Cyberseminar Transcript

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Session: ORPPE Workshop: Continuing Review Tools

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Soundia Duche: Good afternoon everyone and thank you so much for joining us for, I believe this is our third workshop. We're going to be focusing on continuing review tools as Petrice mentioned. I'll be leading the presentation but of course can't do this alone and so I'm pleased to be joined by Dr. Molly Klote, our director of the Office of Research Protection Policy and Education. Dr. Karen Jeans is here with me and then we have Dr. Kristina Borror also who's the director of Policy and Education, yes in ORO. Sorry, Kristina. And so they'll chime in whenever they have something they want to add.

So again as Petrice mentioned, since this is a workshop we're going to be limiting questions to the topic which is continuing review tools, but feel free to ask questions about continuing review. Because we only have an hour, our workshops are highly targeted and we're trying to be more hands on in our workshops. And so we're going to be providing you tools. Eventually we're going to be working through an issue together as part of our workshop series, but because we have a short amount of time we unfortunately can't take questions off topic. So you can submit them, but you won't hear them be asked and addressed on today's call.

So for today's session we are going to, I'm going to give a brief review of continuing review requirements. This is not going to be everything about continuing review. I would have you all hear for two hours and you know I can do that [chuckling]. We conducted a continuing review webinar, a long and deep dive into continuing review back in April of 2018. I’ve put up a link to that recording. That session went over all of the nuts and bolts of continuing review. It had case studies. We talked about expedited review and continuing review. We talked about setting approval dates. We talked about expiration dates and lapses. We went into detail about substantive and meaningful continuing review. So all of that information you can find, I will warn you it's about an hour and twenty minute lecture component and then we had some great questions on that recording, during that presentation that had been picked up on the recording. But today we're really just going to briefly go over continuing review requirements and it's important to kind of set the stage because when we go over the tools it's important for folks to know how these requirements are featured in the tools that we'll be discussing. So after we do our brief review of continuing review requirements, we'll talk also about research that does not require continuing review. As we all know we're now under the new common rule, the revised common rule, and the 2018 requirements have some exceptions for continuing review, so we'll talk about that. And then we'll go into the forms which were sent out earlier this morning to everyone and I'll be able to link to them from here. But as Petrice mentioned if you didn't get it we'll be sure to get those out to you. And then we'll touch briefly on study closures.

So why does the IRB conduct continuing review? And really it's because they have to. Both the common rule and the FDA regulations require continuing review. Now, under the revised common rule, the new 2018 requirements, not all research requires continuing review. But prior to January 21st, all non-exempt human subjects research did require continuing review and all non-exempt human subjects research that's subject to the pre-2018 requirements will continue to require continuing review. And so we do it because we have to. FDA regulations require continuing review for all FDA-regulated research. But that doesn't really fully capture the spirit and the importance of continuing review because while we have to do it, we need to do it. Continuing review is really one of the most important aspects and responsibilities of the IRB and oftentimes it gets pushed to the side. People just see it as another form they have to complete. But unlike the initial review which gets all the attention because you can't start your study right, until you get your approval, you probably won't get your funding if you're funded until you have your approval from the IRB and the R&D committee. Continuing review however is one of the things that finally, now that the study has started, the IRB has gone ahead and spent a lot of time making sure that the study will protect participants as best as possible based on the plan, now the study is actually ongoing. And so continuing review is the process that allows the IRB to really now do their continuing assessment to make sure that what was planned is what actually is occurring. And not necessarily because of investigator negligence or misconduct, but just because as you're conducting the research, things that were not expected occur. You might have increased risk in a certain category that you didn't anticipate. And so, when the IRB conducts continuing review, they are able to look at all of the information, everything that occurred during that review period. They're going to be looking at some of the information that you've already submitted already. Your reportable events - they're going to be really looking to see if there are trends in reportable events in a particular aspect. They're going to be briefly looking again at the amendments. If there are anything that we've missed that we may need to tweak. And so it's a monitoring mechanism that the IRB uses to help best protect subjects that have now enrolled and are participating in the research.

In terms of how often must continuing review be conducted, and remember this is for research that requires continuing review because now we're operating under two sets of regulations. But if continuing review is required, well then, in terms of how often it has to be conducted, it has to be conducted at intervals appropriate to the degree of risk, but not less than once per year. And that pertains to both the pre-2018 requirements and the 2018 requirements. There's no difference. If continuing review is required well then you have to conduct it a minimum once a year.

Now, in terms of the intervals, I just want to touch briefly on it. Many times by default the IRB is going with the one-year approval period and nine times out of ten that's probably appropriate. But, you want to remember that the IRB is charged with really assessing the study and anticipated risk and therefore determining what is an appropriate interval for conducting review. When do they need to bring that study back? And sometimes that will be, I'm sorry give us one second. Sometimes that will be based on the timing, right? But sometimes that will be based on an event occurring. And so for example, the IRB may say, you know this study [unintelligible]

So continuing. So we were talking about the intervals. And really what I just wanted to drive home is that the intervals are based on the risk assessment. And it could be based on a certain amount of passage of time, six months, three months, maximum one year. Or it could be based on an event occurring. After X number of subjects are enrolled or after, whatever it is, it could be based on the IRB wanting to come back and see the study because there's something [unintelligible 07:35] novel about this and we want to make sure before we get too far into they study want to reassess early and so you need to bring the study back.

Now, what happens if the approval expires? What happens if the IRB sets the approval date and that could be, like I said, it could be at the six-month mark, it could be at the year mark. Let's go with the six month. The IRB sets the approval period. The continuing review has to occur within six months of the study being approved and that day comes and approval, continuing review hasn't occurred. Approval expired. And what that means is that the investigator has to stop all research activities, including but not limited to, interactions with the subjects, enrollment of new subjects and data analysis. Now of course there's a caveat in that if stopping the study would end up being more of a, result in danger or harm to certain subjects, well then there's a process by which the investigator is required to quickly alert the IRB and the chair in particular, with respect to which subjects may be harmed by stopping the study. But the key thing to remember is that if the IRB sets the continuing review date and says that approval expires on X date, if that continuing review, studies that require continuing review, if continuing review has not occurred then the approval lapses. And the regulations do not allow any prolongation of the approval period. Nor do they allow continuation of the research past the approval period. And so even if the IRB sets the approval expiration at six months and you say but oh, we have up until a year. Well no, they set it at six months. That continuing review has to be conducted during the timeframe that the IRB has set, because presumably they've set it because there's some criteria and risk assessment that makes them feel they want to see it back.

Dr. Karen Jeans: Hi. This is Karen. I wanted to interject here because in the prior VHA Handbook 1200.05, we had a policy requirement that the IRB chair, in consultation with the chief of staff, determined if the subjects on the list may continue participating in the research interventions or interactions. Now, what I want to emphasize here is that just because we removed that requirement does not mean that the chair has to make that decision solely on his or herself's own decision. I mean many of these issues involving participating in research interventions when this occurs, involves clinical interventions. And so the chair is more than willing and able to reach out to whoever is needed to consult. So that was an issue that had been raised to us, was it solely the chair's responsibility. It does not mean the chair has to do this in isolation. So we want to reinforce that.

Soundia Duche: Thank you. Great point, Karen. And so when conducting continuing review for research that requires continuing review, well that continuing review, that process, remember I said it's one of the most important things that the IRB does, so we want to make sure that the IRB review is substantive and meaningful. It's not sufficient to just receive the information and not really review it and then sign off on another one year approval. No, the IRB has to review the information in order to make an assessment. And in terms of what information they receive, some of that information will be information they've already had as they've been monitoring the study. They've been approving amendments. They've been getting reportable events. They have the current up-to-date approved consent form. Some of that information is going to be information that they're going to have to request from the investigator because they don't have the information. The key is that the IRB needs to conduct a substantive and meaningful continuing review. And what that means is one, they need to make sure that all the approval criteria continue to be met, the IRB approval criteria. But in making those determinations, they're probably going to be more focused on risk because that's that new piece of information. Now they have that information because the study is ongoing. And so now they need to see okay, is there anything based on the information we've received as the study is ongoing that we feel increases the risk to subjects or is there anything that we need to maybe re-evaluate, re-assess study procedures, inclusion exclusion criteria, are they still appropriate? Is there any new information that subjects would want to know that might influence their decision to participate in the research? Those are the types of things that the IRB is going to be taking into consideration when performing this substantive and meaningful review.

Now this slide just shows the type of information that the IRB would rely on. And again as I mentioned, some of this information they already have. The common rule nor VHA Directive 1200.05, neither of them specify or stipulate what documents are required. But the information has to be available to the IRB to perform this substantive and meaningful review. And so the continuing review guidance document, this is the one that dates back to 2014. It's still on the website because it is still valid. I linked to it I think at the end of the presentation there's a link to it. But this, it provides a list of information that the IRB would customarily want to review while conducting continuing review. Now, we did receive a question prior to the training where someone asked hey, we talked to our colleagues at other offices and not everybody has the same list of continuing review requirements. Not everybody says you have to have all 16 things or 15 things on their applications. Is that okay? Because we have certain things, but they seem to not require that the investigator submit all of the information. So I asked Karen if she could just chat a little bit about that.

Dr. Karen Jeans: Yeah, so this is Karen. And so, I think where I am coming from on this, and the site that asked this question, it's really relevant because it reflects the changing times. The question that the site asked about was submitting copies of the last approved stamped IRB consent form. The copy of the protocol that had been most recently approved by the IRB, oral scripts, information sheets. If we're dealing with impaired decision making. You know, there was an [unintelligible 14:16] document involved. And so, when you think about this, and this goes back to our guidance back in 2014 and even OHRP’s continuing review guidance, it was written at a time when we don't have electronic platforms. Many of us rely right now, on different types of electronic platforms. So it gets to the issue of, if I'm using for example an electronic platform, what is the usefulness of me pulling out of my electronic file, that by the way is the IRB file, that document, and resubmitting it to the IRB? And so the issue is always, and it goes back to something that Soundia just said, you have to have the materials needed in order to do an evaluation to determine whether or not the criteria are met. And so in the absence of a policy requirement that says you have to submit these documents, my issue as I'm thinking out loud on this, is what is indeed the usefulness of having that information sent back to the IRB? Does it really serve a purpose? Are there other ways to have a check with the investigator that this is the informed consent form you're approved to be using? And I'm thinking of VA right now. We have an incredible system, unlike any other system in the entire country, where we have informed consent audits that are done yearly with 100% source documents. So we always know, in terms of the job of our incredible RCOs, what version of the informed consent is being used because otherwise it can be kept as compliance audits. So when that kind of mechanism is in place to prevent exactly what this is talking about, the question is, and I'm going to use Dr. Klote's phrase, what is the value added? And so, because that really is what it's doing. I think we all have to re-evaluate why are we doing what we're doing? Is it just because it's just old practice or not? So I would argue with you, and I would love to hear Dr. Borror comment on this as well because it's such a great question, because there's no right or wrong on this. But again, it's a thoughtful process of when do you really need to do this, especially in the context of how we monitor and survey this issue in VA, whether or not that really is something that the IRB has to have as part of continuing review application materials for submission. And I'll kick this off to Dr. Borror.

Dr. Kristina Borror: I agree completely with you Dr. Jeans and note that if there have been no changes to the materials that were provided to the IRB for the previous review, you know perhaps it would be acceptable to just note that and then the materials that they already have in their records, particularly if these are electronic, those could be materials to look at. So I think that in a lot of cases that's going to be the case, the things that will change would be the number of subjects accrued and so forth. So yeah, I agree completely.

Soundia Duche: Thanks Kristina. And so now I want to touch briefly on research that does not require a continuing review. So exempt research, and this is continuing review by the IRB. Exempt research is research that is not overseen by the IRB because it's exempt from IRB oversight and meeting the common rule requirements for approval. And so exempt research does not, has never had to undergo continuing review by the IRB. So no changes there. As I mentioned, we are now subject to the 2018 requirements for any research that is approved on or after January 21st by the IRB. But we also have research studies, don't forget, that are under the pre-2018 requirements. For those studies that are subject to the 2018 requirements, the 2018 requirements specify categories of research that do not require continuing review. One of them is research that is eligible for expedited review. So any new research study that is eligible for expedited review and is approved by the IRB on or after January 21st does not require a continuing review. Also, research that is subject to the 2018 requirements that has progressed to the point that it only involves one or both of the following. And that is data analysis, and that can include analysis of identifiable information and identifiable biospecimens and or research that is at the point where it only involves access to follow-up clinical data obtained from procedures that subjects undergo as part of clinical care. Essentially, the research related interventions and interactions are done, subjects are only undergoing regular clinical care and maybe were accessing that information to be able to perform additional, get some additional insight into how the subject is faring now that the research interventions are done. So under those two circumstances, if a study that is subject to the 2018 requirements, was approved let's say by convened board review and initially underwent continuing review, and it progresses to one of these points, well then it no longer requires continuing review.

And this is critical because in the 2018 requirements it states that if an IRB decides to conduct continuing review on a research activity that does not require continuing review as we just went over, well then the IRB has to justify that and they have to document their rationale for why they seek to conduct continuing review. And there are going to be many instances, and very legitimate instances where the IRB will say no, we feel in our opinion, based on review of the study, based on the particular research intervention proposed, based on the investigator and their qualifications or their experience conducting studies, based on a myriad of information that the IRB has at their hand, that this project should undergo continuing review. And so they would justify it. Similarly, they may say, based on our expertise at our institution, maybe we're not comfortable with certain types of activities or using certain, a particular intervention or drug because it's new to us and so any study that fits this particular category, we feel it needs continuing review. There can be lots of different types of justifications. Some of them may be a policy thing and so that justification might be found in the SOP. The key thing is though that the IRB has to document the rationale somewhere of why they want to conduct continuing review. And remember, and this is important, as studies progress you're going to have to continuously reassess to say has the study progressed to the point that it no longer requires continuing review. And if we decide to conduct continuing review on it, we have to justify it. So you're tracking now, continuously, has my study moved into one of the categories that no longer requires continuing review? The other thing, to make life just a little interesting, some of you eventually will begin transitioning studies. And so you're going to transition studies. And so during the transition you're going to determine okay, does it meet one of the criteria that no longer requires continuing review up front and if you decide you still wanted to conduct continuing review, you'd have to justify it. As that transition study progresses in the same way as any new study, you’re going to have to continuously assess at every continuing review, has it progressed to the point where it doesn't, or even if you're still going to require a continuing review, you have to justify why. And so that's just something to continue to remember.

In terms of when should an IRB assess whether a study requires continuing review. Initially, at the initial review and approval. That's normally where the IRB states the approval is for X time period and approval will expire on X date. And so at that point, if the IRB says that this study needs to undergo continuing review and it falls into one of the categories that does not require continuing review because it's subject to the 2018 requirements, you would need to justify it then. That would be in the meeting minutes if it let's say goes to a convened board or it could be in the reviewer forms. Essentially just some documentation in the study file. And the study file does include the meeting minutes because the meeting minutes do reference that study. So it doesn't have to be one [unintelligible 22:54], but you have to be able to point to that justification somewhere for that study. Or you point to you SOP saying that no this was a policy decision for all studies that fall into this category and this is such a study. And then as I mentioned already at continuing review you want to reassess. And you may decide initially you wanted this to undergo continuing review and now we're comfortable and so it no longer requires continuing review. So when you finish that continuing review, when you say the approval period is for another 12 months, you would say nope, it doesn't require it anymore because it has met our requirements. It never required continuing review to begin with and so you would have that information in your protocol file, probably in your reviewer form or something. I have some examples we're going to talk about right now actually.

I have a Continuing Review Application Form here, this is actually the VA Central IRB's application. I'm not going to go into it too much. We wanted to be able to give you something to look at. Just to show you how the information, they've chosen to capture the information for a meaningful and substantive review. Let's see here. And what's interesting is whether this study is subject to the pre-2018 requirements or the 2018 requirements in terms of collecting the information, there's really no difference. If a study requires continuing review, well then it's going to be assessed similarly. One of the key things though, and I like this section three here, the current project status. This is really important piece that you probably want to make sure you incorporate something like this in your application because this is where you can easily see what stage the research is at and therefore this can help answer a question, you know, has it progressed to one of the categories of research that no longer requires continuing review if you're dealing with a study that's subject to the 2018 requirements. I'm not going to go into this form any more than that. But you have it in your arsenal.

The Continuing Review Reviewer Form. Now this is one of the forms that's in the documents for the mini moon shoot and so we made some tweaks to it as we thought through. Because a lot of times, this is all about thinking through the logic. So the IRB receives the continuing review application form that I just showed you. Now that reviewer has their reviewer checklist and they need to use it to say and to conduct right, this meaningful continuing review. So they're going to see in section one, the principle investigator’s general information about the study. They're going to see, you know ask questions about participant enrollment, any recruitment issues, any DSMB reports applicable. Informed consent and HIPAA authorization issues they're asking for. Any additional information submitted by the PI that might again influence the information and the [unintelligible 25:52] need additional information that subjects should be aware of. And again, this is the VA Central IRB application, so you would need to tweak it and we have a corresponding application in the documents for the mini moon shoot, we're going to be making a few tweaks to it and publish those. This section seven is what I just want to draw your attention to but hopefully I didn't go too far.

So research subject to the 2018 requirements. So the IRB required continuing review because the study either required it or the IRB felt that they wanted to do it. So, the continuing review comes in in the application, the reviewer has to conduct the continuing review. They conduct it. Now they get to the crossroads where they have to determine for the next year, does this research still require continuing review. So the first question that's asked is, is the research study subject to the 2018 requirements? If it's not, if it's subject to the pre-2018 requirements, there's no assessment, no decision, you conduct continuing review because you have to. Pre-2018 studies have to undergo continuing review. But if the study is subject to the 2018 requirements because it was approved initially on or after January 21st or it was transitioned at some point, well then you do have to assess, remember we talked about that, was the study eligible for expedited review when it was initially approved? Has it progressed to one of these two phases? Data analysis or progressed to the point of only obtaining follow-up clinical data. And in red you see in brackets continuing review is not required for all of these things. So now that you've conducted your first continuing review for the study, you've decided, you've checked here that the study is subject to the 2018 requirements and continuing review is not required because it meets one of these boxes here, well then now the IRB reviewer, or if it's a convened board, has to determine if they want the study to undergo continuing review again. If the answer is yes for the subsequent year, they have to include a justification. And so in this particular case they would include it on this form.

There is a question at the end here because some sites may decide that hey, at the continuing review application or review period, that's when they want to do a little quick look at the protocol and see hey, would the study be eligible for transition. And so we just put this question here, does the IRB reviewer recommend assessing the study for transition to the 2018 requirements because that's something that some people might do at continuing review. And if yes, then it directs the reviewer to a transition form.

In terms of the reviewer recommendation, they've completed the continuing review. If continuing review is required for the next year, they would state the frequency. They would state if it's approved, if it has to go to the convened board. If for the next year no continuing review is required, they would check none and proceed there. So again, this is just an example and it might show you some useful things to include in your form.

Because some studies now, under the 2018 requirements do not require continuing review, how is the IRB going to track their research? Some IRBs may decide that they want to continue to get some type of status updates from investigators, just so they keep track of essentially their book of business, their research portfolio so that they don't have a whole bunch of studies that remain open just because a researcher is not required to submit continuing review. And remember, just because you're not submitting continuing review doesn't mean you still don't have to report your reportable events and your amendments and those types of things. But, if the site decides to require some type of status update, we want to just stress that status update is not continuing review. That continuing review IRB approval criteria do not have to be met, so you don't have to create a form that mimics the continuing review form is really what we're trying to get at. You can make it as short or long as you feel needs, just get the key information that you need to just get a sense of what's going on with the study. And again, because this is not continuing review, if the investigator or the study team does not submit it, if it's submitted and you guys don't look at it because you only look at it every six months or only look at it every year or you only receive it every year, right? There's no cycle that this update has to be on. It's really up to you if you decide to do an update. Well, nothing expires. Approval does not expire so you really want to make sure people understand that.

Okay, here's an example of a status report update form. It's very short. This is one of the documents that's again on the mini moon shoot and is currently being posted to our website. I don't know what happened, but anyway it's available to you all. Really don't want to say much about it except that it's short and that they get the key information.

Dr. Karen Jeans: And this is Karen. I just want to say, we are still getting the documents up. It takes a long time because they have to be 508 compliant. So they are in the process of going up. They have been sent, so I'll be checking in this afternoon on that.

Soundia Duche: Okay, excellent. Thanks Karen. All right, and then just wrapping up. Just want to briefly touch on study closures because this was just the perfect place to do that. There's no regulatory requirement. The requirements, FDA regulations and the common rule are silent on closing human research studies. That doesn't mean you should not do it though and that it's not required. If the study as approved by the IRB is completed, then it should be closed. So how do you determine if closing a study is appropriate? If all your research-related interventions and interactions are completed. If you're done analyzing identifiable information. If you're only looking at deidentified information. You have to be careful with that. It really has to be completely deidentified, the data. You want to say something Karen?

Dr. Karen Jeans: This is Karen. I think it's also the perfect point to talk about this because she's talked about study closure in relation to the Institutional Review Board. But a lot of times, especially here in VA, we get this last point she just talked about is really relevant. When an activity no longer involves analysis of identifiable data as described in the IRB-approved protocol, you know, the study is over if that's all that was left and the study can be closed. But let's say they want to continue analysis of deidentified data. And the question we receive a lot here in ORD is can the study be closed with the IRB but be open with the Research and Development committee? And I always ask the question well, how are you doing that? And the answer is usually well it only involves deidentified information. But that's why Soundia made a very key point that I don't want to get lost here, is it has to be truly deidentified. And so if the investigator has access to the identity of the subjects, it's not deidentified. So that's a key issue to remember when it's stated that what's really deidentified information as long as the investigator has access to the key, it's identifiable.

Soundia Duche: And coded information is not deidentified information if the individuals, the investigator has access to the code, okay? So something to keep in mind.

All right. So we are ready for any questions.

Unidentified speaker: Okay, thanks Soundia. No final remarks?

Dr. Karen Jeans: So I do want to, I think because of the question that was asked earlier about the list of documents and I was referencing, we were referencing ORD's guidance of 2014. We do expect to have released next week, the continuing review guidance which is updated not only to revise our position on studies that require continuing review, but also those that continuing review is no longer required. And so that will be coming next week. So I do want to reinforce that and let everybody know that it's coming imminently. So that's really it and I thought that was a really great presentation Soundia.

Unidentified speaker: So let's get to the questions.

Dr. Petrice Longenecker: All right, thank you. This is Petrice. So as a local policy can the IRB and/or the ACOS for research decide to continue to conduct continuing review on all studies and include that in the IRB SOPs? If so, would justification still need to be addressed at each subsequent continuing review?

Unidentified speaker: So as a policy, this is Dr. Klote. Yeah this is a toughy because as a policy, the policy is that you don't conduct continuing review on studies that don't require continuing review. And that is the common rule, rule right? And it's really, the requirement is that it's on a protocol-by-protocol basis that that decision gets made if in fact you do decide to inflict continuing review on a study that otherwise would not require it. And the reasons for that should be pretty specific to that specific protocol. And the whole point of this is to decrease burden on the IRB so that they can focus on the things that are really important and free up their time away from things that aren't as risky to the institution. So, I would never recommend to an institution to just want to even blanket this. My feeling would be that if you're trying to put out a blanket statement like this, do you not fully understand why we're trying to get away from continuing review on every study anyway.

Dr. Karen Jeans: And for example, this is Karen just to add on. There may be certain categories of studies that if those studies meet those criteria as a justification for example, let's go for any investigator that had the determination of serious non-compliance in the last year. And I'm just throwing examples out of cases. Any study that involves a phase one study, even though it goes into that phase where it would be eligible, and actually the default would be it will have no continuing review conducted unless there's justification. There's different examples. But to unilaterally apply a blanket that we're not going to apply the regulation and we're going to justify it because of what? Yeah, so there has to be a true, there has to be a justification that there's a reason why you're doing it. You can do categories, but it can't just be we're not going to exercise this regulatory requirement.

Dr. Petrice Longenecker: Okay, next question. Regarding the continuing review checklist, are you saying an IRB member must determine whether a study is eligible to apply for transition, or is this something IRB staff can make?

Soundia Duche: If I gave you that impression, I wasn't really trying to speak to who makes the determination, but just that some institutions are using the continuing review, at the time of continuing review, as an opportunity to assess a study to determine if it's eligible for transition. And so in the reviewer checklist, since they were conducting the continuing review, it was included there. A, does the IRB reviewer feel that the study should be assessed, at which point it directs them to the transition checklist which I didn't include and it's not clear on who would complete that. It’s not necessarily the case that it's the IRB reviewer. Dr. Klote?

Dr. Molly Klote: Yeah, so to this point, I also just want to reiterate that the decision to transition a study while it can be, you could say hey, this could be eligible, it really needs to be negotiated with the investigator. The IRB does have the authority to just say hey, we're transitioning you, meet our requirements, but some studies that you want to transition are going to have impacts on the investigator and on their time and all sorts of things, so it really should be a negotiated process. Though as Soundia said, at the time, continuing review is sort of a natural time to take a look at a study or when the next amendment comes in or the next action that the IRB takes a look at, to look and see if this is a study that it would make sense and sort of would be easier on everybody if it got transitioned over.

Dr. Petrice Longenecker: Okay. Next question. Can the site have access to the continuing reviewers comments?

Soundia Duche: Yeah, the checklist. Because oftentimes the site or the investigator?

Dr. Karen Jeans: Yeah, I'm not understanding. What's the site mean?

Unidentified speaker: Yeah no, these aren't live so we can't.

Unidentified speaker: You're right, so yeah.

Unidentified speaker: Maybe they can submit a follow up?

Unidentified speaker: So if you're talking about like something sent into the Central IRB and a reviewer checks it, there should be comments sent back. The actual comments that the investigator writes, the checklist itself might not be sent back to you directly, but all the substantive comments that they make, because sometimes a reviewer will write things down that you look at it and you say oh, I know what they meant by that and you can answer those questions without having to bother the investigator or the institution with those questions. If you're talking about things that are coming into the Central IRB. But again, the question is kind of vague so I'm not sure.

Dr. Petrice Longenecker: Okay, I requested that she clarify if possible. For research that does not require continuing review could the IRB document almost any rationale for the need for continuing review? For example, study conducted by an investigator previously known for having findings of non-compliance? Study conducted by students? So two different examples.

Unidentified speakers: [Unintelligible 40:21-40:24].

Dr. Karen Jeans: Right, so they are reasonable rationale of course to require this. And the two examples that you give are fine requirements. Findings of non-compliance, study conducted by a student. All good stuff, things that may require more oversight. Now, study conducted by a student, maybe the IRB would put that oversight on the mentee of that student rather than on the IRB itself, but those certainly are things that you could document it as justification.

Unidentified speaker: Next question?

Dr. Petrice Longenecker: Is continuing review still required for exempt studies?

Unidentified speaker: Okay, so as Soundia mentioned earlier in her talk, continuing review has never, and is still not a requirement for exempt studies, by the IRB I should say. By the IRB. So when you look at what the R&DC committee requires, if the R&DC, under the new 1200.01, is the only committee that is reviewing that, there are no subcommittees. There's no IRB. There's no other committee at your institution that serves as the primary committee for that study, then the term continuing review is used which is not my favorite term for this. I would like to change it to continuing oversight or something. But, that there is a continuing oversight process called continuing review required by that committee since no other committee will look at it.

Dr. Petrice Longenecker: Okay. Expedited categories eight and nine. So expedited review categories eight and nine are specifically to conduct continuing review of research previously approved by the convened IRB or continuing review of research not conducted under an investigational new drug application or investigational device exemption. But the project no longer involves greater than minimal risk interventions or interactions, [unintelligible 42:38] data analysis or closed to enrollment etc. With the new common rule, continuing review is not required for any expedited review categories. These expedited review categories do not look consistent with the elimination of continuing review for expedited studies.

Unidentified speaker: And you're right. And it's not all of the categories. I think it's one of the eights and then the category nine. And OHRP is aware of this and largely the issue is because the expedited review list has not been revised yet, we have this conflict. OHRP recently released a draft guidance document that ORD and ORO are reviewing and plan to assess and come up with our take on it and then we're going to get to make our own call and provide guidance to our VA investigators on how to treat those categories. Dr. Borror.

Unidentified speaker: Yeah. Kristina do you want to say anything about this?

Dr. Kristina Borror: No. I just, I think that the plan is that the expedited review categories will be updated. It's just not going to happen tomorrow.

Unidentified speaker: So stay tuned. We are aware. So thank you. It was a great question and it's something we're aware of and we'll be digesting that information and talking between the two departments in the next few days.

Dr. Petrice Longenecker: Okay, so I have a follow-up on that question. Can the site have access to the CR comments and that is the PI or SC investigator have access to the continuing reviewers comments?

Unidentified speaker: Right. So this is [unintelligible 44:20] at the Central IRB. And so I think my prior answer still remains which is you get a summary of the reviewers comments that are addressed back to the site. And if the investigator is not receiving those comments, then certainly get in touch with your point of contact at the Central IRB office because the investigator should be getting reviewer comments.

Soundia Duche: Right, but the checklist themselves, and this is not unique to continuing review, it's amendments, it's everything. Checklists themselves typically, and this is not unique to VA Central IRB or VA, but checklists in general are not something that's shared with the investigator. As Dr. Klote mentioned, the actionable items that the investigator has to take, that summary, that's what's shared and that's the information that they have to move on.

Molly Klote: And to be honest, sometimes the reviewers comments, we have to take them and fix them and make them into reasonable questions that they you know, they'll write something on there that we then have to interpret and make into something that you can answer. Over.

Dr. Petrice Longenecker: Okay. Can you clarify what studies require continuing review by the R&D committee, and if so whether it needs to be done in full committee or not.

Karen Jeans: Okay, so under the new 1200.01 that was released yesterday, let me address the second part of your question first which is the new option under 1200.01 which is, what do we call it, designated review? Designated review. I keep thinking delegated review, but no it's called designated review. And it's a lot like sort of the expedited review process for the IRB where you only need one member of the committee to do it. If you look at 1200.01 it tells you what sort of items the R&D committee can apply designated review. It's pretty broad what they can do designated review for. So lots of things don't have to go to full committee. There still is a requirement for that designated reviewer to report everything that they do to the full committee. The designated reviewer can require changes to the study, approve, do all the things that the full committee could do.

And so then onto the first part of your question, what studies require continuing review? It would be anything where the R&D committee is the primary committee, meaning there's no other subcommittee that is doing continuing review on that. And that includes if you're using an external IRB, right? So if you've got an IRB outside of the VA that's reviewing your study, that means the R&D committee is not the primary committee reviewing that and therefore the continuing reviews and amendments would not need to come to that committee. But for things overseen by the R&DC committee, where they are the primary committee, amendments, continuing review, reportable events, those sort of things all go to that committee. Over.

Dr. Petrice Longenecker: Okay. Doesn't the R&D committee have to review studies before the study lapse date? This question is specific to studies that will be transitioned from expedited category five to exempt category four.

Unidentified speaker: I'm going to guess that this question, doesn't have to review studies before the\_. Wait. No, no I thought I read it wrong. Wait. [Unintelligible 48:06-48:08]. Okay, so there\_

Unidentified speaker: Before the study lapse date. So this question is specific to studies that will be transitioned from expedited category five, which is studies that have been approved under the pre-2018 requirements, and you want to move them to exempt category four. So I don't understand, does the R&D committee have to review studies before the study lapse date? I'm not\_

Unidentified speaker: I think there's a couple of things being mixed together here. So I think the first question we want is does R&D committee have to review studies before the study lapse date? The R&D committee is only conducting continuing review, like Dr. Klote just said, on studies that they oversee that are not overseen by any other committee, right? So if the IRB is overseeing a study, so they're overseeing an expedited category five under the pre-2018 requirements, that study is not going to go to the R&D committee for continuing review. That's totally managed by the IRB. Now\_

Unidentified speaker: Sorry. I think this questions is asking [unintelligible 49:12-49:13] transition to exempt.

Unidentified speaker: Right. Right.

Unidentified speaker: And it will go to [unintelligible 49:17].

Unidentified speaker: Right. And so when a study transitions from expedited category five to exempt category four, that study transition is interesting because that date of transition then kind of resets, in a sense maybe, the approval date for R&D committee continuing review.

Unidentified speaker: Because there was, because as an exempt study it would be totally reset and new, not that you have to go back and re-approve it, and in fact I think we mentioned this maybe at the last talk or something, is the idea that if it's already had, it's like if it's going to go to category four, well if it goes to category four it won't need limited IRB review at all. So under category four, it doesn't need any special reviews or anything like that so you can just take it to an exempt status, restart it whatever day you transition it and call that it's new birthday.

Unidentified speaker: But won't it already have an R&D committee date from the initial R&D approval?

Unidentified speaker: Yeah, but you could reset that because\_

Unidentified speaker: \_[unintelligible 50:24]. So I'm confused when it says it already has an R&D committee date. If the R&D committee for this study would have initially approved the study, just like it will now. And so, but there is no, it does not conduct continuing review. There is no, there never has been an ORD policy requirement in years for the R&D to conduct continuing review on studies in which there's an oversight of another committee. So I'm, there is [unintelligible 50:58-50:59].

Unidentified speaker: [Unintelligible 50:58-51:02] it won't be under the oversight of the IRB anymore.

Unidentified speaker: Right, correct.

Unidentified speaker: And at that point then the study will move to R&D oversight and you could use the transition date or you know, give it a new birth date, but the R&D committee will now assume oversight for continuing review of that study.

Unidentified speaker: That is a great question.

Unidentified speaker: [Unintelligible 51:24-51:25].

Unidentified speaker: It’s all about the nuances.

Unidentified speaker: It is. Absolutely. Yes. They really are.

Unidentified speaker: [Unintelligible 51:30] and that's why that was such a rich question.

Unidentified speaker: Okay.

Dr. Petrice Longenecker: How should annual COI, so conflict of interest, and training requirements be handled if a study meets the criteria for an expedited review and no further continuing reviews are required?

Unidentified speaker: You know what, we're going to have a separate session just on conflict of interest because this is a really deep question, and we've only got a couple of minutes left, and we can really get lost in this if we do this right now. And we get it, that you're dealing with this within continuing review. We will have a really solid answer for you in the next couple of weeks.

Unidentified speaker: But there is no annual ORD training requirement, so\_

Unidentified speaker: Well that's true. You can take that out.

Unidentified speaker: Right. Yeah.

Unidentified speaker: But we'll get that to you. Maybe we'll do a workshop on it.

Unidentified speaker: [Unintelligible 52:19-52:20].

Unidentified speaker: Yeah. I don't think they mean, maybe they don't mean annual training. I don't know.

Dr. Petrice Longenecker: Okay. I see the new directive 1200.01 states in section nine twice the R&D committee does not need to approve continuing reviews and amendments, but should be provided sufficient documentation in the committee minutes that are provided to the R&D committee. I do realize that local R&Ds can still mandate review of amendments and CRs since the directive does not prohibit it, but I wonder if we'll see any change in the future when it comes to local R&D continuing review following Central IRB or local IRB review. Do you foresee a change in local R&D continuing review? I'll make my screen a little smaller?

Unidentified speaker: So the R&D Committee does not need to review continuing reviews and amendments when it is not the primary committee. So when you read 1200.01, you've got to be very careful because there's really three sections in there. It's when the R&DC is the reviewing committee, then there's a section on when the R&DC, you know the relationship, when there's an external IRB and then there's a section where it says when the R&DC is not the primary committee reviewing. So just be careful of those three sections otherwise it can get confusing when you read 1200.01. Could a local R&D require continuing review? Theoretically. I mean local policy, you can always go super regulatory, but we would, I mean again, what is the value-add really? I think you'd have to look and say, what is that review doing for the institution because the R&D committee should be focused on the institutional requirements of that study. And so what are you gaining from an institutional perspective from all that, the administrative work that goes in to requiring these. And other than that, I don't know what else to say about that.

Dr. Petrice Longenecker: Okay. Maybe time for one more question. Let's say a study under the 2018 requirements for the new common rule is required to have continuing review so an approval period is set by the IRB. Then during that approval period the status of the study changes to data analysis only. Must the continuing review for that approval period still occur and then continuing review is no longer needed going forward, or is the continuing review for that approval period no longer needed at all since the status has changed?

Dr. Molly Klote: Okay, so this in my opinion, gets into the idea, like when people try to close a study like a month before their continuing review is due. But a lot happened in that eleven months and the IRB has a responsibility to know what happened. So you know, even if it's six months. If there was something that happened during that time, A, if it was serious it should have been reported anyway. But if there were adverse events and things that the IRB should be aware of, I have always been of the mind that anytime you transition something and it's not going to need continuing review, the IRB should take one last look at all the things that otherwise would have gone into that final continuing review. It's not specifically called out in the regulations. I think it's more of a best practice. So, really needs to be addressed in your SOP. My recommendation to you, and maybe we'll let Dr. Borror comment on this if you would Kristina, to just what you've seen as best practices across VA.

Dr. Kristina Borror: Thanks. Yeah, I agree. And note that the regulation says that continuing review is not required for research that's eligible for expedited review in accordance with 16.110. And so if it's eligible for expedited review, it sounds like this study would be at that point, even though it hadn't had sort of a final continuing review. But I agree with Dr. Klote completely that it would probably be a really good idea for the facility or the IRB to say we're going to do some final review because the study did change at this point and before we'd do away with continuing review completely.

Unidentified speaker: And the other thing, just to chime in, is normally it would be at continuing review that the IRB is informed of that, normally. That's not to say that a study team can't send them an email alerting them, but typically if a study required continuing review and the study team is completing the continuing review application, that's when they first alert the IRB that the study has progressed to the point where it only involves data analysis. That's what typically occurs and so it would be in that process of conducting the continuing review that the IRB becomes aware of that.

Soundia Duche: So I think that's it. I want to thank everybody for participating. If we did not get to your question, we will try to get to it offline or send us an email to the VHAC or ORD regulatory mailbox and we will respond to you. Thank you so much for attending and participating. Have a good evening everyone. Bye-bye.

[ END OF AUDIO ]