Office of Science Policy put out that you might find useful.

And then here are the links to all the different policies and regulations that relate to what I've talked about here, and I hope that wasn't too terribly fast, but we'll answer questions, I understand, at the end.

Dawn Corbett: Okay. So I am up next. I am Dawn Corbett, the NIH Inclusion Policy Officer. I know we're about an hour in, and you all have gotten a lot of information, so feel free to stretch if you need to. We're not going to take an official break, but I think we've saved the best for last, and I'm going to talk to you about inclusion of diverse populations in NIH-funded clinical research. So to provide a little context for what I'm going to be talking about today, I

wanted to highlight a recent report by the National Academies of Science, Engineering And Medicine that focused on improving representation in clinical-trials research.

I've included a link to the full report here, but this report provided a number of recommendations for the scientific community to consider in improving the inclusion of women and individuals from racial and ethnic minority groups in clinical research studies. It was a really comprehensive view, and one of the insights from the report which I have here indicates, "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." And I think this quote really speaks to why am I talking about inclusion today.

I'm talking about inclusion today because, for the last 30 years, NIH has been part of this paradigm shift to ensuring the inclusion of populations that were historically excluded from clinical research studies, and this includes women of child-bearing age. In particular, it includes racial and ethnic minority groups, and it includes individuals of various ages, including children and older adults. And so I'm going to talk about policies and… processes, but I'd like you to keep in mind what we're really talking about today is how we shift this paradigm to make sure that populations that were historically excluded from clinical research are included going forward so that we understand how our interventions work in different populations and make sure that our knowledge is generalizable to all populations.

So I'm going to start by talking about one of our two inclusion policies, which is our policy on inclusion of women and minorities in NIH research, and this policy requires that all NIH-funded clinical research studies include women and members of racial and ethnic minority groups unless there was a compelling rationale for exclusion. So just to clarify, what is covered by this policy? When NIH talks about clinical research, we mean almost all human-subjects research as was explained by Lyndi early on. So if you're doing human-subjects research, with very few exceptions, you are probably going to be required to include women and members of racial and ethnic minority groups. The one exception to that is studies that meet the criteria for exemption four, which Lyndi talked about earlier, which are largely working with secondary data and that those do not require inclusion, but the rest do.

And then if you're doing an NIH-defined Phase III clinical trial, those later stage trials require .. . have some additional requirements, including analysis of the primary outcome by sex or gender, race and ethnicity, and those results need to be reported in the progress report and, if you have a grant, in the RPPR Project's outcome section. If you happen to have an NIH-defined Phase III clinical trial that's also an applicable clinical trial, which is an FDA-regulated .. . generally involving an FDA-regulated drug or device, those also must report results of these analyses in clinicaltrials.gov. I don't think we have too many small business applicants that fall into this category, but if you do, keep in mind those additional requirements would apply, but almost all of you who are doing human subjects research will be required to include women and members of racial and ethnic minority groups.

And then another policy that applies is the NIH inclusion across the lifespan policy. This policy requires that individuals of all ages be included in NIH human subjects research unless there are scientific or ethical reasons not to do so. So important to point here that when .. . For both inclusion across the lifespan policy and the policy on inclusion of women and minorities, there are limited cases when individuals from certain groups do not need to be included. For example, if you're doing a study on prostate cancer, you would not need to include individuals whose sex at birth is female in most cases in case you're looking at caregivers or something like that. Likewise if you're doing a study on Alzheimer's disease, you would not need to include children in that study in general because children do not get Alzheimer's disease. So there are cases when it's okay to exclude, but they need to be based on science or that there's an ethical reason.

Maybe it's unethical to include children in this Phase I tolerability study because they're a vulnerable population, but we would expect them to be included later on for example. So keep in mind, the reason for exclusion cannot be based on convenience, and it cannot be based on cost. In fact, the law that underscores the policy on inclusion of women and minorities, which brought the policy about, specifically mentions that cost is not an acceptable reason for excluding these groups. The inclusion across the lifespan policy also requires submission of data on the participants that participate in your studies, and this includes individual level data on the sex or gender, the race, the ethnicity and the age of enrollment of each participant. So I'm

going to talk a little bit about how these policies play out throughout the NIH funding cycle. For those of you who've submitted grant applications and are familiar with our processes, this may be very familiar to you, but just wanted to review.

Where I'm going to start today is with your grant application or your contract proposal, and then your application will be going through peer review. After peer review, we have a period Just In Time, and that period is when NIH staff may request information for certain applications within a fundable range, and then if you're funded, study monitoring and progress reporting, and so we have different requirements throughout the process starting with inclusion plans and an enrollment report, which I'll talk about in a bit more detail in a moment, and then once we get to Just In Time, you'll provide any information that the NIH staff may ask for at that time, and then in monitoring, there are some requirements for providing us data about the participants in your studies as well as results of analyses. You're required to do those. So let's start with what's required when you're applying for funding.

So when you apply for funding, you're required to provide inclusion plans, both for women and racial and ethnic minorities and individuals across the lifespan, so you'll provide two inclusion plans. You'll also provide minimum and maximum age limits and inclusion enrollment report. This information is all provided on the PHS human subjects research and clinical trial information form, which is the form where we have the human subjects information about your study all in one place. It has five sections, and the section that I'll be talking about today is section two, the study population characteristics where the inclusion information is included. So what do you need to include in your plan on inclusion of women and minorities? So in that plan, you'll want to provide a description of the plan distribution by sex or gender, race and ethnicity, and you should provide a rationale for the selection, why do you expect the population to look as it does, why have you selected that population.

Often, this is going to be based, for example, on prevalence data or incidence data. Usually, we would expect the individuals in your study to look like the people with the condition, and if not, there should generally be a justification. You should also provide a justification for any exclusions, so as I mentioned, if you want to exclude children, if you're going to exclude older adults, if you're going to exclude women, this should all .. . In the inclusion of women and

minorities plan, you would describe exclusions for women or members of racial and ethnic minority groups in particular.

You'll also describe your proposed outreach programs for recruitment, and then if you're doing an NIH-defined Phase III trial, you'll describe any plans for analyses by sex or gender, race and ethnicity. In your across the lifespan, this is where you address the inclusion of individuals of all ages in your study. So there, you'll provide your rationale for the age distribution, similarly, why have you chosen this age distribution, keeping in mind, there should be a reason for any group that's excluded based on age. And you'll want to talk about how the age distribution will contribute to your analysis. For the inclusion across the lifespan, you're also going to provide a description of a study team expertise and the appropriateness of facilities for the included age groups, when you're working with children, for example, you have a pediatrician on staff or pediatric consultant, how will people get to and from your place, is it accessible, that kind of thing.

So you should provide that in the inclusion across the lifespan plan. As I mentioned, you'll provide an inclusion enrollment report, so this is a table that shows us what you expect the demographics of your participants to look like, or if you're using existing data in your application, you may show us what those participants look like if you know that already. The first page of that is pretty straightforward. You're going to provide a title. You indicate whether you would use an existing data set or resource. So for example, if you're doing a secondary analysis study where you were working with biospecimens that were already collected, this would be considered an existing data set or resource, and you want to check yes to that. You don't have all the same requirements that will come into play with those, such as the need for individual level data. But you do still need to provide aggregate data for those, and then you'll indicate whether the study is domestic or foreign.

There's some additional optional fields and a comment field if needed. As I mentioned, in an application, you're generally going to provide planned enrollment, but you may provide actual enrollment. Particularly if you're working with an existing data set or resource, you may provide that as well. So after you submit that information, your inclusion plans or inclusion enrollment report and specify your age limits, that information is going to go to peer review. We have peer

review guidelines that are published on our website where we will be looking at your plan, first, to see if it's complete, did you include everything that you were supposed to include, and then is it scientifically appropriate? So is the population that you're studying appropriate to the scientific .. . to the question. And then they're going to be looking, at is it realistic?

So you may have come up with a wonderful plan, but you haven't given enough information for review to understand if you will actually be able to implement that. So that may be a case when peer review may bring up some concerns if the plan is not realistic. The peer review will be looking at those plans according to the guidelines, and then in your summary statement, you will receive on your summary statement a summary of that discussion. It may include comments about inclusion. It will also include a number of codes, which you can see here. They are called the gender, minority and age codes. Those codes, the first part of that code is a number, which is simply a descriptor of the population that's included, and the second part of that code is an A or a U. A means that review found it to be scientifically acceptable. U means that they found it to be scientifically unacceptable.

Something to keep in mind, if your inclusion plans are found to be unacceptable, that application cannot be paid until those concerns are resolved. So if you get through the point of peer review and now you've found that NIH is ready to .. . you've met a certain threshold and NIH has requested some additional information to prepare for funding, we would call that period the Just In Time period. So in Just In Time, you'll receive a notification, and often the IC staff will reach out to you for some additional information. For most people, they don't have to provide anything for inclusion here. They've provided everything in their application, but if you did have an unacceptable score, the IC will be reaching out to you, and you will likely have to provide some additional information such as a revised inclusion plan.

You may also need to provide some updates or corrections if any information was missing in your application or if there were, for example, revisions due to peer review or programmatic adjustments during that time. And then once you're funded, there's still some things that you'll need to do for inclusion. So every year, at least, you'll need to provide cumulative actual inclusion enrollment data in progress reports. So you'll be reporting the sex or gender, the race, the ethnicity and in most cases, the age at enrollment of the participants. If you're doing an

NIH-defined Phase III clinical trial, you'll also report the status and the results of analyses by sex or gender, race and ethnicity, and as I mentioned, for those ACTs, the applicable clinical trials that involve FDA-regulated drug and devices, those studies that are also NIH-defined Phase III clinical trials will need to report the results of their analyses in clinicaltrials.gov within 1 year of their primary completion date. And then if you have delayed onset studies, these are studies that maybe you can't describe in the application, and so what you do is you put a delayed onset record in there and let us know that you're going to be doing this study but you don't have all the details yet.

Once you do have details about those studies, then you will need to provide the full human PHS Human subjects and Clinical Trials Information Form, and that will include your inclusion plans and your enrollment reports once you can describe your study. I mentioned each year in progress reports, you will need to provide updated enrollment data. NIH in the past has collected aggregate tables with the sex or gender, race and ethnicity of participants. Starting for applications that were submitted January 25, 2019, or later, in progress reports, you must provide individual level participant data that look like this. They look like a spreadsheet. It's in a CSV file where you provided the race, the ethnicity, the sex or gender, the age and the age unit for each participant. And these data can be updated and corrected using our human subjects system.

This is available starting with the Just In Time period and post-award. You would go into the human subjects system, which is through the ERA Common Status Module to make any updates, and we have a lot of training and tutorials available about the use of the human subjects system on our HHS training page. So I've given you a lot of information about our requirements. Before I move on to talk a little bit more, I wanted to do a quick knowledge check. So this is a true or false question, and if the chat is open, you can go ahead and answer this question in the chat. Thank you. Looks like chat is open. Cost is an acceptable reason to exclude women from NIH clinical research study. Oh, you guys are great. Yes. False, false. Okay.

You all got this one, so very good. So as you may recall, the NIH inclusion policies were really developed, first, in response to the concern that women of childbearing age were routinely excluded from clinical research studies due to concerns about harm to the fetus and safety

concerns on the cost of pregnancy tests, and so the law specifically stipulated that cost is not an acceptable reason to exclude women and members of racial and ethnic minority groups from clinical research studies, so very good. Okay, this one .. . next one is a little bit harder. I have a case study for you. So in this case study, you can just give me a yes or no. I have a thumbs-up or thumbs-down here. A researcher proposes a study to examine use of a smartphone app to improve glycemic control in diabetic individuals.

The study excludes individuals who do not speak English because the consent form is available only in English. What do you think? Is this acceptable, yes or no? Wear your peer review hat here. What you would you say if you were a reviewer? You guys are on a roll here. No, yes, no, nope. So in this case, I would agree with the majority here that, no, this generally is .. . would not be acceptable. Why? Because you would be disproportionately excluding individuals who do not speak English, which disproportionately excludes members of racial and ethnic minority groups. So some of the people here, great. You gave some ideas about what you can do: translate the form into Spanish or other languages of the population with whom you're working. We would expect you to tell us in this case why can't the consent form be translated into another language.

And I think in most cases, it probably can, and Neil, you mentioned it might depend on the populations, right, and this is in particular when there are measures that haven't been validated that certain populations can get a little trickier. For a consent form, you would need to .. . We would expect you to explain why you couldn't be .. . why it couldn't be translated, and generally, we want you to make every effort that you could to do it. So based just on this information, I would say yeah, maybe not. Yeah, some good comments here. Smartphones have apps to translate. There's so many languages. You can't translate into all languages. That's true, Brian, so there are limitations, agreed. All right. Let's move on for the sake of time. So I think you all for the most part we were in agreement. You have some important nuances that you all brought up, and those are exactly the kinds of things that you'll want to think about.

I think I just gave you the answer here, but let's move on to this one. This is something actually we see fairly commonly. A researcher proposes a study for a new drug that will exclude individuals over 60 because of the likelihood of comorbidities in this group. What do you think

as a reviewer? Is this okay, yes or no? Okay. A little mixed. Yeses, no's, it depends. Acceptable. It's a safety concern. Yes, follow up. It depends. All right. I'm seeing some really good answers here, so I would agree with it depends, but I would say in this case, you've not provided me a reason, and remember, the policy .. . You have to provide me a reason for exclusion.

I'm guessing that they probably excluded individuals over 60 because of concerns about comorbidities, maybe hypertension, for example, which is very common in individuals over 60, but what we would expect is you can exclude people due to those safety concerns, so exclude people with hypertension. Do your screening and see if people have hypertension rather than wholesale excluding these groups, so yeah, very good, Daniel. We would expect you to screen for comorbidities if there were safety concerns. If there are legitimate safety concerns specifically based on age, and find this with children, e.g., more commonly, then you can .. . You should explain that. So if this was all the information that I got, and I've seen this before, I would say this is unacceptable.

I need more information, but the investigator may be able to come back and say, "Hey, look, this is why I excluded individuals over 60," and we likely could come to some understanding, but keep in mind that you need to provide the reason. Don't assume that peer review will say, "Oh, there must be a safety concern." Peer review should not have to assume anything. That should be spelled out for them. Yeah, so there's some really good comments. You might have to do staged. Very good. So now that I've talked a lot about process and we've [Indistinct] a little bit about how we can think about these things, I do want to give you some information about things to think about when you're designing your study. So while we talked about grant application going forward, really inclusion needs to be thought of from the very beginning of your study design, preferably with the involvement of community groups, participants and others. Some things to think about: limiting your exclusion/exclusion criteria. So this is really important particularly as your study moves through phases.

The FDA has provided some guidance in the couple years. You need to think about if those criteria should be broadened and really make sure that all of your inclusion/exclusion criteria are there for a reason, not simply because, "Everybody has 18 to 65, so I will too." Why can't individuals under 18 be included in your study? Why can't individuals over 65? If there's a

reason, that's okay, but there should always be a reason. Weighing the risks of exclusion versus participation. So this is particularly important for groups like pregnant and lactating people, also children, so some populations have extra protections, but we also have to remember that if they're not included in research, we don't get the benefit from research. We don't have as much information about how interventions work, and our knowledge may not be generalizable to those groups. So we always need to make sure that we're taking into consideration both the benefits and risks of research to the participants and also the benefits and risks of excluding those groups to the population as well.

We want to .. . And you want to design your studies thinking about participant and caregiver burden. If you have multiple studies, if it's multiple procedures, if they have to come in person, they have to .. . And maybe they have to sit in a waiting room for long periods of time, which can be harder for some groups than others. As a mother who's done that with a 4-year-old, okay, it's not fun. It's even less fun with a 2-year-old. So when you're thinking of designing your studies, keep in mind the participant and the caregiver burden and how can you make it easier for people to participate. Virtual visits are one way.

Work great for some groups, not so much for others, but there are lots of creative ideas out there for doing this. Considering diversity within populations, right? So groups are not a monolith. They vary in terms of size and in terms of cognitive abilities, race, ethnicity, age, et cetera. So we have to understand that there's not one enrollment method. There's not one method that we should use with this group of participants and another group of participants, but participants are diverse. Make sure considering that in your design. Make sure you're assessing and adjusting your recruitment and retention.

So there should be something .. . We require reporting once a year on enrollment, but I would encourage you to be looking at this regularly. What does your enrollment look like. Do you need to adjust strategies? Are things working out as you expect? And finally, the Inclusion Across the Lifespan II workshop, which this feedback came from back in 2020, also identified a need for researcher training and resources, so this is one of those. We have other resources on our website that I'll share with you soon. We also have some NIH inclusion data on our website if you are curious, if you have ever submitted data to NIH, yes, this is what we do with them in

addition to monitoring your grant, we publish this data, and we make them public, and you can look at the race, ethnicity, sex or gender and the age of participants by all of the research condition and disease categories.

So if you want to take a look and see what participant enrollment in NIH clinical research looks like, this is available on NIH RePORT website. And finally, I'll just share with you some additional resources that we have on our website. We have information about the inclusion of women and racial and ethnic minorities, also inclusion across the lifespan. So if you have any questions, I encourage you to check that out. So that's all that I have, and I'm happy to move into the Q and A portion of this session.

Question and Answer Session

Stephanie Fertig: This has been fantastic. Thanks to all of you for the wealth of information that you've provided today, and I know we got a number of questions around slides and what will be available, and the great news is all of these resources will be available online through our website. You'll be receiving an e-mail with a link to those resources within about a week or so. We want to make sure that everything is adequately accessible, and they're going to be available to get that information. So we do have a number of questions in the chat box. I'm sure you are .. . you all are probably not surprised, but if you do have additional questions, please put your questions in the Q and A, and I know that several of you have .. .

We were able to answer some of those as we were going through, but this is a great opportunity for us to kind of answer some of these live. So we did have a number of questions around what is the definition of a clinical trial, and so I'm going to bring up a couple of those. Give me 1 minute. So there was a couple of questions about, is utilizing national data for analysis considered human subjects research? So what if you're getting data that is broadly accessible but maybe you're not the one who actually collected that data? Oh, and you have to, please, take yourself off mute. Yes, this is the difficulty.

Lyndi Lahl: So the question is if you're using data that's available publicly, I guess, that is .. . Would it be considered human subjects? I just want to make sure I'm answering the right question.

Stephanie Fertig: So the question as stated, and I think that's a really good point that you just brought up. Is utilizing national data for analysis considered human subjects research? But I think you pointed out a really important point, which is public versus non-public data, and that wasn't distinguished, so I think that's an important to maybe talk about.

Lyndi Lahl: Yeah, so if the data is publicly available, it likely will be exemption four, so .. . And we've talked about exemption four. Dawn talked about it. So if it's exemption four, it is human subjects research, but it is exempt, and so it doesn't have to report inclusion data, and there's no IRB review. Now, if it's data that's not publicly available, if there's identifiers associated with it, it would be existing data, so it would be secondary use.

Again, it depends if it meets the categories. It likely would still meet exemption four but not under the first criteria which would be if it is available publicly. Depending on if it's provided without identifiers .. . I answered a chat question a few minutes ago about if it's provided and it's coded or not .. . if it's coded. So there are identifiers, but those aren't provided to the investigator, it may or may not be human subjects. At this .. . It can get kind of tricky, but likely, it's going to be exempt. So that's .. .

Stephanie Fertig: And I think this is why .. . I'm going to do a quick plug for something during my presentation. This is why reaching out and having those conversations early with program officers .. . I know myself as a program officer, I received a number of questions about what was and was not clinical trials, and if there were specific questions, I was able to get additional information from the potential applicant and go to our clinical trials office within the specific institute that I was in, and we were able to have those conversations well in advance of that person applying so they knew what they needed to include within their application, and so I think what you're going to start hearing about .. . hearing here with some of the answers to these questions is the dreaded it depends, but I think that's so important.

So there was another question where .. . Can the employees of the company be used as human subjects in a small preliminary study for device validation, assuming that the device is non-contact and risk free? So I think it's important to talk about there's a couple of things here. One,

use of employees in a company, but also the question of risk and how risk factors into human subjects research.

Lyndi Lahl: Yeah, thanks. And we actually hear this on a somewhere regular basis, this very thing. I think that using employees to test a device even if you think it's a very low risk or minimal risk is a little controversial. There's certainly a convenience sample, but you need to have IRB review for that, and you're going to need to get informed consent, and those employees can't be coerced into participating in the study.

They can't be told, "Well, this is a condition of your employment. You have to participate in this study." So there's a lot of ethical reasons that perhaps employees are not the best subjects even if it is a small pilot study, you only have an N of five. Okay. And then what was the other part of the question? Sorry.

Stephanie Fertig: No, and the question around risk and how risk is .. . really factors into that clinical trials definition, which is a little bit of a trick question.

Lyndi Lahl: I don't know, Pam, if you want to address that.

Dr. Pamela Kearney: Yeah, I'll just underscore what Lyndi said about being very, very careful using employees because you just .. . Because it's not even coercion, which is threat of harm, it could be undue influence. They may be afraid to say no because they're afraid that their supervisor won't like them anymore or that people just kind of roll their eyes and look at them whatever .. . I had a situation one time when I was on an IRB where they were trying to use people in a lab for what they considered to be this kind of low risk thing, but there was a participant .. . there was a person in the lab who was pregnant and didn't want to tell anybody yet, and they weren't really sure what would happen or if it was .. . It seemed low risk, but they just didn't want to do it, and it caused a lot of ill feelings, so .. . But as far as risk goes. Risk is not part of the definition of clinical trial. It is not part of any of the four questions. You can have the Zen effective gardening on .. . what is the Zen effect of gardening .. . What is the risk? They might get a mosquito bite? So they .. .

There really is very minimal risk, and there was a question in the chat that I answered just by texting, can exempt research be clinical trials? The answer is yes. If it meets the definition of a

clinical trial, you can have a study that is exempt but still be a clinical trial and still require all of the clinical trial reporting and the consent posting and everything else. Risk is not part of the definition of clinical trial.

Stephanie Fertig: And that's one I used to have to answer a lot as a program officer as well, and so very, very important. One of the questions that we got was, well, wait a minute, what's the difference between clinical trials and a feasibility study? What are the major differences? And this individual is discussing how they're in the digital health space but are not .. . are specifically looking at usability of the application. So they're not looking at health outcomes, but they're looking at usability, and I used to get this question a lot around the usability of a device, so not interested in its health effects yet, but can people just use it?

Dr. Pamela Kearney: All right. Now, this is a tricky question, and you have to be very careful with this one. Feasibility studies can be clinical trials. You have to be careful. Now, if you are literally just testing to test, testing to test, where you're not looking at the effect on the person, you are literally just looking at how well something performs. So you're doing it alongside of the gold standard, and you're not using it for any health reasons. It's not part of the clinical decision making. You're just simply doing it alongside of the gold standard, and you're comparing the two to say, "How well did we do?" So you're not using it in any way. What I find .. . and you have to be very careful .. . is that the devil is always in the details on an application.

You have to be very careful. Unfortunately, what I have seen, when people are doing feasibility studies is that they have a questionnaire, and they list a bunch of questions on the questionnaire for the person who did this, how easy was it, did it meet this need or that need or whatever, but then they go into efficacy. They ask one question about efficacy. Just be careful. Don't throw an efficacy question in there if you are doing feasibility. Make sure you keep it feasibility because if any part of that trial, any part of that study is a clinical trial, the whole thing is a clinical trial, and that is the one that I see the most where they have a questionnaire, and they've asked three or four questions about efficacy, and they didn't really…

It wasn't an efficacy study. They were just curious, and they threw it in. But just be very careful. True feasibility, testing to test studies are not considered clinical trials because you're not

looking at a biomedical effect on the person. You're just looking at how well the thing performs. But if you go into efficacy at all, then you have crossed the line into clinical trials, so just be very careful.

Stephanie Fertig: Thank you, and I know there seems to be a little bit of an echo, so we do hear that, but hopefully we can figure out the issue there. And I think this leads to .. . that kind of is very similar to a question that we received around developing software that helps understand something about people, so the development process requires feedback and performance measures, but study is not attempting to further knowledge about humans, and my comment would be, it really depends, and that is something that, to Pam's comment now, where that's something where I would take those specific aims, what you plan to study, provide that information to the program officers, start having that conversation because even if you're still getting feedback and measuring .. . making measurements from a human being, that could .. . that starts to move you into a clinical trial, even if it's more about does this software work.

So I think that .. . There is a delicate balance there, and it's so important to reach out because it really is dependent upon how the study is done. A couple more about the specifics around the clinical trial, the definition, and then we're going to slip into IRBs. So a question about determining what .. . With determining identifiable data and biospecimens. Sometimes a diagnostic image may not have the identity, so the diagnostic image itself may not be identifiable, but may include information via headers. What is the responsibility of the PI to place a firewall there? What if .. . how does that .. . And I guess this moves more into exemptions there, but the question of how is that handled, particularly if a PI doesn't have a control over it?

Dr. Pamela Kearney: Lyndi, do you want to take this one regarding identifiability?

Lyndi Lahl: I guess I don't quite understand how you could get identifiability from a header. That's .. . So I don't know [Indistinct]

Dr. Pamela Kearney: I think I can explain it, and then you can jump in. If I .. . I didn't see the question in print, so .. . But what I'm hearing is, just from being a physician, I know that when you get X-ray .. . radiology information, that often embedded in that image are certain types of

identifiers, and they can be name, medical record number and that sort of thing, and they're embedded in the image.

And whenever we use them, even we have permission to use them in presentations and people who are fellow physicians and that sort of thing, we always had to go to radiology and have them remove those headers .. . remove that identification. But I don't know that Lyndi, if you have heard anything about that, but if there are .. . If there's embedded identification, then it's identifiable.

Lyndi Lahl: Thanks. I was thinking Excel spreadsheet and header, so I wasn't thinking .. . Yeah. So that helps. Thanks. Yeah .. .

Dr. Pamela Kearney: And I could be wrong, but that's the way I heard that question, so .. .

Lyndi Lahl: Yeah. So you don't have to be doing exempt human subjects research. If it's secondary research and you have identifiers, and you .. . Likely, if those aren't scrubbed, that it would be non-exempt human subjects research. It doesn't mean that you're going to have to get a consent from the participants because the reviewing IRB may be able to waive informed consent if it meets all the criteria. So it's not something that you wouldn't be able to do the research at all. I'm going to use Stephanie's words: "It depends."

Stephanie Fertig: Well, I have to say, and this is the question about gray zone examples, and one of the questions is who ultimately decides if a human subjects is or is not clinical trials particularly for these gray zone examples? Is it the program officer, peer reviewers, scientific review officers? Who makes that determination?

Dr. Pamela Kearney: Okay. I guess I jump in here. When you submit something, the first responsibility is on the applicant to make sure that they go through. It's really kind of everyone at NIH is responsible for .. . if they see something that looks like a clinical trial that's misclassified. The DRR, the Division of Receipt and Referral, does not routinely look at studies to see if they are clinical trials or not. If they see one and they note it, then they will take action, but generally, unfortunately for the program officers, it generally falls to the POs when they're looking at this. Ideally, if something is misclassified, it is discovered well before review. Occasionally reviewers will see it that it doesn't .. . isn't supposed to come up in review that is

sent to the SROs, and then if it turns out to be misclassified, it will be submitted for withdrawal after review. So it's .. . And if the PO has any questions, there is an internal process within NIH where there is my office actually if the POs have questions, and it generally goes through the ICs. Each IC has their own process, so if there's a question, a PO has a question, we'll go through their IC's process. Some of them have committees.

There are a couple of them. Every IC is a little bit different, so depending on which announcement, which IC sponsored the FOA, they will do a .. . Some have one person. Some have a committee, and if the IC can't agree, then they will send it up through our office. There's an office in OER, and we will take a look at them. There's a process that they send it to us. We take a look at it, and then we run it all the way up to Mike Lauer, who is the NIH Deputy Director of the Office of Extramural Research, and his decision is final. So once it's determined .. . And we're pretty consistent. We have a process by which we have a couple people that look at these, and we're very consistent. We have precedent cases that came through that we base decisions on and so forth.

Stephanie Fertig: And I have to say, as a program officer, the process does work, but it works best when you reach out to us ahead of time. Much better to have that all happen before you apply than after you apply. So I did get a couple of questions in here, and I'm going to jump in and answer these, which is around market studies for when we're talking about what discipline with regards to research processes. And so just as a quick reminder, SBIR and STTRs are research and development projects.

We do not support commercial activities, and market research is considered a commercial activity, and so I encourage you, if you do have specific questions about what is or is not considered research and development in the SBIR STTR program, you can find information about that in the instructions in the SF424. The SF424 instructions are a wealth of information, and that includes what we define as commercialization. So it really depends when we're talking about the kinds of research, and I know market research has the word research in it, but for the purposes of an SBIR and STTR grant, that is considered commercial. That is considered a commercial process. Okay. There's a bunch of questions about IRBs, and I used to get a ton of questions about IRBs too, so let's launch in. And one of the first ones was, well, what if a small

business owner applicant doesn't have a preexisting IRB committee? What are they supposed to do?

Lyndi Lahl: So if they are planning to do non-exempt human subjects research, they're going to have to have an IRB. That does not mean they have to convene an IRB themselves. They can certainly rely on an IRB that is external to their organization, and a lot of institutions do that. They could go to an academic university and ask if they would be able to review on behalf of them. They could go to a commercial IRB. There's a number of ways to do that. There's probably going to be a fee involved, and they certainly are going to need a written agreement between their institution and the reviewing IRB that will be reviewing on their behalf.

Stephanie Fertig: If somebody has an IRB and they've already approved .. . And that IRB has indicated that the research is exempt, will NIH still need the human subjects form to be completed for NIH grants?

Lyndi Lahl: So we have that human subjects and clinical trials form, and they do need to fill out the applicable information. They can mark down which exemption or exemption categories that applies, but they're still going to need to provide additional information, and as Dawn mentioned earlier, that's also going to need to include the inclusion plans for .. . unless it's exemption number four, they would need to have that information as well, and clinical trial information if it is an exemption that's also a clinical trial.

Stephanie Fertig: If someone is relying on their academic collaborator's IRB, are they covered by their FWA?

Lyndi Lahl: FWAs are different from IRBs. The FWA is for the institution. There is a form that the institution .. . A high person in the institution needs to sign off it's the signatory official. That's submitted electronically to OHRP, and OHRP reviews and approves that and issues the FWA, and I think it's issued for a period of 5 years. The IRB review is separate. It could be within the institution. It could be an IRB external the institution but just because you are relying on somebody else's IRB does not mean that you have your own FWA.

And I actually answered a similar question in the chat, and I said you can .. I guess the question was, "Do I have to get an FWA?" And I said, well, you have to be covered by an FWA, and in

general, you are going to have to apply for an FWA and get it yourself. There is a process that an FWA institution can extend its assurance to cover your .. . you and your activities. It's unlikely that they would do so because then that institution is taking on the liability of covering somebody that's external to their organization.

Stephanie Fertig: And we have another question about IRBs, which is the company submitted a single IRB as a sponsor with a commercial IRB, but our university partner who is actually doing the clinical study is required to submit an IRB with the university. What should I do? And I think we see a lot of questions about single IRBs and how to handle multiple IRBs and particularly when you have universities or multiple universities involved.

Lyndi Lahl: Yeah, we see a lot of questions about single IRBs. There is a process to be able to request an exception to the use of a single IRB depending on whether the research is subject to only the NIH single IRB policy or it's subject to the revised Common Rule single IRB requirement will depend on the justification that would need to be provided to require that exception, but I have to tell you that it is rare that NIH approves exceptions to the use of single IRB, so it is unlikely that that would be approved anyway. And the bottom line is, if it's not approved, everybody has to rely on the same IRB for that review. So it doesn't really matter if the university requires a .. . their own IRB review it.

They can certainly do their own review, but it's non-binding review. The institution and the investigator would need to rely on that single IRB review. Okay. The .. . I know there was another one in here. Give me one second to find .. . Because I want to bundle all the IRB ones together. If a start-up needs human subjects research, is not exempt, it's a clinical trial and is not working with an academic or hospital, how can we apply for an IRB? What do .. . particularly if they may not have a lot of experience with clinical trials.

Lyndi Lahl: So it's not .. . So first of all, they need that federal-wide assurance. And when they apply for the federal-wide assurance, they need to designate the IRB that's going to be reviewing on their behalf. When they do that designation on that federal-wide assurance application, they are saying that they already have an agreement in place with this IRB. So if

they don't have their own IRB, they will likely be relying on an IRB external to their institution, so they need to identify that IRB.

They need to get a written agreement in place that they're going to be relying on that IRB. Then they can complete their FWA application. Hopefully get that all through before the award comes up because they need that before the award is issued.

Stephanie Fertig: There are a lot of questions about when an IRB will be required. If they've got an exemption two, if they have .. . Will the involvement of health data always require an IRB? So where can .. . One, where can people find more information about when an IRB is required? What .. . And particularly with involved with exemptions and human subjects data that may not be something where you're immediately like, "Yes, this is an IRB," but, again, that gray zone.

Lyndi Lahl: So that first talk that I did that was about human subjects research, I went through those three questions on determining if your activity involves non- exempt human subjects research. If it involves non-exempt human subjects research, it needs an IRB. If it involves research that is exempt but it's under certain categories, and it's only the criterion for category two, it may or may not need an IRB review. You're going to have to have limited IRB review if it meets any of those categories, and so it's important to look at all the details, figure out if you're actually doing research that is exempt and that meets this one. Exemption two, you can probably do it and not have to do the limited IRB review.

Again, it's the details of how it's going to be conducted, and then the .. . I think you had mentioned something about using health data. Again, it depends if it is .. . If you are recording it without identifiers, then it probably would meet exemption four. If you're doing it under the HIPAA waiver, it might meet exemption four. That's .. . I think it's number three under exemption four. So .. . And when you have questions, contact a program officer. They can help walk you through that.

Stephanie Fertig: And I do want to ask a .. . Moving maybe away from the IRB, we discussed the requirements around clinicaltrials.gov. When you've got an STTR where the PI may be at the academic institution, who fills out the clinicaltrials.gov information? Is it the academic institution? Is it the PI? Is it the company? Who's responsible for that?

Dawn Corbett: I'm happy to take a stab at that one. Our colleagues at NLM, who handle clinicaltrials.gov are not here, but your institution should have a PRS coordinator. Now, if you're a small business, that may be you, but someone at that institution is to be responsible for all the clinicaltrials.gov accounts, and they will assign accounts to PIs, or sometimes institutions opt to just have the PRS coordinator enter everything. If you're not sure who that is at your institution, on the clinicaltrials.gov website, if you Google clinicaltrials.gov PRS coordinator, there's a list that will pop .. . that pops up and lists the current PRS coordinators at all the institutions, so they're the people to get in touch with. If you don't have a PRS account, you can contact register@clinicaltrials.gov. That's also on their website, and they'll set you up with one.

Dr. Pamela Kearney: And just a reminder, remember that the registration and results reporting policy .. . You have to submit a plan in your application about how you're .. . how this is going to be done. So be thinking about said things at the time of application, about who's going to do this and that sort of thing, so make sure you know your plan and put it in your application.

Stephanie Fertig: Now, I know we have a limited amount of time left, but I do want to have .. . I have a couple of questions here around inclusion, and I feel like, Dawn, we can't leave you out with the inclusion questions. So there was a question around if a proposal includes participants that are in a foreign country where those participants .. . and, again, and it's important to note, since this SBIR STTR, that that would only incur in extremely rare circumstances where you might be in a foreign country where there isn't the same racial and ethnic diversity as the United States.

How do you proceed? How is that managed where there might be a situation where you have to do it outside the U.S.? There are very few numbers within the United States, but then there's not the same racial or ethnic diversity.

Dawn Corbett: And I will say that we hold investigators in countries outside the U.S. to the same standards that we hold investigators to the U.S. to, so if you're doing research in a population that's very homogeneous, you need to explain to us why you're doing that .. . why is that necessary. If it's not necessary, then we would expect you just as in the U.S. to collaborate with others to make sure that you're recruiting a more diverse population.

And I would just also add that we want to make sure that the research is generalizable, so I think with any population that you're using, including non-U.S. populations, we need to think about who are the end users here, right? Who are we trying to answer these questions for, and does that population look like them? And if it doesn't, it may not fare very well in peer review without justification.

Stephanie Fertig: And there was a question about reporting and around non-binary sexes and when you're doing research on sexual minorities or any research?

Dawn Corbett: Yeah, and I think this is a good point. So NIH collects participant data on sex or gender to ensure compliance with our policy that women are included in NIH-funded clinical research. Now, the policy does not define women, and we allow the flexibility for investigators to collect either sex or gender based on what's most appropriate to your scientific question. So in terms of how you might report non-binary populations, it's really going to depend. If you're collecting, for example, sex or sex assigned at birth, you may just collect sex assigned at birth from the non-binary populations. We encourage you to collect sex and gender separately. Make it clear what you're collecting. If you're collecting gender, the categories that are available are male, female or unknown or not recorded.

So I wouldn't .. . You can certainly collect information at a more granular level, but when you aggregate them and report them to us, you would have to put it in one of those three categories, and generally with non-binary populations, they'll report as unknown or not recorded if gender is collected.

Stephanie Fertig: And last question for you, are there resources at NIH or just resources in general to help individuals locate underrepresented groups and basically make sure that they're able to get that recruitment and able to meet those goals?

Dawn Corbett: I would definitely start with your program director or your program officer. This is institute specific. Some institutes have, for example, outreach partners who may be able to help you reach diverse groups. Many times, you may be working with community groups, advocacy organizations or other community leaders, so if you're not sure about how to start doing that, your PO is a good place to start.

But in general, you'll want to think about the group that you're trying to recruit, who are the leaders in that group, and those are the people that you're going to want to reach out to, whether they'd be people at a national level or a local level. Many groups, they work with churches or barbershops or that kind of thing, but, again, your PO is the person to talk to if you're unsure, and they can help point you in the right direction.

Stephanie Fertig: Well, I know we are very much out of time. I want to thank all of the panelists again for this extremely informative webinar and answering all of the questions. I know there were questions that we did not get to in the Q and A. I encourage you to reach out. Some of them were SBIR STTR specific. We're going to put the SBIR STTR box .. . e-mail box in the chat. That's seedinfo@nih.gov. We'll post that in the chat for you, and in addition, if you have specific questions about whether or not your specific project is a clinical trial, those are the questions you start asking to your program officer. So oftentimes, again, the program officer can be extremely helpful in determining whether or not you would be considered a clinical trial, and so

I encourage you to reach out to and talk with a program officer well in advance, and they also have access to some other resources that we were discussing today as well and making sure that you have those resources and are able to understand what requirements you have when you're doing human subjects research or .. . and/or a clinical trial. Thank you so much.