Cyberseminar Transcript
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Session: Focus On: Continuing Review
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Welcome everybody. My name is Soundia Duche. I am a program analyst in PRIDE, the Program for Research, Integrity, Development, and Education which is located within ORD, and in the room with me today, assisting me is my colleague, Lucinda Shouse, she is also a program analyst in CSR&D which is Clinical Sciences, Research, and Development Program also located in ORD.

So, today's training is our third ORD Cyberseminar that we've presented this year. We've been doing one a month and we plan to continue that throughout the rest of the year. Today's topic is Continuing Review and this is one of what we're calling our CORE series. Our CORE Cyberseminar series, is really designed to kind of go over the fundamentals of regulatory, oversight, and regulations governing human subjects research and so it's primarily geared towards IRB administrators, IRB chairs, members, research office staff, those who are new to the human subjects protection responsibilities, as well as those that desire a refresher on the topic being discussed. So we're going to go over the fundamentals and then we're also going to go over some changes that we anticipate seeing once the revised Common Rule goes in to effect. It's going to be a long lecture. I'm going to tell you that right now. I timed it late last night and it came in at about an hour, 20 minutes so bear with me. I'm going to try my best to keep you as engaged as possible. I've included some polls to, you know, try to illustrate some points and, again, just keep people engaged. But, we're going to do our best to kind of get through this, quickly, but also clearly. We will have some time at the end for questions. I think we're going to go til 3:45 so I'm hoping we'll have a good 20 minutes for questions at the end. Alright. So, let's get started. The topics we're going to discuss today are why does the IRB conduct continuing review. We're going to go over what constitutes meaningful and substantive continuing review. We're going to talk a lot about that. Then we're going to go into convened IRB versus expedited review when it comes to continuing review and spend some time going over expedited review categories 8 and 9. We're going to touch on lapses in IRB approval, and then finally, we're going to get to continuing review and the revised Common Rule which I know a number of you guys are here waiting for that, but we are going to keep that til the end so that we can kind of get through kind of the fundamentals because the fact of the matter is, right now we're under the current Common Rule regulations and so we want to make sure that everybody understands what their responsibilities are and what the requirements are for conducting continuing review under the current Common Rule requirement and then we'll switch gears and focus on what has changed. Now, I'll be honest, I am in no way an expert on the revised Common Rule. I am still reading it, trying to decipher it, understand it. I have found that for myself, it really helps to kind of focus on a topic and really delve into it in depth and so any CORE trainings that I do this is the approach we're going to take. We're going to kind of focus on the current requirements and then, at the end, touch on

what has changed because that's the best way I learn and I'm hoping that's an effective way to present the information to you all.

So, why does the IRB conduct continuing review?

First and foremost, it's a requirement. The Common Rule requires that an IRB conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. And so we do it because we have to, but we do it because we need to as well. So much of the attention is really spent at the initial review and approval side of the equation. Investigators want the approvals, IRBs are focused on turnaround times, so a lot of attention is spent on, you know, getting the protocol, getting the consent form, getting everything just right, trying to turn things around, meeting deadlines in terms of a sponsor deadline, funding deadlines, all of these things and so, a lot of focus, for metrics purposes especially, is always on the initial review. But, the fact of the matter is, continuing review is almost one of the most important aspects in responsibilities of the IRB because, while the initial protocol focuses on what the investigator expects to see and how he anticipates the study will progress, it's only once the study is ongoing that the IRB and the investigator really is able to see kind of how things play out. That's when, you know, we learn new information, things that we didn't anticipate come to light, new risks are identified and so continuing review is the monitoring mechanism that assures that continued safeguards are in place to protect the rights and welfare of study participants.

So, I thought it'd be interesting to do a short little poll to find out when everyone sends out continuing review reminders and there's no right or wrong answer here, so just be honest. I'm going to ask Heidi, great, she's already pulled up the poll, you know, go ahead and select the most appropriate answer; three months or more, two months before approval expires, one month before approval expires, two weeks before approval expires, or for those who are like, reminders, what reminders? That's okay too. Just be honest. I'm really curious to see kind of how this plays out.

Heidi: Responses are coming in. We'll give everyone a few more moments to respond before we close the poll and go through the results here. Looks like we've slowed down so I'm going to close this out. And what we're seeing is 39% of the audience saying three months or more before approval expires, 43% saying two months before approval expires, 15% one month before approval expires, 1% two weeks before approval expires, and 2% no reminders sent. Thank you everyone.

Soundia: Great. Thank you Heidi. Alright, like I said, there's no right or wrong answer, however, you know, it's everyone's responsibility that continuing review occurs and it occurs prior to the approval expiring because the regulations do not allow any prolongation of the approval period, nor does it allow continuation of research past the approval period. And, so, one thing you want to keep in mind for those who, you know, selected three months or more, which is absolutely fine, you want to make sure that you send out the notice in sufficient time to be able to allow for, you know, a lot of back and forth between the IRB and the investigator

but you don't want to send it out so far in advance that essentially it's disregarded because the investigator knows, okay it's four or five months ahead and this is not due for another x number of months so they just ignore it, or they complete it, but they completed it so far in advance that by the time the IRB actually reviews the information that was submitted, it's no longer relevant and so you want to find the sweet spot and each of you knows kind of through experience, right, what really works best for your facility, what works best for your investigator. There is no requirement. No regulatory requirement to send out a reminder so for the 1% that said that they don't send out reminders, there is nothing wrong with that. However, just remember that it can be the IRB's fault that approval expires and that is if, you know, the IRB misplaces the materials. That has occurred and, therefore, doesn't conduct their review in time or doesn't track it appropriately. A number of sites have been, and when I say sites I'm not saying VA sites per se, but a number of institutions have been cited by OHRP for not adequately tracking continuing review and coming up with a system to ensure that continuing review occurs on time. Normally that system tends to involve reminders but no regulatory requirement to do so. So, want to keep in mind that really, under no circumstances, can approval extend beyond one year from the previous date of approval.

So, with respect to how often continuing review must be conducted. The frequency of continuing review really should be based on the IRBs ongoing assessment of the risks associated with the study. Most of us tend to do continuing review on an annual basis and nothing is wrong with that and maybe nine times out of the 10 that's the appropriate time frame. However, you want to make sure that you thought through, both in your policies and in your actions, right, what factors you would want to consider for reviewing a project more frequently than annually. I always like to kind of look at either ORO or OHRP or FDA determinations to see kind of what's out there and what they've cited facilities for. I will say that I didn't see that much in recent times when it comes to continuing review, but I found some determination letters dating back to 2012 and 2014 and 15. In a December 2012 letter from OHRP to the University of Washington, and I am citing them because it's publicly available information, but, University of Washington was cited for not adequately describing in their policies and procedures how the IRB decides or determines when a protocol should be reviewed more frequently than annually. And, in fact, the letter goes on to say that the auditors believe that some IRB members, including the chair, were not aware that the IRB's have the authority to require IRB review of a project more often than annually. So that's the first thing and they also went on to say that during their onsite reviews, that various IRB members stated that their respective IRBs never approve research for less than a year and so you really want to make sure that your policies and procedures that you've thought through what factors that you would use to determine a more frequent review period, but you don't want to stop there. You don't want to just, you know, put it in your SOPs and you've checked the box and that's gone. You want to try to make sure that you adhere to those SOPs and that you take that into consideration when your actually conducting the review at the time of the initial approval and each subsequent renewal. Some factors that you might want to consider in terms of, you know, determining if a protocol or group of studies meeting these criteria should be reviewed more frequently might include things like particular studies that have a greater risk to subjects than usual or that involve particular subclasses of vulnerable subjects maybe, even

studies maybe that the IRB is not familiar with the design of, or the drug that's being used, you know, things like that. Those would be factors that the IRB might want to consider when determining, okay, these projects should be reviewed more frequently than annually. If you have investigators that are new to being the principal investigator, that's a great reason that you may want to bring that protocol back to the table and reassess it because you have a new PI. So, anything published in the literature area, that's another one, you know, whereby, you know, if there's some new information that raises concern, you know, that would be a reason that you might want to put a study on a more frequent renewal period. So, I keep saying, you know, or let me just stress that, you know, the frequency of continuing review doesn't have to be limited to the passage of a specific time. It can also be looked at as a certain event occurring, So, the IRB is free to say you know we want to see this protocol again after x number of subjects have completed, you know, x activity. So maybe after five subjects have undergone their second visit or their fifth visit, whatever is the case, the IRB can come up with criteria that they want to be met before they see the protocol back. As long as that occurs before one year that's fine. So, when you're writing this in the letter, you want to make it clear that, you know, that if it's before five subjects have completed x assessment it's either that incident is met, or one year. You want to make sure that you don't go beyond the one year so just be sure that your letters are written correctly. The second part of this requirement talks about the IRB needing to have policies and procedures for determining which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB reviews. Similar thing, when I looked at some citations, University of Washington and Howard both were cited for this and what's interesting is the Howard University citation, which was an OHRP determination letter dating back to 2015 was not limited to just them not having this in their SOPs because actually their SOPs did reference the fact that they would do this verification. What did they say, they would conduct this verification from sources other than the investigator and no material changes have occurred but they didn't state what factors they would be using to identify which projects fall in this category so what types of projects would the IRB look at and determine, you know, need verification from outside sources. Similar things that we talked about when we looked at the frequency of review maybe, you know, studies that the IRB is unfamiliar with the design that might require verification from other sources, anything complex. Studies conducted by researchers who've previously been cited for failing to adhere to the regulations so you want to, again, make sure your SOPs state that you'll be doing this. State the factors that you'll be using to determine which protocols would meet the criteria. Talk about what types of verification you could do. It could be things like requesting DMC minutes. It could be things like requesting an audit from the RCOs. Additional things, you know, the IRB could actually say we want to interview subjects right, directly who've done this study because this is a new design, we're not familiar with it. We want to make sure maybe the subjects understand the difference between clinical care and research and so we want to interview them after they've, you know, been involved in the study. Those are the types of things you want to kind of think through, incorporate in your SOPs, and then bring them out when you're reviewing the protocol so that, you know, if you have a protocol or study that would fall into, that you use these options, right? You've written them in your SOPs but that you also utilize them. Last thing I just want to say in terms of how often continuing review must be conducted, as long as the study is open and a study has to be open if identifiable information

is being analyzed, or obtained, then continuing review must occur and so, you have to continue to conduct continuing review as long as you're dealing with human subjects research. So, identifiable information being analyzed, obtained, that would be considered human subjects research.

So the IRB is asked to conduct substantive and meaningful continuing review. We're going to talk, spend a nice chunk of time on that. What does that look like? First and foremost, the IRB has to be able to ensure that all approval criteria continue to be met. In order to be able to approve a study for continuation, the same approval criteria that they review during the initial approval as well as any additional requirements, let's say for vulnerable populations; if it's pregnant women, prisoners, children, all of those requirements have to continue to be met in order for the IRB to approve continuation of the study. So, they have to be able to say all the approval criteria continue to be met. But really what they're focused on, during continuing review, is assessing risks, trying to make sure that any newly identified risks are factored in or communicated to subjects if necessary, protocol is, hold on, I'm seeing some feedback, okay, thank you. The protocol, if it needs to be revised to incorporate that, it's done. So they're going to be looking at whether risks continue to be minimized, whether the risks to subjects are reasonable in relation to the anticipated benefits, and whether the safeguards in place at the time of the original approval are, in fact, adequate to ensure the safety of subjects. If additional risks have been identified or are identified, do the study procedures need to be revised to reduce the risk? Do we need to amend, let's say, inclusion/exclusion criteria, is that something that needs to be changed? For informed consent, are they going to be looking at the informed consent form? Are they going to be asking for the most current updated informed consent form. Are they going to be looking to see is it, one are you using the right informed consent form right, it's a great time to check in and make sure. Is the informed consent accurate and complete given any new information that has come to light. They're going to be looking to make sure the informed consent form, HIPPA and protocol are consistent. If there have been changes to the protocol, particularly when it comes to risks and information that the subjects would be interested in and would be key for them to, you know, to use in determining if they are going to participate in the research, has that information been incorporated into the informed consent form. Are there any significant new findings that may affect the subjects willingness to participate, then be sure, make sure that those are provided to subjects and figure out a best way to do that. Whether that involves, you know, releasing a letter, or whether they feel it's so important that it rises to the level of getting a subject to re-sign a consent form. That's not always required, but these are all the types of things that the IRB is taking into account during continuing review. And, so, in order for them to conduct this substantive and meaningful continuing review, they need to obtain the information from the investigator and, there's a long list of things that they need to obtain. I think I've covered this in four or five slides. I know the current version of handbook 1200.05 does not have the laundry list of what's required but ORD has a guidance document on the website that outlines the types of things that need to be submitted. OHRP has a guidance document on continuing review that also covers the types of things that need to be submitted by the investigator and, so like I said, there's a lot of information. I'm not going to go through each one because that would take too long but I've kind of put a checkmark next to the ones that I'm going to talk

about a little bit more just to give you a flavor of why that information is important and what are some of the things that the IRB would look for when they're analyzing that information.

So, one of the things is number of subjects accrued and withdrawn, including the reason for those that have withdrawn during the past review period and since inception. The IRB is going to use this information to determine if accrual is progressing as planned. If it's not, what can be changed? Can anything be changed? They might ask questions as to why accrual is significantly lagging. If it does continue to significantly lag over the course of the study, they're going to be concerned as to whether it's, you know, ethical to continue to enroll subjects in the study that might not be powered enough to answer the question at hand, the question being investigated.

Summary of complaints, I put a check mark next to that, that's huge. The IRB wants to understand and know if there've been complaints, what are the nature of the complaints? Are these complaints related to something to do with the research, the risk of the research, are the claims maybe related to the investigator or research staff and, therefore, maybe something that lends itself to them needing to be re-educated to ensure subject safety?

We already talked about the current informed consent form, the HIPPA form, information that may impact on the risk benefit ratio, such as SAEs and complaints, these are all things that we're going to be looking at to make sure that risk to subjects continue to be minimized and that, if there's any new information that is pertinent, that they need to make sure it gets in the hands of the subjects, that they're able to do so via some type of notification, the consent form, those types of things.

Summaries, recommendations, minutes from the Data Monitoring Committee. All those types of things kind of help the IRB get a bigger picture as to what's going on in the study, particularly, from multi-center studies, right? The local IRB really only sees what's going on at their facilities and if accrual is lagging at their facility, they really might not get a good sense of what's going on globally, what other sites have experienced. The Data Monitoring Committee is in a much better position to be able to better identify trends, be able to identify uptakes in certain unanticipated events and things because they see, kind of, take a birds eye view and see what's going on globally from all the sites participating and, therefore, any recommendations and minutes from the Data Monitoring Committee is very useful to the IRB in helping them make sure that if there's anything that they need to make sure is revised, or information conveyed to research subjects at their site, that they're able to obtain that information and proceed accordingly.

Finally, research findings to date, relevant multi-center trial reports, any new scientific findings in the literature. I don't know if many of your applications still do this but, back in the day, I know that we used to ask for a literature search and that used to be something that, you know, the research coordinator would just quickly do and, you know, print out a list of relevant publications that met the key word and, you know, that's really not that helpful. Essentially what they're looking for is, is there any new information out there either that would directly affect the study or maybe even in the class of drugs, if it's a drug study. You know, an IRB

member may come across some useful information just during their own, you know, clinical duties using a similar drug as what's being used in the study and may bring that information back and say, you know, we've been noticing x incidents with this class of drugs. I know that, you know, we have two studies using the drug from that same class, you know, let's ask for some more information. Maybe we need to talk to the pharmacy and see what other information is out there and make sure that, you know, we're adequately protecting our subjects and, if there's any additional risks that were unreported, or that we were previously unaware of that we get that information included in the protocol and possibly in the consent form. So that's what's really driving, you know, those requests for research findings to date and new scientific findings in the literature.

Alright, so similar to initial approval, continuing review can be conducted either by the convened IRB or via expedited review and, then, what we're going to do here is we're going to kind of talk about first convened IRB review, how that's done when it comes to continuing review and then we're going to shift focus and talk about expedited review when it comes to continuing review.

And, so, in terms of what needs to be reviewed by whom? When you're conducting continuing review by the Convened Board, OHRP recommends that, at a minimum, all IRB members should receive a copy of the protocol summary and the report, normally this is the continuing review application and that describe the progress of the research and includes all the information that we just went over a couple of slides back and that, at least, one voting member of the IRB receives a copy of the complete protocol, including any modifications previously approved by the IRB and that individual will really be charged with leading the discussion. It's important, though, that all IRB members have access to the complete IRB protocol file and relevant minutes and so normally this is done by ensuring that this information is on a SharePoint site or, if you have a nice fancy database that, you know, everybody has access to the database anyway and, so, it's just to make sure that the information is accessible to everybody, all the members of the IRB.

When it comes to determinations that can be made during continuing review of the Convened Board, they have the same determinations that can be made during initial approval; which is, that they can approve the study for continuation. They can approve the study with minor modifications, and we will talk a little bit about that. They can require substantive conditions and conditions whereby then they can no longer make or substantiate that the approval criteria have been met and so they would need to defer approval. They can also, I guess, disapprove continuation of the study. I must say, I personally haven't seen that but that doesn't mean it can't be done. Don't ask me how because I haven't necessarily seen that but they would have that ability to do that.

When it comes to expedited review. When can you do continuing review by expedited review? Anytime you have a minimal risk study that was originally approved and qualified for expedited review categories 1 through 7, and nothing has changed that would affect their eligibility for the categories 1 through 7, then those studies can also be reviewed by expedited review when

they come in. There are also two expedited review categories, 8 and 9, which we're going to be talking about at length today, that are designated really for continuing review. And so, for those studies that were not initially approved by expedited review, if they meet categories 8 or 9, then they could be reviewed by expedited review going forward and we're going to have a lecture, or training on expedited review next month, that's my plan, so stay tuned for that, that's when we'll cover more information on categories 1 through 7 and actually the process of expedited review even though we will touch on it here.

Ultimately, the expedited reviewer is responsible for making the determination that the study remains minimal risk and is eligible for categories 1 through 7 or 8 or 9. That doesn't mean, though, that when the protocol first comes in, the administrative office staff, they can do their initial assessment and they can flag it for expedited review. But, ultimately, its' the expedited reviewer who makes the final determination.

In terms of who can perform continuing review by expedited review, it's very similar to who can perform, actually it's the same, as to who can perform expedited review of initial protocols, and that is the IRB chair or an experienced IRB voting member whose designated by the chair, or, yeah I guess that's it. The expedited reviewer should receive and review all the documentation and the complete protocol because, you know, unless they defer to the convened board, they're the ones responsible for ensuring that the protocol can be continued and granting that approval.

Alright, what determinations can be made by the expedited reviewer when doing the continuing review? They can approve the study for continuation. They can approve the study with modifications, in which case they're going to be working back and forth with the investigator to identify any issues prior to them being able to issue an approval, or they can defer the continuing review to the convened board. Again, this is why it's important really to make sure you give yourself enough time between sending out your notices, getting the continuing review materials in, because, even though a study may have originally been eligible for expedited review, things can change. Or that expedited reviewer can just, you know, decide that he's identified something, he or she, has identified something and really feels in order to be able to approve the study, they want some feedback from the convened board. And so you want to make sure you allow enough time that should that continuing review need to go to the convened board, that you have time to do so without the approval expiring.

Alright, so, we're going to be talking a little bit about approval periods and dates but, before we do that, I think it's important to kind of talk about the types of things that you really need to make sure you consider and specify in your SOPs. One, your SOPs does need to make it very clear how your IRB determines the effective date of initial approval, and we're going to be talking about that a little more in depth. Your IRB needs to make clear how you calculate your continuing review. So, for example, if it's a one year approval that's been granted, do you calculate it from October 1st, 2017 to October 1st, 2018? That's the way I do it because I like to keep things simple but, you know, I know a lot of people calculate it from October 1st, 2017 to September 30th, 2018. There's no right or wrong way when it comes to these two options but

you need to make sure that your SOPs specify how you're doing it and, honestly, including an example is probably the best approach to take to make it very clear. Your SOPs need to specify whether your IRB will maintain the anniversary date of approval using the 30 day rule. We're going to talk about that as well. And then, finally, you want to make sure you specify how your IRB will communicate the date and period of approval to the investigator.

So let's talk about dates, and we have some examples and case studies to go over. I'm going to first talk about initial approval dates for continuing review, renewal dates, all of these types of things. We're going to talk about convened boards first and then we're going to talk about expedited reviews. Expedited reviews is a lot straight forward, more straight forward. So, for convened board, if the convened IRB issues a straight approval and, let me pause here, I'm talking first about the initial approval of the protocol. I need to talk about that first so we can talk about establishing the first continuing review date. So, if the convened IRB issues a straight approval of the initial approved protocol, they've already worked out all the particulars back and forth outside of committee before it comes to the meeting, everything goes swimmingly and they have no changes, they issue an approval. Well then the effective date of the initial approval of that study is the date the IRB meets. That's pretty straight forward. In that case then, the first continuing review must occur latest one year after the date of the IRB meeting, one year after the effective date of the initial approval which, in this case, was the date of the IRB meeting. No changes are required. Very straight forward. As an example, if the convened IRB issues a straight approval on April 16, 2018, then the first continuing review must occur latest April 16, 2019. If the IRB wants a more frequent continuing review, no problem, they would specify it, but it cannot, continuing review could not occur later than August 16, 2019, one year post the approval - April, sorry, thank you Lucinda, not August, April.

Alright, so, next scenario. Our convened IRB reviews a protocol for initial review and the convened IRB issues approval with minor modifications. Essentially the convened IRBs says, you know, we need some changes, but all the information and if the exact changes we specify are made, than all the approval criteria will have been met and we can approve this study. So, in cases where the convened IRB issues approval with minor modifications, then the effective date of the initial approval, the date when you would release that letter to the investigator right, saying your protocol is approved, will be the date that the modifications have been verified, or confirmed. So, if the convened IRB says we need to approve with minor mods, then the date of the initial approval will be the date that those modifications have been confirmed, or verified. That's the date you would release the letter. The first continuing review now must occur latest the date that those modifications have been verified or confirmed. That's the latest possible date that that first continuing review can occur, and I know this may differ than how we did things years ago back under the old 1200.05, but the new 1200.05 in order to kind of bring us more in line with kind of how everybody else does things, removed some of the restrictions that we had back in 2010 which was the earlier version and, so, we have more flexibility now. So let me tell you what that means. Let's give an example. If the convened IRB issues approval with minor mods on April 16th, 2018 and they designate someone, an IRB member or someone else, it's up to IRB, this is not expedited review. This is verification. Many times people use those words interchangeably. They are not. The IRB approves the protocol.

They require minor modifications and then they designate someone to verify that those changes have made. That individual that they designate to do that verification should have the correct qualifications and experience for whatever those changes are, okay? So, in our example, the IRB has designated an IRB member to do the verification. The investigator submits the revisions on April 30th and the IRB member reviews it that same day. The protocol at that point, they've assessed that everything, all the required modifications have been made. The initial letter of approval can be released. The first continuing review then must occur, at the latest, April 30th, 2019. One year from the date that that letter was released. Now, I know some of you, I don't know if the questions have already started coming in on that topic, but, you know, it is okay. There is no problem if the IRB says that we're going to make our continuing review date based on the date that the convened IRB issued the approval with minor mods. That's not a problem so long as you specify what you're going to do in your SOPs. And that's why I started with, it's very important that your SOPs specify how you are going to make these determinations when it comes to setting the initial effective date of the initial approval and the dates of your continuing review. This applies to the initial continuing review. And the reason that there is this flexibility is because, as many of you know, sometimes it can take months for the investigator to respond and address those modifications. Sometimes it can take three, four months to get that in and so, rather than issuing the approval letter three to four months later and then have the continuing review be shortened by those three to four months, so than it's a what, eight or nine month approval period, you have the option of setting the first continuing review date as one year post the date when that letter was released, which is essentially the effective date of initial approval. That's an option. That doesn't mean that's what you have to do. Your SOPs will dictate what you have to do, so you specify in your SOPs what you have to do. So, let's go with a little case study to kind of really hone in on that point.

So our first case study here deals with continuing review expiration dates for the convened board. We have a protocol that undergoes its initial review by the convened IRB on April 10th, 2018. The IRB approves it with minor mods for a one year period and designates an IRB member to verify that the changes have been made. On April 20th, our investigator submits a response addressing the mods, which are reviewed and deemed satisfactory by the reviewer on April 24th, 2018. Our question is, what is the latest date the continuing review must occur by? And, Heidi, if you can pull up that poll for Case Study 1 that would be awesome. Perfect. Thank you Heidi. Our options are April 10th, 2019 which is one year from the date that the IRB approved the study. The second option is April 20th, 2019 which is one year from the date that the investigator submitted a response addressing the modifications. The third option is April 24th which is one year after the reviewer has determined that the modifications were satisfactory. Fourth option is either A or C, April 10th or April 24th, and the fifth option is none of the above.

Heidi: And responses are coming in. Again, we'll give everyone just a few more moments to respond and then we'll go through the results here. It looks like we've slowed down so I'm going to close that out and what we're seeing is 10% of the audience is saying April 10th, 2019. 10% of the audience saying April 20th, 2019, 49% of the audience saying April 24th, 2019. 27% saying either A or C, and 4% saying none of the above. Thank you everyone.

Soundia: Thank you. This is great. And, so, the answer that we're going to go with and talk about is D, either A or C so those who said A are correct. Those who said C are correct. Really it's either A or C because it depends on what your SOP states and that's why it's very important that the SOPs specify how you are going to establish that initial date of continuing review and that will determine what is required. I think one or two people said April 20th and why is that wrong? That's the date that the investigator submitted the response but, remember, the designated reviewer has to verify that the changes have been made. And, so, I know that we are going kind of fast through these cases and you don't have the screen up so no worries there. When you get your handout you'll have the full case study with the cases presented and the answers, but this is a great, great, great discussion here.

So, now let's talk about after the initial approval, and this is probably more similar to what people are familiar with. So once you've established the first continuing review, any subsequent continuing reviews have to occur within a year of the last continuing review and so, in this case, for any renewals after the initial approval by the convened IRB, we're still talking about convened IRB, if the convened IRB issues approval, or approval with minor mods, at a meeting, than the renewal date is set as the date of the meeting at which either of these two determinations is made. Not the date that the conditions are verified. That's really limited to the initial approval to give one flexibility to be able to not eat into the continuing review period, essentially, because it may take months for the investigator to respond. So, after the initial date of approval, after the first continuing review, all subsequent approvals have to occur latest one year from the date of that meeting where approval, or approval with minor mods, is determined. And there's a caveat, which is the 30 day rule, which we will talk about in a second. If the convened IRB, during that continuing review, defers the approval, well then, it has to go back to the board to be approved. And so the next renewal date, the continuing review renewal date, would be the date at the meeting, whenever that meeting occurs by which the IRB approves continuation of the study either straight approval or approval with minor mods.

So, the 30 day rule is basically there to allow the investigator, and the IRB, to maintain an anniversary date. You know, as we talked about, the thought is it's easier for investigators and the IRB to be able to know that every year this protocol expires on this date and so in order to maintain that anniversary date, the rules allow for continuing review to occur up to 30 days before the IRB approval period expires. If continuing review occurs up to 30 days before the IRB approval expires, the IRB can retain the anniversary date as the date by which the next continuing review must occur. However, in order to use the 30 day rule, you have to include that in your SOPs if that's what your IRB does or follows, if applicable. So, for an example, if the convened IRB approval is granted on May 1st, 2017, the IRB is able to conduct its next review, in time, between April 1st and May 1st, 2018 and still reapprove the research for another one year period expiring on May 1st, 2019. It's essentially allowing you to maintain that anniversary date to make it easier for everybody.

Let's talk about expedited review. Much more straight forward when it comes to calculations of dates and all of that stuff. Mainly because you have an expedited reviewer, one reviewer,

whose doing the review and so, essentially, the date the expedited reviewer either approves the study, approves continuation of the study, initial or otherwise, or approves the study with modifications and, let me stop, sorry. So the date the expedited reviewer approves the initial study, that then is the date of the effective approval, and the continuing review approval date is set as the date that the expedited reviewer completes their review and issues the approval letter. The next continuing review will be, at most, one year later. If the expedited reviewer approves the initial study with modifications, well then, those modifications have to be addressed in order for the approval to stand and that would be the date by which the next continuing review would occur, if it's a one year approval. If the expedited reviewer defers review to the convened IRB, then we're going to follow the convened IRB requirement. I hope that made sense but we'll talk about it a little bit more.

This slide probably is a little redundant but, essentially, it's just saying that renewal dates, any subsequent continuing review dates, also must occur no later than one year after the last approval, with the caveat being the 30 day rule. So, if the last approval was granted on January 15th, 2018, then continuing review approval must occur at latest January 15th, 2019. Expedited review is a lot more straight forward when it comes to all these calculations and dates.

We'll do another quick case study, though, to kind of hone in on that point. In this example we have a protocol that's expiring on January 15th, 2018 that's submitted for continuing review. The study continues to qualify for expedited review. On December 10th, 2017, the expedited reviewer reviews the study and requests a number of clarifications from the investigator. The investigator submits the requested information on December 29th, 2017. The expedited reviewer confirms that all issues have been addressed and the study is approved for another one year period. Our question is, the next expiration date for the study should be? I'm going to ask Heidi to pull up the poll and I'm sorry that we can't keep the case up for those who maybe don't have the slides, but the next expiration date, the options are: 1) December 10th, 2018, which is one year after the expedited reviewer reviewed the study but requested clarifications from the investigator. December 29th, 2018, which is one year after the expedited reviewer reviewed the information submitted by the investigator and confirmed that all modifications had been made. January 15th, 2019, which is one year after the protocol expired, the previous year, one year later than when the protocol originally expired. Either B or C, December 29th or January 15th, or none of the above.

Heidi: And responses are coming in. Again, we'll give everyone a few more moments to respond before we close the poll question out and go through the results. It looks like we've slowed down there so I'm going to close it out and what we're seeing is 4% of the audience saying December 10th, 2018; 20% of the audience saying December 29th 2018; 17% of the audience saying January 15th, 2019; 57% of the audience saying either B or C and 3% none of the above. Thank you every one.

Soundia: Thank you Heidi. This is great. The majority of people said the correct answer which is D, either B or C. And, again, and I want to reiterate and I hope through these examples what we're trying to get you to make sure is that your SOPs state which approach you're going to

follow. B was December 29th, 2018 which is one year after the investigator submitted the requested information and the reviewer confirmed that everything had been correctly made and C was January 15th, 2019, which is one year after the protocol expired. If your SOP specified that you used the 30 day rule and you want to maintain the anniversary date of January 15 than it would be C. So, SOPs really dictate what the expiration date should be and that's what you're going to be held to when auditors, or whoever comes and checks your records, to determine if you've let approval lapse or not. So, SOPs, SOPs, SOPs.

Alright, expedited review categories 8 and 9.

Expedited review category 8 is for continuing review of research that previously was not eligible for expedited review but because it meets one of three sets of criteria, it can now be reviewed by expedited review when it comes into the office. So category 8 can be used for research which is closed to the enrollment of new subjects and all subjects have completed all research related interventions. Now, recall, interventions include both physical procedures by which you gather data as well as manipulations of the subject or the subject's environment. So all subjects have completed all research related interventions and the only remaining research related activity is the long term follow up of subjects. And in OHRP's Continuing Review Guidance, they consider long term follow up to include minimal risk interactions, interactions not interventions, such as surveys as well as collection of follow up data from procedures where interventions that are being done as part of routine clinical care, so essentially like record review, you're looking in the medical records. So, if the continuing review comes in and it meets these three criteria, all three apply, then it can be sent to the expediting reviewer for continuing review by expedited review. Also, category 8 can be used for studies where no subjects have been enrolled at your local facility and when we say no subjects have been enrolled, we mean no subjects have ever been enrolled, not just during the past review period, but ever. So no subjects have ever been enrolled and no additional risks have been identified by the investigator or any other facilities where subjects have been enrolled. Now, remember, that's one of the information that's collected on the continuing review application form, you know, has there been any new information that's relevant to the research? And, so, if both those criteria apply, than the study can be reviewed by expedited review category 8 during continuing review. Then, oh, keep in mind that if we're talking about new risks being identified, you really want to look at whether there is any information, both at your facility or any other facilities where the research is being conducted, and that's where our data monitoring committee reports are helpful. And, then, finally, category 8 can be used in cases where the only remaining research activity is the analysis of identifiable data. Remember, we said, if identifiable data is still being analyzed, then the study has to stay open and continuing review has to occur, at least according to our current regulations. Continuing review has to still occur. And, so, in all of these cases when your continuing review comes in, your research office staff can take a look at it and identify whether it meets category 8. If they feel it does, they can send it on to an expedited reviewer and the expedited reviewer would have to confirm that category 8 does apply. If they do, continuing review can occur by expedited review.

Category 9 is sometimes seen as a little trickier, mainly because it requires that the IRB has previously documented a determination, or a determination in there, in the minutes of a previous IRB meeting. Let's talk about it a little bit. Expedited review by continuing review by category 9. I'm sorry, continuing review by expedited review, category 9, can be used if; 1) The research is not subject to an IND or an IDE. So that's straight forward. You look in the file, you know, you should know if it's a study under an IND or IDE. 2) If expedited review categories 2 through 8 do not apply. 3) If the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk. 4) That no additional risks have been identified by the investigator, or in the case of multi-site studies, by an institution engaged in the research since the last review. So, as we said, the first two things are straightforward. You know, has the research, is the research subject to an IND or IDE, if not, great. Do expedited review categories 2 through 8 apply? If they don't, we're looking good. The third one, has the IRB determined and documented at a convened meeting, that the research involves no greater than minimal risk. That, you have to look in the meeting minutes for and its important then, really, that your meeting minutes have this information. Sometimes that information is going to be more in the protocol file, right? Or the reviewer may have made that determination, yes, the study is minimal risk, but we're going to have it reviewed by the convened IRB for x reason. So, you really want to get in the habit of making sure that that type of information is included in the IRB minutes because, if it is, when that study comes into the office, the administrative staff can just take a look at the past meeting minutes and if they see that the IRB has determined that the study is minimal risk and that information is in the minutes, you're good. And then, provided that no additional risks have been identified, that continuing review can be sent to the expedited reviewer and they can conduct continuing review as long as they don't feel otherwise. So, you really want to get in the practice of making sure if you're not including that type of information in your meeting minutes, you should as it makes it easier for everybody going forward as you're trying to determine if category 9 could apply or not after the fact.

So, we have a case study. We have two case studies. Our last two case studies are both on continuing review by expedited review. And this particular case, we have a research study evaluating cytokine levels in subjects diagnosed with rheumatoid arthritis. We have 50 subjects that are going to be enrolled per year, over the next five years. They're going to have 20 ml of blood collected from them four times per week for six weeks. We are told that the research study is not conducted under an IND or an IDE and the meeting minutes from the initial approval note that the study was deemed no greater than minimal risk. We are also told that no additional risks have been identified during the approval period. So, Heidi, if you can bring up our case. Great. Awesome. So our options are, our question is at continuing review, the study is eligible for review by A) the convened IRB, B) expedited review category 2, expedited review category 2 is our category that deals with collection of blood samples, C) expedited review category 8, which we just discussed or, D) expedited review category 9.

Heidi: And, again, responses are coming in. We'll give everyone a few more moments to respond before we close the poll and go through the results. And it looks like we have slowed down here, so I am going to close it out and what we're seeing is 23% of the audience saying

the convened IRB, 27% saying expedited review category 2, 16% saying expedited review category 8, and 34% saying expedited review category 9. Thank you everyone.

Soundia: Thank you. So, the correct answer, the answer we were looking for, because there were a few correct answers, we are going to talk about that. The answer we were looking for, let's use that terminology, is D, expedited review category 9. For those of you who selected convened IRB. You are correct. A study is always eligible for review by convened IRB. So, you're correct. For those who said expedited review category 2 which deals with blood samples. That doesn't apply in this case because of the frequency of the blood draws. Expedited review category 2 is limited to two times per week, whereas, in this particular case, we were collecting blood four times a week. And I put that in, not to be sly or anything, but really just as a plug for our upcoming presentation on expedited review because that's where we're going to really kind of get into those particulars so I didn't expect anyone to get, to really get, you know, remember the nuances. Heck, I always have to look at my list of expedited review categories. But that's just kind of a plug for our upcoming training. Yeah. Some of you put expedited review category 9, category 8, I'm sorry. And for those who put expedited review category 8, remember interventions are still ongoing, right? We're collecting blood and those types of things, so category 8 would not apply.

Our last case study is about a research study that's evaluating the effects of urban pollution on pulmonary status in healthy adults. Subjects will undergo monthly surveys regarding exercise and pulmonary symptoms and a single chest x-ray five years after enrollment. Now, the study was initially reviewed by the convened IRB and the meeting minutes indicate that the study involves no greater than minimal risk. So Heidi, if you can pull up our poll. Alright, so our options are, our question rather is, at the time of the continuing review, the study is eligible for review by A) the convened IRB, so we already know that's right so please don't choose that, B) expedited review category 4. Category 4 is our category that deals with the collection of data through noninvasive procedures. Expedited review category 8, which we've talked about. Expedited review category 9, which we've talked about, or additional information is needed.

Heidi: And responses are coming in. Again, we'll give everyone a few more moments to respond before we close the poll out and go through the results. And it looks like we've slowed down here so I'm going to close this out and what we're seeing is 5% of the audience saying the convened IRB, 19% of the audience saying expedited review category 4, 8% of the audience saying expedited review category 8, 8% of the audience saying expedited review category 9, and 61% of the audience saying additional information is needed. Thank you everyone.

Soundia: Excellent. Thank you Heidi. And, so, majority of you gave us the answer we're looking for, which is E, additional information is needed. Specifically, we were not told whether the study was conducted under an IND or an IDE and nor were we told whether any additional risks had been identified since the last review. So that's why additional information is needed to determine if we are eligible for expedited review category 9 or not. Expedited review category 4 is collection of data through noninvasive procedures but it actually excludes x-rays, so because we threw that x-ray in, expedited review category 4 right off the bat would not

apply. And, then, lastly I think a few of you chose expedited review category 8. Remember expedited review category 8 requires that no interventions, research related interventions, cannot be ongoing for any of the categories 8s, A, B, or C, and so, yeah, at the site at least. So that would not apply. Alright, we're almost in the home stretch.

We're going to talk very briefly, very briefly, about lapses in IRB approval and then get to what everyone's really be waiting for, which is the revised Common Rule. So, I'm going to kind of race through this a little bit but the slides have all the information you need. Okay, just want to reiterate that there is no provision for any grace period to extend the conduct of research beyond the expiration date of IRB approval. Okay? There's also no provision to grant approval for greater than one year, so, if approval expires than approval expires. Everything has to stop. The local research office must promptly notify the investigator that approval has expired and the investigator is required to stop all research activities, and that includes enrolling new subjects, continuing research interventions or interactions with currently enrolled subjects, as well as data analysis. Everything has to stop. In turn, the investigator needs to submit to the IRB a list of research subjects who could be harmed by stopping study procedures and then the IRB chair, in consultation with the Chief of Staff, will determine if any of the subjects on that list can continue participating in research interventions or interactions. I just want to mention again that a lapse in approval is not a study suspension. Neither ORO or OHRP consider it a study suspension. It's a lapse in approval. The approval expired and continuing review had not been conducted and so it would not require prompt reporting so that's something to keep in mind. However, if the IRB notices a pattern, let's say of lapses from a particular investigator who never gets her continuing review materials in, well then they may want to cite that investigator for serious or continuing noncompliance. And if that determination was made, then, you know, one would follow the reporting requirements for those reportable events, but a lapse is not looked at as a study suspension.

Once study approval has expired, IRB re-review and re-approval must occur before the study can resume. The IRB can't just say, okay, now we retrospectively grant approval to cover the period that the protocol was lapsed. The approval was lapsed. In terms of what has to be re-reviewed, however, what has to be resubmitted in order for the IRB to conduct this re-review, that is really going to be based on your SOPs. Your local policies will dictate what procedures you'll follow to restart a study after a lapse in IRB approval. There is nothing wrong with looking at and using and reviewing the same continuing review materials that were submitted, you know, just because the study lapsed doesn't mean that that information is necessarily, you know, no longer relevant. But, again, your SOPs have to specify, you know, how long after expiration you will allow the IRB to perform continuing review using the same continuing review materials that were already submitted vs. requiring them to submit new information or updated information. So that's really something, again, we want to make sure that your SOPs take that into consideration and you think through what you will require.

Alright, continuing review and the revised Common Rule. Now this is what the majority of you are waiting for, so thanks for hanging in there with me, I appreciate it. Before we talk about this, let me just address a few things because I know everyone knows that recently we had a

notice of proposed rulemaking that was published on, I think last week, April 20th which is soliciting comments to delay the effective date of the revised Common Rule by another six months. Right now, we are in a current delay and so right now we would have to initiate the revised Common Rule procedures and requirements by July 19th, 2018. So, what this, now this does is delay it by an additional six months, which would put us at January 21st, 2019. Essentially delaying the effective date of the revised Common Rule for one full year from when it was first supposed to be initiated, which was January 21st of this year. And so comments are due in May, on May 21st and so, until those comments are in and reviewed, we don't know which way things are going to go. With the notice, there were three, what did they call it, burden reducing provisions were proposed. The adoption of three burden reducing provisions were proposed. Again, whether those will be adopted or not remains to be seen. We'll see what the comments come in at and what's decided about those three burden reducing provisions. If I recall correctly, one of them has to do with the definition of research and there have been some changes to the definition of research in the new Common Rule. I'll be honest, I'm not as familiar with it but my understanding is, the new definition would make certain activities no longer research and, therefore, no longer subject to review by the IRB and, therefore, that's, you know, that would reduce the burden to the investigator and IRB.

The second one has to do with continuing review. Which we are going to talk about. The notice proposes allowing institutions to implement some of the revisions to the continuing review requirements during the six month period of delay.

And then, finally, the third burden reducing measure has to do with, I believe, it's the IRB reviewing grants, removing that requirement and allowing investigators to implement that change early, within these six months.

In terms of what will be decided, again, we don't know. I will say this, though, that if those three burden reducing provisions go into effect, it is still up to each institution to determine whether they want to adopt those or not. So, just because they go into effect, VA policy will still have to let us know which way we're going to go, whether we're going to allow the adoption of those burden reducing provisions, or not. I think that is all that I have to say, oh, except for the fact that we are working under the assumption that we will have another six month delay and that we won't have to implement the revised Common Rule until January 21st, 2019. We firmly believe that. That's the assumption that we're working towards and, as we know more information, we'll definitely make sure you're aware.

So, let's talk a little bit about what's changed, or rather, what's not changed. Yeah. So, continuing review under the revised Common Rule. What has stayed the same? Well, IRBs still have to follow written procedures for conducting initial and continuing review of research and reporting their findings and actions to the investigator and institution. No change there. What also has stayed the same, is that the IRBs must continue to determine which projects require review more often than annually and which projects need verification from sources other than the investigators though no material changes have occurred since the previous review. So we talked at length about that earlier on in this training in the session and, so, please make sure to

go back and revise your SOPs if you haven't been clear about that because that's an issue that, one of the few issues that seem to come up on ORHP side visits when it comes to continuing review. Well that, and just not conducting continuing review in time.

Alright, what has changed? Well, the regulations say that IRBs shall conduct continuing review of research requiring review by the convened IRB at intervals appropriate to the degree of risk but not less than once per year, so there's no change there, except in the following cases and they outline three cases whereby continuing review would no longer continue by the IRB. So, 1) research that is eligible for expedited review; research that has progressed to certain points, and I will talk about that; and research reviewed by the IRB in accordance with limited IRB review provisions, and I'm going to talk about that. That applies to certain research that is eligible for exempt review. Okay? So those are three categories of research that, going forward, once the revised Common Rule is implemented, will no longer required continuing review by the IRB. If an IRB chooses to conduct continuing review of research that meets those criteria or falls into those categories, the IRB is required to document the rational for conducting continuing review of this research that no longer requires continuing review. I think in some of the previous versions of the NPRMs, proposals that were circulated years ago, one of the things they were thinking of, or proposing, is while they eliminated the continuing review requirements for these categories of research, maybe requiring some type of annual check in whereby investigators had to submit something to let the IRBs know the status of the research. That requirement did not make it in to the revised Common Rule so there is no requirement for an update to the IRB in the revised Common Rule. That does not mean VA policy may not come up with something though that requires some type of update. I don't know what it's going to look like but, you know, once we have the new handbook out and published, we'll be able to do some training on that.

But let's talk a little bit about what these categories of research are that will no longer require continuing review. The first being expedited review. That's straight forward. So research that initially qualified for expedited review would no longer require continuing review. It didn't say explicitly that research that has progressed to the point of only involving activities that qualify for expedited review would no longer require continuing review but normally that's the way we interpret things and that's the way we've kind of treated things in the past. So, research that initially qualified for expedited review, would no longer require continuing review. Research that has progressed to the point that it only involves one or both of the following; data analysis, inclusive of analysis of identifiable private information or identifiable specimens and/or access to follow up clinical data obtained from procedures that subjects undergo as part of clinical care. It sounds a lot to me like we're looking at, you know, some of the criteria for category 8, continuing review, right? So, research that has progressed to that point, where it's only data analysis including if its identifiable information which is not the case now, but if it's analysis of identifiable information or specimens, or just accessing follow up clinical data, one would no longer require continuing review by the IRB.

The next and last category is research reviewed by the IRB using, what's called, limited IRB review, which is a new term in the revised Common Rule. So limited IRB review really applies to

four specific categories of exempt research. In limited IRB review, the IRB does not have to ensure that all of the 111 approval criteria are met. Instead, they conduct a review but they're focused on certain specific aspects. Mainly, the IRB review is limited to 1) Determining that adequate provisions to protect the privacy of subjects and maintain the confidentiality of their data exists and/or they're looking specifically at whether broad consent is appropriately obtained and documented. A waiver of documentation is appropriate. So, we're going to talk a little bit about this. I know some of you may be wondering, well, why would they, if limited IRB review really only applies to four categories of exempt research, why would they need to specify that these categories no longer require continuing review, because exempt research, you know, by its nature, right, does not require IRB oversight and, thus, does not require continuing review by the IRB. What's unique here are that these four categories, were only, are only allowed to be deemed exempt because the IRB conducts this limited IRB review. There's eight categories of exempt research in the new revised Common Rule. Four of these categories are only the exemption, or sub-categories, but there are four instances where research is allowed to be deemed exempt if a limited IRB review is conducted and the IRB is able to assure that these one or two things that we just talked about are met.

So, let's talk a little bit about that and this presentation is not on exempt but I have to touch on it a little bit for the purpose of illustrating this point, but we will be conducting training on exempt research and limited IRB in the future.

So, the first category of research that would require limited IRB review, and thus be exempt from continuing review, is research involving educational tests, surveys, interviews, or observation of public behavior if the information is obtained or recorded such that the identity of human subjects can be readily ascertained and the IRB conducts a limited IRB review to ensure that adequate provisions exist to protect the privacy of subjects and maintain the confidentiality of their data. So, in this case, this is actually very similar to the previous exempt category 2 where we dealt with surveys and interviews and such, only difference is that back then, that information really could not be identifiable where, as now, they've allowed it to be identifiable but they said, hey, the IRB conducts this limited IRB review where they assess the proposal and ensure that there are adequate provisions to protect the privacy of subject and maintain the confidentiality of their data. So, if the research meets that criteria, it would not require continuing review.

The next category is research involving benign behavioral interventions and that's a new term. But, benign behavioral interventions, when identifiable information, here we go again, identifiable information is collected from an adult through verbal, written, or audiovisual recordings and the subject prospectively agrees to both the intervention and data collection and the IRB conducts a limited IRB review to ensure that adequate provisions exist to protect the privacy of subject and maintain the confidentiality of their data. So, in this case, benign interventions, and the regulations give examples, are such things as observing a subject play games online, do online games, or solve a puzzle, things like that, or complete simple tasks that the IRB, that the investigator asked them to do. So, those are two examples.

The next two examples of when exempt research requiring limited IRB review would not require a continuing review, deals with secondary storage or maintenance of identifiable specimens or information for secondary research or the use of identifiable private information or specimens for secondary research. So, the first one on the slide here, is the storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research if the IRB conducts a limited IRB review and determines that broad consent is appropriately documented, obtained and documented, or waiver of documentation is appropriate and adequate provisions exist to protect the privacy of subjects and the confidentiality of their data.

The second one involves, as I mentioned, the use of specimens that have been collected or secondary use of specimens that have been collected for research. So research involving the use of identifiable private information or identifiable biospecimens for secondary research if one broad consent was appropriately obtained, documented, or documentation is waived if appropriate, the IRB conducts a limited IRB review and determines that adequate provisions exist to protect the privacy of subjects and maintain the confidentiality of their data and the research to be conducted is within the scope of the broad consent, and lastly, there are no plans to return individual research results to subjects. So, those are the four cases whereby continuing review would not be required even though the IRB did conduct a review, this limited IRB review.

Again, we're going to have a whole lecture on exempt research and exempt criteria and determinations and categories, as well as what the Revised Common Rule looks like when it comes to exemptions. So, this brings us to the end of our very long presentation. Thank you for hanging in with me. The majority of you did stick around, at least based on the numbers that we're seeing in the attendance list. We do have some time for questions because we're going til 3:45. Here's a list of references for you to have. I do want to say, well here's my contact information. Feel free to contact me, if you have questions. This training, as is the case with all of our trainings, once the recording is available sometime next week it'll be posted on the PRIDE website under Cyberseminars. Before Heidi goes into questions, I'm going to leave this on the screen and just want to talk a little bit about what we have planned for the future. So ORD and ORO have been in discussions on kind of how best to ensure that the field is educated on the revised Common Rule and we want to make sure that we use all of our resources effectively and, so, we've come up with a list of tentative topics and a tentative schedule to cover various topics in the revised common rule. And some of these trainings will be led by ORD and some of the trainings will be led by ORO. So, here's the schedule. This will be distributed online, I would say sometime next week. We just confirmed the dates yesterday afternoon so we're all really excited and our plan is, you'll see, those who are maybe looking at the dates, you know, I've slated from about October on where it's a lot of trainings on the revised VHA Handbook 1200.05 because out thoughts and hope is that we will have a new revised handbook by then in time to launch the new revised Common Rule in January, third week of January or so, in 2019.

So, with that said, Heidi, if we have any questions, we're ready to take them.

Heidi: It looks like we do have a few pending questions here. The first one, I took a note because I thought you might need some context with this one. This one came in around slide 25 and the question would be ACOS/R acknowledgement letter be?

Soundia: Okay, one second, let me go to slide 25. Slide 25. Alright, so we're talking about different approval dates, maybe we were talking about the approval date for the initial approval and the question was, what date would the ACOS for research acknowledgement letter be?

Heidi: Yeah.

Soundia: I really am not sure. I would think. I don't know if that would change based on when the IRB has reviewed the research and approved the research. I'm sorry I don't know the answer to that question. I know that the IRB reviews it and then the study would need to go to the R&D committee for review and then at some point, after that, the ACOS for research would sign off on it. That's at least my understanding. So, I'm not quite sure one date has anything to do with the other except for the fact that the investigator can't start the research until both the IRB and R&D have approved the research study.

Heidi: Okay, they sent in a couple of other follow ups here. You guys have to bear with me because I'm not a subject matter expert and you guys send in acronyms I have no idea what you're talking about so please be really nice when you're sending questions in, but this was for CR and the 30 day rule.

Soundia: Okay for CR and 30 day rule, remember the 30 day rule is really there to allow the IRB to be able to maintain the anniversary date because the thought is that, you know, everybody functions, things function more effectively if everyone knows that on x date the approval is going to recur, or that's when the renewal period is, so I see what you're saying. So, if the IRB reviews the study three days before, let's just say, the expiration and the institution uses the 30 day rule, they would set the next approval, right, they would say approval expires, they would maintain the anniversary date so that would be when the approval expires. What date would the ACOS acknowledgement letter be? Again, I'm not sure I know the answer to that. I do know that the IRB made the decision three days before so that's legitimate. They made that decision. I do know that the continuing review expires on the anniversary date. In this case, what the rule is saying is you will not be penalized for going over a year, in a sense, from the date the IRB made the decision if you're following the 30 day rule and, therefore, you're reviewing the continuing review up to 30 days before. So I hope that helps. The date that the IRB makes the decision is the date that the IRB makes the decision. The date that the approval expires is the date that the IRB specifies that approval expires and you have documentation that you use the 30 day rule in your SOPs so if anybody comes later on, any auditors, you point to the fact that we used the 30 day rule. The date that the IRB reviewed it was three days before the expiration so it was within the 30 day window.

Heidi: Okay. Great. Thank you. The next question I have here. Can a continuing review be expedited under category 8(b) if a risk determination of greater than minimal risk was made at initial review and no additional risks have been identified and no subjects have been enrolled to date?

Soundia: Okay. Yes. I believe that answer's yes because, remember, the whole point of continuing review by category 8 is for research that was not eligible for expedited review to begin with, and one of the reasons sometimes research that was not expedited initially was because it was greater than minimal risk. However, so the categories a, b, and c, if you're dealing with no subjects have been enrolled to date, so no subjects have yet to be enrolled, then as of this date and time, category 8 (b) would apply. The research has not been conducted, so, while the overall category is, it is greater than minimal risk, no risks have been encountered, right, because no subjects have been enrolled to date and no additional risks have been identified so, to me, yes, this clearly fits in with 8 (b), continuing review of research where no subjects have been enrolled to date and no additional risks have been identified. Now, the minute you enroll a subject though, the following year, than that study would no longer be eligible for continuing review of research under 8 (b), unless category 9 applies and you just told me that initially the IRB deemed it greater than minimal risk so likelihood is category 9 would not apply. I hope that helps.

Heidi: Great. Thank you. Okay the next question I have here. Does a convened committee need to make a determination that a study is eligible for continuing review under category 9.

Soundia: Great question. According to the guidance document, OHRP's guidance document, and its included in the reference for anybody who wants to go and really read up on that because it's important to make sure that you understand the specifics. No, they do not need to say that category 9 specifically applies. What needs to be documented is that the study involves no greater than minimal risk, or at least that the current state of affairs in the study has progressed to the point than it is no greater than minimal risk.

Heidi: Great. Thank you. The next question here. Where is the date of the CR, or studies that are approved with contingencies or minor modifications discussed in a handbook? We always use the date of convened review for calculating the date of next CR, not the later date the modifications were approved.

Soundia: Yep, yep, yep. It's no longer in the handbook and that's one of the things that I referenced earlier. So the previous, I think it it's 2010 handbook, was very specific and very restrictive in terms of what was allowed and what was not allowed. In 2014, with the revision of the handbook, the thought was that VA ORD wanted to align ourselves more with the Common Rule and take out a lot of VA-isms, VA specific requirements, VA specific restrictions and, so, in the handbook, in VHA handbook 1200.05 right now, really all it states is continuing review must occur annually. The next place you go is our Guidance Document on Continuing Review which outlines, you know, a number of good things that you need to know to help you

conduct continuing review to help guide you in terms of what's submitted. But, no, it does not go into date calculations. Again, it leaves it open. The third place I would suggest you go, is the OHRP Guidance Document, the 2010 Guidance Document, and that outlines examples of how to calculate this. So, essentially, by removing the restrictions from the handbook, provided that your SOPS clearly outline how you plan to proceed, you're able to use and proceed with more flexibility and there's guidance documents from OHRP to support this approach. I hope that helps.

Heidi: Great. Thank you. And that actually is all of the questions that we have in right now.

Soundia: Awesome. We are at 3:32. I want to thank everybody for participating, for sticking with me through this long presentation. I hope it was helpful. Before people sign off, hold on, because some of you guys are dropping like flies already. There is a survey that always pops up when you close out and I haven't been good about asking people to please take a moment and fill it out because we do read the comments and it helps us to improve the presentations. If I need to talk slower, if I need to, I don't know, whatever you think I need to do, but I do take it into consideration and try to adjust future presentations based on the feedback. We also ask for any topics that you would like to see in the future. This list of proposed, this tentative schedule, is really going to be focused more on issues related to the revised Common Rule. I do have a topic on working with the VA Central IRB because that's something near and dear to my heart being here within PRIDE and something that we've been wanting to do. This list is not exhaustive though. That does not mean that we won't try to get some additional ORD trainings in, so to the extent there are things you would like to see. There are definitely things that I would like to train on, and, our hope is I can still get a few additional topics in, but what we needed to do was make sure we could come up with a plan for addressing issues pertinent to the revised Common Rule and let, you the field know that hey, we're working on it, we have some things planned, and this is what we propose. So please fill out the survey, give us some feedback, we appreciate it, and we need it.

Thank you and thank you Heidi for everything, thank you Lucinda. I hope you all found this presentation helpful. Have a great evening.

Heidi: Thank you everyone for joining us. We'll be sending out information on the next session as soon as we have that available.

[END OF AUDIO]