Lyndi Lahl: Good afternoon. My name is Lyndi Lahl, and I am the NIH human subjects officer and moderator for this session. Thank you for joining today's presentation, which is the review of the common rule and its application in human research. Today's format is a live session, and we will have question and answer period with the presenters. Please only put your questions in the Q and A box, the chat is reserved for the panelist, and I will now turn it over to Dr. Lau.

Yvonne Lau: Hello, everybody, so my name is Yvonne Lau. I'm the director for the division of education and development at the HHS office for Human Research Protections. I'm delighted to be here, to be talking to you about some of the basics of the common rule. I'll try to make this session as interesting for you as possible. To start with, just to remind you, the opinions expressed here are not ... Are my own, and not necessarily represent those of the Department of Health and Human Services. And the other thing is I try to simplify some of the regulatory language for you, so if you want to find the actual text, you can go to our website. So here are our learning objectives for today. I'm going to talk a little bit about how the federal regulations come about. Give you some clarification as to what the role of OHRP is versus the NIH, and the FDA, and the most interesting part for you I guess would be to explain to you what human subjects research means, and what exemption means, and I hope that that information would be really helpful for you when you complete your NIH grants application process. So let's start. Common rule defines research as a systematic investigation designed to develop or contribute to generalizable knowledge. So the ultimate goal of us doing research is to generate this generalizable knowledge that hopefully would advance the common good, and that's the reason why the public generally supports scientific research. Now when we involve humans in our research projects, we are really using them as a means to achieve this end. Now as a scientist, most of us are trained to be very pragmatic, so we want to get to our results and we want to get there quick. Very often as we do that, and if our research involves human subjects, we may not be able to manage the competing interests, and we may forget to adequately protect the rights and welfare of these individual research participants, and when that happens we will be using them, really merely as our tool towards a different end. So that's not very good, right? And this was exactly what happened at the syphilis study that began in the '30s. I'm not going to bore you with the details since I'm sure many of you are familiar with this study. The study went on for 4 decades. What I just want to say is that one of the most egregious things for me about this study is the fact that when penicillin, an effective treatment for syphilis became available in the '40s, this information was not provided to the research participants, and there was also the efforts to prevent this information from getting to the participants. I find that to be really egregious, and I guess the public did too, and that was reason how we ... Congress needed to act and decided to act at the time. So in the late '70s, they introduced the National Research Acts, and got a group of specialists, ethicists and researchers together, and they come up with the ethical principles supporting ethical research in the Belmont Report. And later on there was also regulations put together and collectively we call it the common rule, and that's what we've been using in the last 2 decades. The common rule underwent some revision a few years back, and so now we have the new version, which is sometimes referred to as the 2018 requirements. So the requirements and the regulations, they did not come about for no reasons. Many of them have strong basis on the principles that appeared the in Belmont Report. So respect for persons being a very important principle when we involve humans in our research projects, right? And that's being translated into the requirement for informed consent that is provided voluntarily and with participants adequately understanding the information they need to make a decision about participation. The second principle in the Belmont Report is beneficence. That is maximizing the good and minimizing the harm. So we have in the regulations, requirements, that research minimize risks of harm to prospective participants, or to participants, and it's able to balance the risk and the benefit. And last but not least, the principle of justice, which is translated into an equitable selection of subjects and that also requires us to link burdens to benefits as we think about how we recruit and who we recruit, subjects for our research. This then takes me to the second part of this presentation, to tell you a little bit about the different offices and organizations. First of all, first I want to just reemphasize the fact that the regulations are not there to trip you and to create difficulty for researchers. The regulations and the requirements and regulations were developed really with protecting the rights and welfare of individual subjects in mind, but at the same time, trying to provide the best opportunity to further research that promotes society's interests. So the Office for Human Research Protections, or what we call OHRP holds the regulatory authority for the [Indistinct] of regulation called 45-CFR, code of federal regulation 46, part 46. This office provides leadership in protecting human rights, human subjects in research conducted or supported by the Department of Health and Human Services. Now regulation requirements for protections apply only to non-exempt human subjects research that is conducted or supported by HHS. That's the jurisdiction for our office, and later on you'll know that this set of regulations actually apply quite generally across the federal departments and agencies as well. So OHRP has three divisions, Division of Policy and Assurances, Division of Education. That's where I came from. And the Division of Compliance Oversight. So 45-CFR 46, there are actually five sub parts to this set of regulations. Four of them are particularly designed to protect research participants, B-C-D, for vulnerable populations. So part A provides the foundation sets of regulations, the baseline sets of regulations on how research ought to be conducted. And we call it the common rule. The reason why it's generally referred to as the common rule is because, as I've mentioned earlier, many federal departments and agencies have adopted this subpart, codified them in their respective regulations as well. So that's why it's called the common rule, it's applied commonly across the federal government. So part B-C-D, so parts that need to be adhered to if you receive funding from the Department of Health and Human Services for your research. Please note that the regulatory framework only provides a baseline standard for human research protections. So mere adherence to the regulations does not necessarily mean that your research study has no ethical concerns, or presents no risks to participants. In fact, often the expectation is that you will do more, and you think about this more. So the goal is not just to adhere and comply with regulations, the goal is really to really think about doing research ethically and responsible. So many of you are confused about these different organizations. OHRP actually does not come under the NIH, as many people might mistakenly think. So OHRP actually comes under the Office of the Secretary in the Department of Health and Human Services. And NIH and FDA being very big, as individually, each of them are, they also actually come under the Department of Health and Human Services. So what does that mean, and what do they do, really? So what's the difference between all these three different places that seem to have something to do with human subject's protections. National Institute of Health, NIH, it's a sponsor of research. They develop policies to support the research of the sponsor, right? But the policies that they develop, if it involves regulations and ethics in human subject's protections, they must not conflict with regulations that OHRP oversees, the 45-CFR 46 that we just talked about. FDA has a totally different rule. Well, not rule, totally different function. So FDA regulates clinical investigations involving drugs, devices and biologics, to make sure that they are safe for public use. So FDA really is looking at making sure that things that are available to the consumers on the markets, that they are safe. That's their function. NIH's function is making sure that the research they sponsor are done ethically, right? And sort of meet what the interest would be in terms of research development. So what about the OHRP? It regulates HHS conducted or supported human research. All NIH nonexempt human subjects research comes under OHRP's oversight. NIH research that are also clinical investigations involving drugs, devices and biologics will also come under FDA's oversight. So I hope this explanation helps you understand how we're related to one another. Basically if you want money to do your research, NIH is the organization that you look to. It's under HHS, right? And then if you are, sort of developing a new drug or a new device and you want to put it on the market at some point so you're doing clinical research to support that, FDA is the organization that you need to talk to and you need to satisfy. Of course all of this research if it's HHS funded, then that needs to come under our rules and make sure that you comply with them. So I mentioned that the regulations application to nonexempt human subjects research. So what does that mean? This generally means, amongst other things, so I can't give you everything here, so these are just three main points. This generally means that IRB, there's a need for IRB review, and it's the formal IRB review that needs to comply. The whole setup and membership, and what the IRB reviewers need to review. All of those criterias are stipulated actually in the regulations, and the reviewers need to comply with what's written in the regulations, right? It also generally means that informed consent would be required for the research, unless that's waived by the IRB. And it also means that institutions that are receiving the funding to conduct the research, they need to assure the federal government that they would conduct the research in an ethical manner, and in compliance with the regulations. And generally they would be required to provide certification, an IRB certification before the federal agencies would be able to release the money for the nonexempt human subjects research to be conducted. There are also many situations in research where the requirements, the regulatory requirements to protect the human subjects do not apply. What are those situations? When a project is not research, or when a project is not human subjects research, or when a project is exempt human subjects research. All those terms in blue, they have special meanings. So you cannot just use a layperson's perspective to interpret it the way you want. If you want to understand what they mean, you need to go to the regulations, the common rule, and look at what the definitions say. So when the project is not human subjects research, or that it's exempt human subjects research, what does that mean? It means that the common rule requirements, right? Especially with regards to IRB review and informed consent requirements and so on, they do not apply. Investigators and institutions would have the flexibility to do the research outside of those regulations, of those requirements. Now OHRP encourages investigators and institutions to by all means, make use of the flexibility that are available if your research project falls into one of these categories, right? And go ahead and make use of that flexibility to facilitate your research. But we also want to remind you that the fact that your research would be outside the scope of the regulations does not by any means mean that you relinquish your ethical responsibilities for the humans who participate in your research. So please, really the utmost concern really is make sure that you are reminded that you have ethical responsibilities for participant's rights and welfare. Now this provides you with an overview of the human subjects review process for the NIH grant applications. So there are two parts, on the left you have the NIH peer review process in a nutshell, and on the right you have the institutional IRB process. So on the left you start where the yellow arrow is, you submit your application, it goes through scientific peer review. The scientific peer reviewers will also be asked to do a brief review of the adequacy for human protections if your research is considered to involve human subjects, materials and so on. And so they will do a review of that as well before they make their decisions. And then NIH would make a decision as to whether they're ready to fund that particular project. So what happens on the other side? So at your institution, and at this point I want to mention that research grants from the NIH are mostly given to institutions, not the individuals. I think the individual receives grants when ... The grants goes to the individuals, let's put it this way, when it's a training grant I guess, when it's an individualized training grant. Okay, I've left the NIH for a while, so don't take my words completely as is, but generally that's the understanding. Grants money for research project goes to institutions, and it's the institution's responsibility over their investigators, the conduct of the investigators and so on. So at the institution, the institution potentially, if they are going to get these grants they need to make sure that there's some sort of an IRB process in place, especially for the nonexempt human subjects research, we talked about that earlier. So what investigators would do is they submit the study to something called an IRB office, and sometimes it's called the human research protection program. It depends. If you are really small organization, or if you are getting a company, small business getting a small grant for research, and you may not actually have such an establishment in your organization. In which case, if your research is nonexempt human subjects research you probably have to rely on the designated independent IRB somewhere. So at the IRB, when your research projects go to the IRB office and the IRB office will look at it and do an initial review, and then decide if this needs to go to the actual IRB board for the regulatory type of review. One way or another, the IRB office is there, hopefully, to help investigators with getting their projects and the human subjects protections part in place. Now once that's done, so again, for nonexempt human subjects research, you need to get an IBR certification. That yes, the IRB board has looked at it, or the IRB reviewers have looked at it in the manner dictated by the regulations, and that they certify that, and now you're ready to send this back to NIH for the grant money to be released. All right, now the most interesting part. I said that I would talk about human subjects research, and remember what I said earlier, the definition ... There are definitions for all those terms, and you must not use your, just a lay perspective, to interpret these terms. So you must always go and check the definitions or the descriptions in the regulations. So in the common rule, human subject is defined as a living individual about whom an investigator conducting research obtains information or biospecimens through intervention or interaction with the individual for the purpose of the research. Sorry. All right, so that's one part of the definition, living individual. Investigator would be obtaining information about this living individual, directly through interacting, like talking to them, doing surveys, communicating with them, or through some sort of interventions. Asking them to do some activities or doing some things on them, like taking a biopsy or some blood samples, et cetera. So for the purpose of the research, for the purpose of this research, the investigators need to go and interact, or do something with individual living subjects, right? To collect that information for research. This is what we call primary ... Generally refer to as primary research. And this is human subjects research. It meets the first part of this definition of what human subject is. Research itself, I've already given you the brief definition, so I'm assuming that it already satisfied the criteria for what constitutes research, so that's an assumption here. So assuming that, if it also satisfied this statement here, then it would be called human subjects research. Now some investigators get confused. They may actually, on may occasions they may have the occasions to send the project out and somebody else may be doing part of it for them. So let's just take surveys. So they may hire a company to do some surveys on their behalf. They provide the questions and the survey company's asked to collect the information, or that they may sort of subcontract to an organization that takes blood and do biopsies, and then they ask this organization to do the intervention procedures for them. And then as a result, these agencies will provide them with the information that they want with or without identifiers, or the biospecimens with or without identifiers associated. And then investigators get confused, now is that human subjects research? No, I tell you, for the purpose of the research those activities were done. So regardless of who did them, they were done specifically for the purpose of that activity, that makes it human subjects research. I hope this point is clearly conveyed across to you. So once you've decided it's human subjects research, it's primary research, you have two options. You can look at whether the research meets the condition of one of the eight exemptions that are available in the common rule. If it does then it could be an exempt human subjects research. If it does not then it will simply be straightforward case of a nonexempt human subjects research, and if you remember what we said earlier, then that means that it comes under the scope of the common rule regulatory requirements, and generally that would mean a more formal process of IB review, and that generally informed consent will be required, and all the rest of it. All right, so on your grants submission, you would check yes to human subjects involvement, and then I left here the part about exempt research, I left it as a question mark because it really depends on whether the entire study fit into one or more of the exempt categories. If you check yes here, be prepared to provide a clear justification for why that particular exemption is satisfied. And I'll say a little bit more about exemptions later on. So I already said there are two parts to this definition for human subjects. So this is the other part. Let's say it doesn't meet the first part, you're not actually for the purpose of this research going to do anything directly in terms of interacting with individuals or collecting their stuff. But instead what you have is simply, and you may get it from a different source, that collected it for other reasons, and I'll go into some of those other reasons in a minute. But what you really have is just you have some identifiable private information or identifiable biospecimen that belong to living individuals. That's all you have, you're not actually going to go out and do any collection for the purpose of this research. You're not interacting [Indistinct] with people for the purpose of this research. What you have, it's like maybe you're getting it from medical records and all that information was collected for routine clinical care. Or that you're able to get information that some other researchers, in some other research project, that they collected, and that they're willing to provide their information to you for your research purpose, and that process does not require them going out specifically for your research to collect more information on materials. So this is the case that we're talking about, and generally we would call that secondary research. It is human subjects research, it is secondary research. The key word here is identifiable. So materials identifiable, at least at the time of access. At some point particularly at the beginning point of that process. So with the two together you're doing secondary research, and that the materials you have for the secondary research that you work with are identifiable at some point in time to you or your research team. That would also be called human subjects research, and the same situation applies. So you have two options, you have to decide whether it qualifies. The entire research fits into the conditions for one or more of the exemptions available to you in the common rule, or if not, then you just have to simply go ahead and follow the regulatory requirements for IRB review and informed consent, et cetera. So again, this is the same scenario as one, right? You check yes to human subjects involvement, and then you have to make a decision about exemption. Now I already said the key word there was identifiable. What does that mean? It again, confuses the heck out of everybody. Identifiable has a special definition under the common rule, and it is this. Identifiable private information or identifiable biospecimens refers to private information or biospecimens for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information or biospecimens. To change this around and just explain to you in layperson's terms, it just means simply that do the investigators on this team, can readily link the materials, the private information on the biospecimens back to a living individual? Can you readily link them back? It's a subjective determination. It doesn't have the nice list that HIPAA provides. So it's not something on the list, and if there's something on the list then it's identifiable. It is something that you have to consider and take into context of the situation of the research. The common rule does not define these other associated terms like coded, de-identified or anonymized. And so I would suggest that you do not sort of rely on using those terms to try to explain your case to either your IRB office or your scientific reviewers, because it is really confusing. When you use those words I actually don't know what you mean. So when you say coded, does it mean that okay, it has a code? The information and all you're seeing mostly, most of the time is just the code to that. So this set of information belong to XY123, and this next set, XY124. So you have the code. The key for me is actually to ask well, do you actually hold the key linking the code? In other words, is there somewhere that you have a list where you can tell XY123, it's Yvonne, XY124, it's Marianna. If you kind of have that access, or your research team has that access, that to us is identifiable. I also want to just say, unique identifiers themselves may not necessarily mean that it's identifiable under the common rule. What do I mean by that? So if you have like fingerprints, that unique. That's unique identifiers one would say, right? I mean, fingerprints are unique to a person. However, if Yvonne, me, I'm the scientist. I have like 10,000 fingerprints in front of me, and I'm just looking at the patterns and trying to [Indistinct] something out. I may have these fingerprints in front of me, but I have no connection. I don't have the corresponding set of information to tell me this set of fingerprints belong to this individual, that set of fingerprints belong to that other individual. If I don't have that information readily accessible to me, then this would be considered as not identifiable under the common rule. So it's really very contextual based, and you really need to think about it. And that's what IRB reviewers are asked to think about when they consider this definition of identifiable for the application of the common rule. Alright, so let's come back to the definition of human subjects. So we said okay, we were working on the second definition. We said identifiable is a key word here. What if it is really not identifiable, based on the definition that I just explained to you. So the typical situation would be somebody else have access to maybe some medical records, information, or that they might have done a research in the past and that they have information that they're willing to share with this different research team for this new project. And that they would only provide this information to you or these biospecimens to you without also providing any sort of information for you to be able to link them back to their living individuals. So absolutely you, the recipient, the investigator will not be able to link the material back. Your team working on this research will not be able to link them back to living individuals. Then that's a cross for the first part and a cross for the second part. That means this is not human subjects research. So only non-identifiable materials involved, not human subjects research. Of course there's been no interaction or intervention at all for the purposes of research. So then you have a case of not human subjects research. No common rule requirements for this research. And for your NIH grant application, then you check yes to research involving human specimens or data, but you could check no to human subjects involved. All right, so you don't need to worry about any exempt category, and I'll explain that more clearly later on. All right, you don't even have to go into that consideration. But be prepared to provide justification as to why you checked that this is not human subjects research. Essentially you're basically asked to go back to the definition. You would be able to demonstrate that for the purpose of your research there has been no interaction ... There will be no interaction or intervention with living individuals to collect their informational biospecimens for the purposes of research. And that nobody on the research team with you for this research projects can readily link the private information and biospecimens back to living individuals. All right, so those two conditions must be met for this to be called not human subjects research. So coming back to this idea about exempt. If you remember the first two scenarios, you decided in both the first two scenarios you make the determination that was human subjects research, and then you're given the option to consider whether an exempt category works or not. So to start with, before you even considered exempt or exemption, you need to know that your research is human subjects research. If it's human subjects research then you can look at the exemption categories, and if the entire study meets the conditions for one or more exempt categories described in the common rule, then you can invoke the exemptions that work for you, for your research projects. I'm not going to go into the other details, but I want to just say one more thing here, and this is the last point here. Institutions, remember I said that institutions are the ones that receive the funding, not the individual investigators. Institutions are held responsible, so institutions generally rely on experienced individuals in their IRB office or their HRPP, Human Research Protection Program, whatever it's called. To make exemption determinations instead of leaving that task to the individual investigators, making exemption determinations, it's not the same as doing the formal, going through the formal regulatory process of IRB review and approval, they're different. Okay, now these are the eight exempt categories that you can find in the revised common rule. Number one, it involved normal education practices. Exemption two involves interactions through tests, surveys, interviews. Exemption three is a new one, and it involves benign behavioral interventions. Exemption four is entirely for secondary research use of biospecimens or information. So I'm going to leave you to read the rest, and these are only the short descriptions, the brief descriptions of the exemption, in order to be able to invoke on the exemptions, you need to make sure that all the conditions that are described in the common rule for that particular exemption are met. All right, now I'm going to show you one. This is the text description for exemption three, research involving benign behavioral interventions with adults how prospectively agree when information collection is limited to verbal or written responses, including data entry or audiovisual recording, and one of these is met. This is the exact text in the common rule. If you're not familiar with this kind of language, this must be driving you crazy. What exactly does it mean? And I also want to point out, benign behavioral interventions, that does that mean? Are there policies written about this, or actually being written about this, so they've not been published. But there's a special understanding of what benign, what do you mean by benign? What do you mean by behavioral interventions? Adults, what do you mean by that? Who prospectively agree, again, what do you mean? Does it mean formal informed consent, does it mean no consent, what does it mean? And also information collection is limited to verbal or written responses including data entry or audiovisual recording. Okay, what on Earth does all that mean? So what I'm trying to show you and tell you is that it's not easy to understand what all these things actually mean as they're written in the regulations. That is the reason why institutions generally would not let their investigators who only look at these things once in a blue moon to make the determination as to whether their project satisfies an exemption, because if you make the wrong determination and it's not supposed to fall within an exemption, and it doesn't actually meet the conditions required for that exemption, in other words, if it's actually nonexempt human subjects research, and that you've failed to comply with the regulatory requirements that are required for this kind of research, then you are in complete noncompliance, right? And you see how institutions really worry about that, and you don't want to put yourself in that situation to take on that responsibility. So I'm at the end of my presentation, and I just want to tell people at this human research protection training, it's a five lesson training that we have on the OHRP website. It's freely available to investigators and institutions. It satisfies the NIH requirements for training on human research protections for key personnel. The people, the folks at OHRP developed these five lessons based on our highly experience knowledge of how the common rule works, and the 45-CFR 46 works, so you have confidence in that, and you can access it from our website. OHRP website under education and outreach, where it says online training. So this is the link. And with that I'm going to leave you with our contact information. So if you have any questions at all, do feel free to write to OHRP@hhs.gov. Obviously any questions related to our regulations to human subjects protections to the ethics of human subjects protections. Yes, feel free to write us at OHRP@hhs.gov. We have a roster of people who support this mail box, and by all means, go and have a look at the material information that are available on the OHRP website, WWW.hhs.gov/OHRP. And again, I encourage you to take a look at the resources in education and outreach site, because you'll probably find simplified information, resources that have been simplified to help you understand what is required. So with that, I end my presentation and I have some time left for questions. Thank you very much for your attention.

Lyndi Lahl: So we have a number of questions about exemptions, and a lot of them are on exemption four. One of the questions is can you provide some guidance on the differences between exemption four and "not human subjects research that uses biospecimens and data."

Yvonne Lau: So, all right, let's just go back to what I was just saying to you earlier on, you need to go back and look at the definition for human subjects. Let me see if I can just pull up my slides quickly again, just to show you that. Hang on, okay? Sorry. I suppose I ended my screen too quickly. Bear with me. Okay, you might be seeing my notes here. All right, doesn't matter. Don't read my notes, because I've been telling people the notes in my sections, they don't necessarily correspond. I have a tendency to pull [Indistinct] and they may not work. So human subjects. Concentrate on the main screen, right? The definition of human subjects is really important to you. So if your ... So you're not ... So this is secondary research in that space. Secondary research. The material that you're using are either already kind of in existence, in the sense that they are being collected for sort of non-research purposes already, so there's a different reason that they're collected. So either they have been collected or they're being collected, it doesn't matter, but that the materials are collected for non-research purposes. Or if it was collected for research purpose, it's not collected for the purpose of your current research you're proposing as a project to get funding. If you have access to identifiable information then that would be human subjects research. If this is across here, you do not have access to identifiable information, then it would be not human subjects research because it doesn't satisfy either one or two of this definition of human subjects. Let me just show you again. So let's just go back to this identifiable word. So if you have access, and you access is [Indistinct] identifiable. I already explained to you the definition of how we commonly receive what is identifiable. Let me just say a little bit more. So if you are a researcher, and that you did a research in the past, you've collected information and materials in the past, by interacting and intervening with people. So let's just say you did a clinical trial and you have a whole bunch of information, and you're the principal investigator. Now for that research, if you okay, maybe 10 years ago that you did it, and for that project you already stripped all the sort of linking ... Information linking to identifiable ... Individual identifiable information. In other words, even when you go back to your data then, that you collected for that research, and now you want to bring that data now and use that data or use the specimens to do another research project, but it is such that because it was so long ago you've already stripped all the connection. You don't have a means to link the material back to living individuals. Then you would be doing non-identifiable. So in this second research you're using old materials, this is a secondary research and you have no way to link identifiable information, so that would be not human subjects research. So that would be not human subjects research, because it would not satisfy either one or two of the definitions of human subjects. Now on the other hand, if you had kept a link of some sort. Okay, be it that you have not fished out that link for a while, but you actually know where to go and get it, that you can, that there is a means for you to actually link them back somehow, so you can. So that, you would be doing identifiable ... You would be considered as having identifiable research for your secondary research. And your options here would be okay, I can look at the exemptions now, and exemption four is the one of interest here. Because ... Let me just go to exemption four. All right, exemption four. So remember how I said you don't even have to consider exempt categories if the determination for your research is one that does not involve human subjects. So it is only when you have made the determination it is human subjects research, now you consider exemptions. And you look at exemption four. Exemption four, especially for this purpose. So okay, you might have access, you might have had access, but guess what? I don't really care, I don't need to have those identifiable information. And this also goes with like, okay, you may be a medical doctor and you have access to medical records, so you can potentially see all the identifiable information linked to this person with diabetes, and all the other treatment results and so on. But for the purpose of this research, you actually don't need any of that link. You don't need to be able to go back to link it with living individuals, and you're willing to relinquish all that, strip it to a point that you cannot link back. So you see how it is that you start off, that is human subjects research because yeah, one way or another, you're considered to have identifiers. But once you made that determination you look at exemption four, and you say oh, okay, you know what? I would be happy to meet this exemption, because I'm happy to just relinquish all of that and just strip it. And then again, let me remind you, go and read the entire description to exemption four, because it also says something like you will not link back. So not only do you not link, but you would not try to link back. [Indistinct] satisfied the entire conditions described in exemption four, then your research is exempt four. You fit into exempt four. Exempt human subjects research, and exempt human subjects research do not have to follow the very strict, you know, regulatory requirements for IRB, review and informed consent, all that stuff. Does that help?

Lyndi Lahl: I think that was very helpful, I've seen some chat said that they appreciate your response. I have another question about exemption six. It says "in customer exemption studies." They want to know does this include other than just food, i. e. acceptance of use of a product such as a wheelchair, where the person tries it out and tells the investigator how they like it.

Yvonne Lau: You wish, right? I don't have the full description here for exemption six, but it is as far as I can remember, it really only applies to taste and food quality evaluation. And why do you have a special exemption for that? Don't ask me. It has been there even in the old version of the common rule. If you do research that involves tasting food, food quality assessments, things like that, then by all means go and read through that exemption and see if your research applies. If you have a question, send it to us at OHRP@hhs.gov. But unfortunately, it does not apply to anything else.

Lyndi Lahl: I think we might have time for one more question, because it's 1:49. And somebody would like to know if they can call OHRP and have them tell you over the phone if their project is exempt or not.

Yvonne Lau: Okay, so for investigators, while we welcome anybody asking us sort of questions that are within our kind of [Indistinct] we'd be happy to answer them, but generally because institutions are usually relied upon to make the determination of whether a project is exempt human subjects research. Or for that matter, not human subjects research. So institutions are held responsible because they get the grant money. They really want to have an eye over that, and so whatever we say at OHRP, we could help you kind of get it and understand this and all that. You still need to put it together and have it submitted to your IRB office for their determination, and if you think that there may be some disagreement there and you want to really get a clarification, we welcome investigators and IRBs to contact us so that we can try to explain it more properly and more clearly from us, the regulators. So hopefully that would give you more confidence. And further, determinations are difficult and complex. So yeah, you may have heard if you call OHRP they're going to say it depends. So supply us with the detail of the situation, it's really important as well. But we will definitely try our best to help investigators and IRB offices in making the right determinations. So I'm just going to say I'm going to pass it to my colleague Marianna, so that she can tell you about the review process, and then we'll come back. There will be about 5 to 10 minutes left at the end of her session where you can continue to ask more questions about my part of the presentation or her part of the presentation. So with that, I'm passing it to Marianna.

Marianna Azar: Thank you so much, Yvonne. Bear with me for a second, I lost my control panel. Okay, so hopefully you can all see my slides. Excellent, okay. [Indistinct] second. Okay, well thank you so much again, and my name is Marianna Azar, and I am a public health program specialist with the OHRP's division of education and development. And this is part two of our presentation on what investigators should know about IRB review. So quick disclaimer, again, the opinions I may express throughout the course of this presentation are mine, and do not necessarily reflect the policy of HHS or OHRP. And the learning objectives for this part of the presentation are to discuss what IRBs look for when reviewing research, explain how to prepare a research proposal that is addressing regulatory requirements for review, and help you, the investigators, understand ... Sorry, that seems to have gone forward. Understand your responsibility in the protection of human research participants. So before we jump into a discussion of the regulations, I want to remind us what it means to say or to make the determination that the regulatory requirements for the protection of human subjects and research applied. So as Yvonne pointed out, the regulatory requirements applied to nonexempt human subjects research, meaning ...

Yvonne Lau: Marianna, I'm sorry to interrupt. I think that you're not on the right slide. It doesn't seem to be ...

Marianna Azar: Is it the [Indistinct]?

Yvonne Lau: Yeah. Yeah.

Marianna Azar: Thank you so much Yvonne, thank you.

Yvonne Lau: No, it just moved again. It just moved again.

Yvonne Lau: It's very sensitive. I hit the table just now and it moved my slide. Yeah, so just be careful.

Marianna Azar: Yes, thank you. Thank you. Well, so again, as I Yvonne pointed out, the regulations apply to nonexempt human subjects research that is funded by NIH or another common rule department or agency. Which means that if your research does fall into any of the categories that Yvonne outlined in her portion of the presentation, what I'm about to say is not applicable. For another, the regulatory requirements ... When do regulatory requirements apply? A body referred to as an institutional review board or IRB is required to review and approve the research, and the regulations also require the IRB to have a very specific defined membership and setup. And of course when the regulatory requirements apply, there are also specific requirements to obtain informed consent from your research participants, or seek and obtain approval from the IRB for a waiver or alteration of these informed consent requirements. So to dive deeper, what are these regulatory criteria for IRB review and approval of research? Well, the regulations, 45-CFR 46.111 outline criteria that an IRB shall consider and determine or satisfy in order to approve a research study. So you'll recall that Yvonne's presentation outlined the principles of the Belmont Report. Well the 111 review criteria are in essence the implementation of these ethical principles. So think of the regulations as the ethical principles put into practice. So to approve a research study the IRB shall determine that all of these requirements are satisfied. This is to say that if an IRB cannot make these determinations, the proposal cannot be approved. Depending on the level of review, the IRB can outright disapprove a study, or it can table and defer it, and seek input from subject area experts. Or it can return the study to the researcher, so the researcher can provide additional new information, address IRB concerns or questions, and work with the IRB to make changes to their proposed research. So for researchers, which I think many of you in the audience are, understanding and properly addressing the 111 review criteria is key to providing a research proposal and getting it through the IRB review process. Now the regulations also outline conditions for review that federal departments or agencies must consider when evaluating applications, and proposals for research supporter funding. This is to say that when you submit your proposal for NIH funding, if your proposed research will involve human participants, the NIH will, among other things, need to take into consideration the risks to subjects your research may pose. The adequacy of protection against these risks, the potential benefit of the research to the subjects and others that your proposal identifies, and the importance of the knowledge to be gained from your research. So as you can see, there is very clear overlap between the 111 and the 120 review criteria, and for the rest of this presentation, I'm going to walk you through the 111 review criteria and explain what an IRB may consider with each criterion, and what you, the researcher, should think about when addressing each criteria in your grant application, and IRB proposal or protocol. Okay, so let's start with the criterion that risks to subjects be minimized. So the regulations state that this is to be done by using procedures that are consistent with sound research design, which should not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures that are already being performed on to subjects for diagnostic or treatment purposes. So what sort of considerations should this criterion prompt for both the researcher and the IRB? Well, for the research question this criterion should prompt us to ask if the research hypothesis is clear, and clearly outlined. So for example, if you're proposing to conduct research on the impact of social media on teen mental health, your research hypothesis should be clearly stated to reflect this. This is incredibly basic, but part of minimizing risk is sound research design, and that of course starts with a clear research hypothesis. With respect to study design this criterion should prompt us to consider if the design of the research is consistent with what the researcher needs to do to answer the research question. So as an example again, if your researching is to assess the impact of social media on teen mental health, but your study design also calls for a CT scan and collection of saliva samples to test for stress hormone levels, you as the researcher really need to justify and explain why this imaging and specimen collection is required to answer your research question. This is not to say that it's not required, it may be, but the aim is to justify and explain. And this is because the IRB in assessing this criterion is going to ask if the researcher is proposing to do something because they can, or just because they want to, and not because they have to in order to answer the research question. So the IRB may ask, does the researcher actually need this data or specimens, or are they proposing to perform these procedures because of ease, because of poor research design. Again, to take us back to that question, or because of unexplained research hypothesis. So once you've looked at the research hypothesis and the research design, you now have to look at all the procedures that will be performed for research purposes, and you have to consider the likelihood and the seriousness of the risk proposed by each. So again, to stay with our example, we should consider the risk posed by the saliva collection, the proposed CT scan, and any other procedure that will be performed for research purposes. So for example, let's say our research also involves an interview, a survey, collection and analysis of private social media posts and messages, et cetera. And then we look at the seriousness or severity of the risks we identify in each of those procedures, because each procedure is in this example, being conducted for research purposes. For it's part, the IRB is also going to identify the risks and consider their likely severity, and then it's going to ask if your research design minimizes these risks to subjects. So the IRB can ask if instead of performing a CT scan for research purposes only, if perhaps you can piggyback on scans performed for clinical or non-research purposes. If your study is going to involve interviews, surveys, or other interactions with participants, the IRB may focus on where and how you're going to conduct these procedures, since the primary risk is likely to be a breach of participant privacy. So studies subject inclusion and exclusion criteria is also an essential consideration in minimizing risks, and for our study on social media use and teen mental health, if our planned survey or interview procedures are likely to cause potential distress or prompt an emotional response from participants, one way to minimize this risk may be to exclude teens with a history of psychiatric disorders or serious emotional distress. And of course these are just some of the many considerations that may be applicable to the planned or the proposed research. So to help us, to help guide us in thinking about what considerations may be applicable, I wanted to just step back for a moment and talk about the general concept of risk, right? What is risk? Well, risk is the possibility that something unpleasant or unwelcome will occur, right, and note that the idea of potentiality is built into this notion of risk. So merely the possibility that something could occur means that there is a risk of it happening. This touches on the most challenging aspect of thinking about risk, in that it is rarely objectively or absolutely quantifiable. And so it could be very difficult for us to assess risk. Fortunately the regulations do provide us some tools to guide us in this assessment. For example, the regulations provide us with a clear definition of minimal risk which means that the probability and magnitude of harm or discomfort anticipated in the research is not greater in and of itself than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. So as I mentioned earlier, we know that risk is a function of how severe and how likely something may be. And with this definition, we now know that research risks specifically are compared to three standards of reference: One, daily life; two, physical examinations or tests; and three, routine psychological examinations or tests. And so, as researchers, when you think about the risk posed by your research procedures, you should think of them in relation to these three standards of reference. Of course, when assessing the risk of a study, you also need to think about critically about the circumstances in which the risk may occur and who may be impacted. So our planned interviews on the mental and emotional toll of social media use may carry psychological risks if we plan to ask sensitive or possibly triggering questions. And this is likely to happen in the course of participation. Of course, if our participants are identified with their responses, and if their responses include, let's say, sensitive information including information about peers, so they identify as cyber bullies, there may be the additional risk posed by the identifiability of the responses. And the impacted parties, in this particular case, may be those about whom research participants disclose damaging information in addition to the research participant herself. Now, as the researcher, you will also be expected to detail how the risks you've identified will be minimized. Now note that the regulations require that risks be minimized and reasonable, not eliminated. This is a very important consideration because some risks cannot be eliminated completely. So if our study is likely to pose the risk of emotional distress, privacy breeches or sensitive disclosures that may pose the risk of, I don't know, reputational damage, we might be able to minimize these risks by including disclaimers in the informed consent documents and reminders at the start of our interview that subjects should not share information that may allow for direct or indirect identification of others. We could also provide participants with things like referrals to free and accessible mental health resources, such as a website or a call or a text line. And, of course, we can develop a plan for the way that we collect, store and report our data to minimize a potential breach of participant privacy. So again, as an example, we can store data without the names or any other identifiers associated with our participants. And in reporting the data, we could be careful not to report in ways that could allow for identification of our participants. Now the regulations also stipulate that risks to subjects be reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may reasonably be expected to result. So in essence, this criterion amounts to conducting a risk-benefit analysis. So if the primary risk of our research is a breach of participant privacy, and if this risk is minimal based on that definition that I shared with you earlier, perhaps the benefit of the knowledge to be gained about the impact of social media use on teenage mental health is commensurate with the anticipated risk. The thing to note here is that risks are likely to be borne by the individuals participating, whereas the benefits can accrue either to individuals or to others. And so who benefits from your research can be an incredibly important consideration, and this is particularly the case in nontherapeutic or social and behavioral research in which, very often, the subjects don't benefit directly. So the takeaway here is that with a risk-benefit assessment the goal is balance. The risks and benefits must be balanced against each other. Of course, there is not going to be a formula for conducting a risk-benefit analysis. However, there are general concepts that we can employ. So if there is no direct benefit, then serious risks may be justified only if the knowledge to be gained is important and cannot otherwise be obtained. If there is a direct benefit, then a reasonable amount of risk may be justifiable. And if we're studying a new treatment, the risk the research should generally be no higher than the risk posed by the available treatments. This is the case unless the research risk is justified by the potential benefit. And, where applicable, a placebo should not be used when accepted therapy exists. Okay, so now some of you in the audience today may be social scientists such as psychologists, anthropologists, sociologists. Maybe some of you are education experts or public health researchers or related. So in light of that, I want to highlight that social, behavioral and education research or research that utilizes methods that are commonly employed in social and behavioral research has its own particular consideration that must be relevant when talking about risk. Namely, SBER risks are often a lot less obvious and more difficult to identify. So an interview with an adult participant may, on the surface, appear to pose little if any risk. But the topic of the interview, the location of the interview, the person with whom the interview is carried out may all elevate and complicate the risk assessment. So to give you an example, if you plan to interview nurses for a research study on employer-mandated vaccinations and requests for religious exemptions, what you ask and how you ask it may pose various risks including the risk of reputational damage, employability and financial standing, and where you conduct the research may dictate this risk. So if you decide to interview the nurse in a crowded hospital cafeteria, the risk of compromising her privacy or revealing her research participation maybe a factor for your consideration. There's also a lack of empirical data on risk and social and behavioral research which of course only further complicates this risk assessment. So the point that I want to make is that a social and behavioral study may not be inherently risky, but something about it may require careful consideration about what the potential harms may be. Okay, so another criterion of the 1.11 review criteria is that the selection of subjects be equitable. So in making this assessment, the IRB has asked to take into account the purpose of the research and the setting in which the research will be conducted. And so here an IRB may look at who the target population is, ask if the specified target population is appropriate for answering the research question, and if they also consider if you've adequately explained your inclusion and exclusion criteria. So to go back to our example, if your research question pertains to teens in the general population, but your research proposal outlines recruiting teens from, I don't know, a local private prep school with racial, ethnic and socioeconomic demographics not representative of the general population, your inclusion criteria may not be adequately inclusive, and you may be selecting your target population based on convenience or another reason that is not in keeping with an equitable selection of subjects. Of course, on the flip side, if your research proposes to only recruit teens from a Title 1 School located two blocks from your university, this, too, may not be in keeping with an equitable selection of subjects. So all of this is to say that you'll need to carefully consider who you include and exclude for participation and why and offer a clear explanation and justification for your criteria for IRB consideration. This criterion also calls for the IRB to be particularly cognizant of the special problems of research that involves a category of subjects who may be vulnerable to coercion or undue influence, and this includes children or economically or educationally disadvantage persons. So if you revise your inclusion criteria to target the general public, you may need to think about the additional safeguards that may be necessary for inclusion of some who may be economically or educationally disadvantaged among various other types of vulnerabilities. Now note the intersection between equitable selection of subjects and reasonable risk-benefit considerations. So when we talked about a fair distribution of the burdens and benefits of research, we talked about understanding who would bear the burdens and who would receive the benefits of the research. This, of course, factors into considerations of equitable selection of research participants. So to state it another way, if there are benefits to be gained from the research, perhaps our aim should be to maximize these benefits by expanding the reach of the research. So if you're proposing to conduct the study on behavioral modification techniques and smoking cessation, and you cite the high likelihood of helping participants quit smoking as a direct benefit of your research. Well, perhaps the research should be expanded to benefit the maximum or the most diverse number of participants that it can. Even when the benefits are likely indirect, the research population should be diverse enough so that the benefits can be generalizable to the broadest possible group. Likewise, when we talk about the burdens and look at research burdens from the perspective of equitable selection of subjects, we can see that burdens, such as the time, the effort, the cost of research participation, may undermine inclusion efforts because some populations, including those who may be otherwise economically or educationally disadvantaged, may not be able to accept or accommodate these burdens for the sake of the research that you're proposing to do. So if your study requires travel to a hospital in the middle of a workday, this may pose the burden of loss of time and possibly wages, never mind the effort of travel, childcare accommodations and related costs. So when you think about it from this perspective as researchers, it is important to consider measures that could be taken to lessen the burden of participation on prospective research participants. And this includes minor but actually quite significant things like meeting your participants where they are, on their time and, where applicable, providing them with the accommodations to ease the burdens of research participation. Okay, so moving on to our next criterion, the requirement that informed consent be obtained and documented before beginning any research activities. Now, beyond simply seeking and documenting informed consent, note that the informed consent must provide information needed for an informed decision about participation, and that it has to do this in language understandable to the potential participant and under circumstances that promote voluntariness. So huge concepts, we'll unpack these. So for researchers, this really means thinking about what information is the relevant information for informed decision-making. Now note that too much information may overwhelm a prospective participant, but an insufficient amount of detail may result in a participant making a decision without all the relevant facts in mind. So providing information in language understandable to the potential participant can also be a challenge because writing in plain language and clearly describing complex concepts and procedures is really no small feat. And likewise, thinking about what circumstances would promote voluntariness means thinking about research participation from the perspective of your prospective research participants. So would seeking same-day consent in the clinic promote voluntariness, or would providing a prospective participant the information they need to make an informed decision and then leaving them to consider this information for several days be the better approach? Well, it would depend, right? It would depend on the research and the research population, but these are the types of things you need to think about and explain to the IRB. Now I really want to recognize that informed consent considerations are incredibly challenging, and this is the case both for researchers and for IRBs. But I also want to say that informed consent is an incredibly important concept, and it is important for research and public trust in research. And this is because informed consent is the application of the principle of respect for persons. It is the recognition that people must make decisions about research participation for themselves in accordance with their values and their opinions. And moreover, that those whose autonomy may be compromised, such as the elderly or those whose cognitive capacity has been diminished as a result of illness, should be offered additional protections to ensure voluntariness and informed decision-making about research participation. This is effectively all a question of public trust, and we have to remember that it is informed consent that renders research ethical and promotes public trust in the research enterprise. So how do we facilitate informed decision-making? Well, the regulations require that we focus on information that a reasonable person would want to have in order to make an informed decision about participation. And that information that you're providing a reasonable person should be presented in sufficient detail and organized and presented in a way that facilitates understanding of why one might or might not want to participate in the research study. So this is all really easy, right? Well, no, it's actually quite complicated. But the key here is finding a way to communicate in ways that recognize the different starting points of researchers and their prospective research participants. Now this means recognizing that people are generally unfamiliar with the concept of research. So when you, as the researcher, describe your study to a prospective participant, you may talk about it from the high-level scientific aims and goals perspective. But this will likely get lost in translation if the prospective participant has a poor understanding of scientific methods and practices or even what it means to do quote, unquote, research. So this means putting yourself in the shoes of your prospective participant and thinking about how they might hear and understand the information that you are sharing with them. This also means communicating the information that matters to the participant and not to you, as the researcher. So you might be interested in the impact of social media on teen mental health because you are a public health researcher committed to exploring why teens are presenting with mental health symptoms like anxiety, isolation, hopelessness. But your teen participants and their parents, from whom you will seek consent for the child's participation in your study, may instead be interested in their own personal experience of isolation or disengagement, anxiety and maybe their own personal struggles with school. So how do you bridge this divide in perspective while avoiding potential therapeutic misconception? And this is just an example of what you need to think about when you're thinking about what information to communicate and how. And, of course, you also need to remember that the decision to participate or not participate is likely to be a fairly complex one. For a family that assigns stigma to mental illness, the decision to participate in a study that may examine the mental health in their child cannot be an easy one. And so you, as a researcher, need to be sensitive to this when seeking consent and providing information for informed decision-making. So this means that how you explain things really matters. Now consider how researchers typically describe really common practice like randomization. I cannot tell you how many consent forms I've seen that describe randomization as, quote, assignment to a random group, like a flip of a coin, end quote. Except does this truly communicate the information that I, as a prospective participant, need? Is telling me how randomization is done helpful, or would it be better to explain that randomization may mean for me, in the context of my research participation? So rather than explaining the how, maybe explain that I may not choose which group I'll be in, explain that assignment will not be informed by what is best for me as a participant, and that I have to be okay with whatever group I'm ultimately assigned to. And if I'm not okay with that, maybe that's a reason for me not to participate in the research. Now I want you to notice that the way we just described randomization used very plain language, and this is because the use of common everyday words, shorter words, shorter sentences and a conversational style all facilitate understanding. So effective communication also means avoiding things like academic or clinical jargon or acronyms that people may not be familiar with. And explaining terms that you, as a researcher, may use on a daily basis but that may not be a part of everyday communication for regular people or even people who are not in your academic field. Of course, some complex concepts will still require explanation, and so here you can think about breaking them up into sections using graphics or even pictures or short videos to explain these concepts. What I want you to take away from this is that a consent form or a consent process does not have to be a written document or only a written document with no supplementary information in, let's say, the form of a video or another helpful graphic or something related. So work with your IRB and be creative and thoughtful about the way that you deliver this information. So we've touched on some of these things already but informed consent considerations also apply to who will seek conformed consent. So if you're a prominent researcher or a clinician, can you be sure that your patients will feel comfortable declining your invitation for research participation? What if you're just a junior researcher or a graduate student, but your prospective participant is an undocumented migrant with a fear of authority, and you are perceived as an authority figure? What more needs to be done or said in these circumstances to ensure voluntariness? Or, otherwise stated, who should seek consent to ensure that it is given voluntarily? Now the example we've been exploring throughout the course of this presentation involves research with children, and one of the additional consideration for research involving children is that there's likely the requirement to seek parental consent and the assent of the child. And we've also touched on additional protections for those with impaired decision-making capacity or diminished autonomy, and without going into extensive detail, research with these populations may require you to consider involving a legally authorized representative or possibly a substitute decision-maker. Of course depending on the research and the intended research population, there may be much more to think about, including but absolutely not limited to translating consent materials for non-English speakers, finding alternate ways of communicating information to subjects who may be illiterate or have limited literacy, keeping in mind cultural norms and seeking consent verbally where written consent may not be culturally appropriate and, of course, seeking consent of the group in addition to the individual in cases where the participant is representative of a specific special population, including those populations that have endured historical research-related harms. So when it comes to informed consent considerations, the important thing is that researchers recognize the need to consider and describe when consent will be sought, how consent will be sought, under what circumstances, by whom and using what tools, documents or other materials. Okay, so moving on now, in some cases the IRB may also require additional data monitoring to ensure the safety of subjects, and I'm not going to go into this in detail. But this is typically done by requiring a Data Safety Monitoring Plan or Board or another plan to monitor the data. And this can be relevant in the case of something like a multisite double-blind clinical study where the Data Safety Monitoring Board alerts researchers to identified safety concerns or adverse events in an effort to ensure the safety of the subjects. So we've touched on this requirement already, but another criterion that pertains to adequate provisions to protect the privacy of your participants and to maintain the confidentiality of the research data. So in our case study, we mentioned conducting interviews and administering surveys to participants. To protect their privacy, you might want to consider things like conducting the interview in a private location absent of the presence of others. Since a lot of research interactions now occur online, this might mean informing your prospective participant that the interview should be conducted in a private room in a house or apartment with a closed door and maybe wearing headphones to prevent others who may be around from hearing the researchers' questions. If the interview is to be recorded, which platforms like Zoom have made incredibly easy, this also means thinking about how this recording will be stored and safeguarded or actually thinking whether the recording should be made in the first place. And, as has become common practice, if the interview that you conduct is going to be transcribed, this also means looking at things like privacy provisions of the transcription service, including those where the transcription is performed by artificial intelligence because such services may store the uploaded recording and use it for all sorts of things, like machine learning and AI-improvement purposes. And where you're conducting private identifiable social media data, let's say that your research is limited to this kind of secondary data analysis, this may also mean stripping the data of personally identifiable information and then maybe storing it on something like an encrypted and password-protected hard drive, rather than let's say a cloud drive shared by the entire graduate student cohort in your department. Okay, so one thing I want to highlight before we come to the end of this presentation is that the 1.11 review criteria are outlined in Subpart A of the regulations, and Yvonne's portion of the presentation touched on this. However, the regulations do of course include three additional subparts that outline additional protections for vulnerable populations. So if your research will involve these groups, additional requirements may apply, and for the example that I've been citing throughout, likely Subpart D considerations, which I'm not going to go into detail, would be applicable. And if your research, let's say, involves adult participants who are not otherwise covered by the other subparts, note that Subpart A of the regulations does require additional safeguards for subjects who are vulnerable to coercion or undue influence, including those with impaired decision-making capacity or those who may be economically or educationally disadvantaged. So, in this case, the thing to consider are the types of vulnerabilities experienced by the subjects and the measures that the researchers will need to employ to protect these participants, or otherwise stated, the measures that will need to be implemented to address the situational vulnerabilities, or lessen the impact of vulnerabilities that may be intrinsic. So your responsibility as a researcher is to identify and consider possible vulnerabilities in your prospective research participants, and then to develop plans for how to address and safeguard potentially vulnerable subjects. And I've touched on various types of vulnerabilities throughout this presentation, and the ways we can safeguard vulnerable subjects in the course of what we've been discussing, and this includes ways to safeguard subjects who may be non-English speakers, undocumented migrants, or others who may be experiencing vulnerabilities stemming from their economic or educational status. So before we end, I also just really want to underline the role that researchers play in the protection of human research participants. Now note that the protection of human research participants is a shared responsibility between the IRB and the researcher. So you as a researcher must educate yourself on the regulatory requirements and the ethical principles underlining these requirements. You also need to remember that conducting research with human participants is a privilege. It is not a right, and of course that research participants are not just a means for you to reach your ends. It is also very important for researchers to see the IRB as their partner in the protection of human research participants. This means working collegiately with your IRB, respecting their time and the effort of not only those who serve on the IRB, but also the IRB support staff, and providing the IRB with a clear, complete and mutually consistent research proposal and study instruments to facilitate the review process and allow for your project to receive approval. What I really want you to take away from all of this is the IRB is not just an obstacle or regulatory or bureaucratic nature. It is your partner in protecting research participants and promoting ethical research, and OHRP is your partner for educating the public about research and research participation. And so I encourage you to visit our website, and check out the resources that we've developed to provide the public with basic information about research and research participation, including things like informational videos, and a list of questions you can ask researchers, a glossary of terms, and a lot more. All of these resources are free, and I think quite significantly, all of them are available in Spanish. And as Yvonne mentioned in her presentation, we're also here for researchers, and our website includes a lot of information geared towards the research community, so please visit these pages and click around their website and watch our educational videos and mini tutorials, and complete the human research protection training that Yvonne mentioned in her portion of the presentation. Thank you so much, and I look forward to your questions.

Lyndi Lahl: Fantastic. Well, we have a lot of questions, and I know we don't have time to get to all of them. So I'm going to pick out ones that are a theme that we've had more that one question on it. So in terms of informed consent, what about research where the study participant is a cluster. I'm assuming it's like a cluster randomization trial, so the entire primary care site ... So do you have anything to say about informed consent under those conditions?

Marianna Azar: Yvonne, do you have anything to say about informed consent under those conditions?

Yvonne Lau: Are we going to start with a really difficult question? I don't know that there is a simple answer to that, but in general we don't really make a distinction between whether the research is done with a cluster of people or not. So if there is a research where living individuals are involved, you are doing interactions, interventions, since you are doing something to them. So it is hard to make a case that you don't actually have contact in such a way that you do cannot interact and get consent from them. That is the most sort of direct answer I can provide you, but I think like I said, cluster randomization and cluster type of research, it's an animal on its own. And I would not want to give you more information here before knowing some of the details that you may be able to provide us. So if you really want to pursue that, by all means send it to OHRP@hhs.gov. And you can send it on as if you don't want to make it ... Don't want the regulators to know who you are, where this is coming from, you can make it like a hypothetical situation. And honestly, we're not there to try and ding people, to get people to be noncompliant. We're there to help you to be compliant, we are there to try and help you do ethical and sound research that respect people. Ultimately that is the goal, and I keep saying that from ... We're the education team we want to tell people to do the right thing, rather than to just comply with the regulations.

Lyndi Lahl: Great. So somebody has asked a question about children. How can we make sure that they have their rights protected while the contact person is their parents.

Marianna Azar: Yeah, that's a tricky one. So one of the things that I often say to researchers is child assent is absolutely necessary, with the exception of cases where the research stands to present a benefit that would not otherwise be available to the child outside of the research participation. Meaning if you're conducting a minimal risk study and the child is either verbally or physically or otherwise not demonstrating assent to participation, that should be a key to you, that should be a note to understand that maybe the child is not a willing participant in the study. You should always think of the child as a standalone research participant, even though parental consent may be required. And so I've often recommended that if you do run into cases where you suspect that the child may not be a willing participant that perhaps you seek their consent slightly out of the area where the parent is whispering in the ear and encouraging participation. But it depends, it depends on the research, it depends on the specifics of the study, but yes, you're absolutely right to be asking this. You must respect the autonomy of the child the way you would any other research participant.

Yvonne Lau: And taking into consideration of the maturity of the child and everything, and that is the thing that your IRB should be able to help you. So the condition that Marianna said, that there's a condition where the child assent is not important, and that's when they sent a benefit directly. The IRB would be able to tell you whether that is the situation where assent can be waived. But if sure of that, basically assent is required, and by that, you actually need an affirmative response. Of course for very young children, and if you're going to subject them to needles I hate needles, I don't want to do ... There are all those actual real life situations, and it's really hard to tell is that a non-assent, is this an assent or is it non-assent? I think those are really difficult, and I don't know that we can actually give an across the board answer. It really is, at the end of the day it's also your clinical experience, working with the nurses who know the child, and at the end of the day again, I want to come back to the same old thing, you're doing all of this because of your interest in respecting that person's interest as much as possible. Whether it be a child or an adult, or anybody else for that matter.

Lyndi Lahl: Great. Well we still have a number of questions about exemption four, so here's another one. So can you speak to when the primary investigator on the research team does not have access to identifiable information, but a co-investigator on the research team does. Would the primary PI need to indicate human subjects even though they don't have access to identifiable information themselves?

Yvonne Lau: So the whole research is ... The research project entirely is seen as one, it's seen as a whole, so anybody on that research team would have some kind of way of accessing identifiable information for that research. Then it is considered to be identifiable, which means that the whole research being submitted to the NIH would be called human subjects research. The next thing, the next question if you remember that you want to then consider is oh, does any of the exemptions apply? And for secondary research like that, the exemption that we're thinking of usually, not the only one, but usually is exemption four. And then what you'll be asking then is look at what it says and how it's described, and ask yourself well, are we willing to strip that? So that nobody on the research team will be able to link the materials back to a living individual, and will not try to do that. If you're able to do that, exemption four would apply to you, and it is equivalent. The actual situation would be equivalent to it being a not human subjects research situation. Meaning that you don't have to then go through the formal IRB review process, blah, blah, blah, informed consent and all of that. So I hope that explains it. In fact, I saw a lot of questions as I was going through the Q and A as Marianna was talking, I thought I'll answer some of these questions. So I kind of wonder if some of the questions came about also because the people asking the question might not have participated in the first presentation since it's advertised as two different ones. In such situation, I urge you to go back and watch that video when it becomes available, and maybe download the set of slides. We provide that with active links as well, and hopefully, and I saw one comment saying the tool that was presented in that presentation was very helpful to help you in determining whether it was human subjects research. Now just coming back to that last question, you mentioned co-investigators. So in the case of submitting that to the NIH, it will be considered as a human subjects research whether or not exemption applies. That's your determination and that's for you to justify. Now I can imagine that okay, well for the purpose of the research, you really want to keep the identifier for whatever purpose. So it's identifiable, it's nonexempt human subjects research. But then you're working with many different institutions, some people may be ... Some investigators in some institutions may at the end of the day really only get to be seeing materials without identifiers, and they wouldn't be linking back or anything. Now there is such thing which is very complex called engagements of that institution. I don't even want to go there, because that is going to confuse the heck out of the majority of this audience here who are investigators. Ask your institution about it. Your institution will be able to help you negotiate and understand the process for your institution. So I'm not going to go there because it's complicated. If you didn't have this concept it's hard enough to understand everything about exempt and non human subjects research, not to speak about engagement or not engagement for the institution.

Lyndi Lahl: Great. Thank you. So there's another question, can you briefly discuss who may obtain informed consent? Are there any guidelines on who may do so?

Marianna Azar: Yvonne, do you want to take that?

Yvonne Lau: The regulations do not stipulate who should be the one getting the informed consent. Some people for clinical research, some people would say well, the PI, often the expert physician involved in that kind of condition would be very good, would be appropriate for that person to get informed consent, because they understand the entire research. They understand the clinical implications and everything. But at the same time, right? I mean myself, having been a surgeon myself and having participated in some research activities in my previous life, I can tell you that it's very hard if you want to do it properly because it's very hard as you try to explain your research to the prospective participants that you do not already introduce bias that are conscious or subconscious, because you see how you pulled on both sides, right? You are presenting the informed consent, the research and the informed consent as a researcher in this case. Obviously as researchers, we are pragmatic, we want people, we believe in our research, we believe that it's a good research, and we want people to recruit. And the faster we can actually get people to participate the faster we'll get a good result from this, a meaningful answer for our question. So there is that strong side that is pulling us to try and maybe say things in a way that subconsciously we are already imparting some sort of bias. And that is very difficult to managed, and I remember when I was doing it at a time, I had this kind of like out of body experience, where I'm kind of almost seeing myself like asking the questions, and there's my extra self behind. Kind of like looking at my, did I say that like in the most sort of unbiased way as much as possible, and that I'm not actually putting unnecessary pressure to influence my patient to participate. It's really, really hard, but some people can do it, and in our society there's no prohibition from having the researchers doing it, and it may be true that the physician researchers m annuity be ultimately the best person to do it. But on the other hand ... Okay, I'll just finish this. You can just train really, really quickly to do it as well.

Lyndi Lahl: So let me go ahead and just wrap this up. Thank you, Yvonne and Marianna, for a wonderful presentation. Lots and lots of comments that have just commended you both for sharing all of the knowledge that you have. For the participants, thank you all for joining, there were well over 1,000 of you for this afternoon session, which I think is fantastic. If you have any additional questions know that you can go to the exhibit hall to get more information, and we do want your feedback. So if you have a moment to provide your thoughts we would really appreciate that. Thank you again, and have a great rest of your day.