

Soundia Duche: Good morning everyone and welcome to the fourth training in our series of educational seminars addressing issues related to research in human subjects protection. My name is Soundia Duche and I will be your presenter today. I am a program analyst in PRIDE, the Program for Research, Integrity, Development and Education. Also in the room with me today are my two colleagues Lucinda Shouse and Theresa Straut who are also regulatory analysts in PRIDE. We are also joined today by Dr. Karen Jeans who is the Associate Regulatory Affairs Director in ORD.

Our focus today will be on continuing reviews and our training is really building on two of our previous trainings, Focus on Expedited Review which I presented in June and Focus on IRB Approval Criteria which Theresa presented in July. And so as Heidi mentioned I will be taking questions at the end of the training. If you have questions at any point during the training go ahead and submit them by using the Q&A functionality in the lower right hand side of the screen. We did receive a number of questions from the field in advance and so we have those questions and we are ready to answer them. What we plan on doing is at the beginning of the Q&A session, while everyone else is submitting questions, I will be turning over the floor to Dr. Jeans and she is going to help address some of the issues that people raised. Let me get started here...

Unidentified Female: I got it, I signed in.

Soundia Duche: I think we need to make sure everyone's phones are on mute; in fact we should not even be able to hear you so I am not quite sure... Heidi if you heard that if you could help us on that that would be great.

Heidi: Yes, I will find out what is going on there.

Soundia Duche: We will go ahead and get started. We will start off by answering the question "Why does the IRB conduct continuing reviews?" We will focus a great deal of our time on what constitutes meaningful and substantial continuing review and then we are really just going to touch on the difference between continuing review by the convened IRB versus expedited review and then really delve more into applying expedited review categories eight and nine, which apply to continuing review. Finally we will round-off our lecture by discussing lapses in IRB approval.

Why does the IRB conduct continuing review? Firstly, the Common Rule requires us to do it and so we do it. An IRB is charged to conduct continuing review of research at intervals appropriate to the degree of risk but not less than once per year. So much of our attention is spent on a daily basis on the IRB's initial review and approval of a research project and that is understandable. Investigators want to get their approval letters as quickly as possible so they can start their research and IRB offices in turn are under a great deal of pressure to get studies approved in a timely manner. So often it seems that so much focus is on the initial review and that is really the focus of the IRB office. But really initial review is just the beginning. During the initial review, the IRB assesses what the investigator plans to do as well as the project's risks and devises ways to mitigate those risks. However it is only once a study has begun that the IRB can truly evaluate the complex interactions of the actual conduct of the study. And so continuing review is really the mechanism by which the IRB is able to monitor participant's safety during the study and continuously reassess risks and benefits to participants once the research is underway.

Now it is the investigators responsibility to submit documents to the IRB in sufficient time for the IRB to conduct a thorough continuing review. However, most IRB's will provide investigators with

courtesy reminders that their continuing review is due. I thought that it would be interesting if we could take a quick little poll. I want to get a sense from you all on when do you send out the first continuing review reminder? Let me access the poll and open it up and I will read out the answers once I get it open. Okay I think we are up now, yep everything looks good, yes and we can start voting. Perfect - so for those on the line, the options are three months or more before approval expires; two months before approval expires, so what we are referring to is your first reminder, one month before approval expires, two weeks before approval expires or you do not send out reminders. So I will give you all just a few more seconds. I see results coming in. I am going to close the poll now and broadcast the results so everyone can see. You should be able to see the results, I am not quite sure why you cannot but while we figure that out, oh thank you Theresa. Okay I am not really sure what has happened but we will work out the technicalities. Essentially, the majority of you all said you send out your first reminder three months or more before approval expires and then about 36% of you said the next highest option, which was two months before approval expires.

The key point we want to make is, there are no right or wrong answers to that obviously, but you want to make sure that you send out the notice in sufficient time to be able to allow for back and forth between the IRB and the investigator during the review. But you do not want to send your reminder out so far in advance that the investigator ends up becoming inundated with reminders and ends up ignoring and forgetting about the request. Or sends in information so far in advance that by the time the IRB is reviewing the documents submitted, things have changed and the materials are no longer relevant and up to date and reflective of the current status of the study. So while the IRB is not required to send out reminder notices, it is important to remember that it can be the IRB's fault that a continuing review does not occur in time. For example, if a reviewer does not complete his review in time or the IRB misplaces the submitted documents, that does happen. In the end whether it is the investigator or the IRB's fault that the approval expired, the regulations do not allow for a grace period or any extension of approval beyond the IRB's approval period. I want to stress that under no circumstances can that approval period extend beyond one year from the previous date of approval. So it is important to remember that both the investigator and the IRB have a responsibility in ensuring that continuing review is conducted on time so that research subjects are not negatively impacted by any lapse of approval.

So how often must continuing review be conducted? The Common Rule specifies that IRBs must have written policies for determining which projects require review more often than annually. We will pause there. The frequency of continuing review really should be based on the IRBs ongoing assessment of the risk associated with the study. Now in preparation for this training and all my trainings actually what I like to do is go on OHRP's website and try to get a sense if there are any recent compliance findings related to the topic at hand. So I was very happy I was able to find something that some of you all may not have discovered.

In December 2012, OHRP cited the University of Washington for not adequately describing in their policies and procedures how the IRB implemented the aforementioned regulatory requirements. That being, that the IRB must have written policies for determining which projects require review more often than annually. The compliance letter states that the auditor believes and I quote, "believes that some IRB members including the Chair may be unaware that IRBs have the authority to require IRB review of a project more often than annually. And that during their onsite reviews various IRB members stated that their respective IRBs had never approved research for less than a year". So I bring this up because we really want to make sure that our VA facilities, in your policies

and procedures - you outline the factors your IRB uses in determining the review period and you make sure that your IRB members are aware that they have this right and they are familiar enough with the factors that they should take into consideration when considering the frequency of continuing review.

What are some of those factors? Well some of the things the IRB should be taking into consideration are the nature, magnitude, and probability of risks to subjects; the vulnerability of the subject population that is being studied; they want to obviously review the serious adverse events; any complaints and compliance risks that they have discovered during the review period. So for example if the IRB sees an uptick in serious adverse events or receives a number of complaints about a research study, or it maybe finds out that the investigator has not been reporting serious adverse events or unanticipated problems, they may feel it prudent to increase the frequency of monitoring for that study or for all studies that that investigator has ongoing. You want to factor in investigator experience, so an IRB may wish to monitor a new investigator more frequently initially or even an experienced investigator that perhaps is delving into new research areas for the first time or using a new product or a new procedure- that might be reason enough to require more frequent monitoring initially. Also the type or phases of the study. For phase one studies or pilot studies, those are great studies to really have more frequent monitoring initially or studies with novel designs or procedures. And then of course if at any point the IRB becomes aware of any new product information or new literature published about the product or the class of products, that also might be reason enough to increase the frequency of monitoring.

Now the frequency of continuing review does not have to be limited to the passage of a specific amount of time so long as review occurs within a year. And so for example the IRB can elect to require continuing review based on the number of subjects enrolled. So they may say that, for example, continuing review must occur after the first five subjects complete a certain milestone. Maybe that is a certain procedure or the first month's visit or they may specify continuing review must occur before the next dose escalation. All of that is absolutely fine, so long as the review occurs before a year has passed.

The second part of the regulation specifies that IRBs must have written policies and procedures for determining which projects need verification from sources other than the investigator that no material changes have occurred since the previous IRB review. And so for example at the VA because we actually have a great RCO system, that is a great opportunity where the IRB may request an RCO audit or obtain copies of reports from the data monitoring committee to gain additional insight on the status of a research study if they become aware of something that they feel they need more information about. And so, last point about this, it is important to remember that as long as the study remains open, it must undergo continuing review by the IRB. And I know sometimes people wonder why, especially if the study is in data analysis phase for goodness sakes! But really and truly there might be new information revealed even during the data analysis phase that the IRB may feel should be communicated to research subjects. So those all are things you want to make sure that the IRB considers as they are deciding on what the review period should be.

VHA Handbook 1200.05 requires the IRB to conduct a substantive and meaningful continuing review, so what does that mean? Well firstly, at continuing review (sorry something just popped up on my screen). At continuing review, all approval criteria must continue to be met. The IRB must ensure that all continuing review criteria continue to be met. And we are not going to delve into continuing review approval criteria which is the same as the initial approval criteria, but I would

definitely suggest that you refer to the cyberseminar Theresa presented in July on IRB Approval Criteria for more information on that if you need a refresher; and that is on our Pride website. The primary focus during continuing review is really to determine whether risks continue to be minimized. It is all about subject protection, research subject's protection. Has any new information emerged either from the literature or during the conduct of the study itself that signifies an increased risk to subjects? Do risks remain reasonable in relation to anticipated benefits? If additional risks are identified, do study procedures need to be revised in order to reduce risk? For example, might the inclusion and exclusion criteria need to be revised as a result of new information discovered during the course of the review; during the course of the conduct of the study? Are the safeguards in place at the time of the original approval still adequate to ensure the safety of subjects and is the informed consent form accurate and complete, in fact is the informed consent process adequate. Does the information in the informed consent form need to be revised so that subjects are kept adequately apprised of any new risks that may affect their willingness to participate in this study. Are any significant new findings that may affect the subject's willingness to continue participation provided to subjects? All of these are some of the factors that the IRB takes into account when performing a meaningful and substantive review. And so how do they do that? Well they end up using information supplied by the investigator. VHA Handbook 1200.05 requires that investigators submit a protocol summary and a status report containing a list of key information. Now our next four slides cover the entire list of required information that the investigator must submit at the time of continuing review. And usually this is covered in the continuing review application for a particular facility so that information is not forgotten or not included in the report. And rather than go over each item that must be addressed, what I am going to do instead is just comment on a few of the items and how that piece of information contributes to the IRB's ability to conduct a substantive and meaningful review. And so I have put a little checkmark next to the items I am going to cover just so you can follow along. But in no way does that lessen the importance of any of the other items that I am electing not to cover.

So first I will talk a little bit about **the number of subjects entered and withdrawn over the review period and since its inception**. Why does the IRB need this information? Well one of the things they use this information for is to determine if accrual is progressing as planned. If not, is there anything that can be changed in the study procedures or recruitment efforts? Some questions they may consider include whether accrual is significantly lagging. If it is, will study objectives be met at the continued rate of accrual and if they determine that they might not be, that there is a strong likelihood they may not be, is it ethical to continue to enroll subjects in research that may not be sufficiently powered to answer the question under investigation. And so while sometimes that particular question of how many subjects are entered and getting the answer right seems taxing, it really has some significant ramifications in terms of how the IRB assesses the progress of the study and the ethics of subjecting subject's to potential risks.

**Summary of complaints:** What they are looking for here is have there been any complaints and if so, really what is the nature of those complaints? Does the investigator or research staff need to be re-educated in order to ensure subject safety?

We have already touched a little bit on the **informed consent form and HIPAA**, mainly they want to make sure that the consent form and HIPAA remain consistent with each other especially as amendments are submitted, study procedures change, adverse events occur that result in the IRB requiring changes to the study. They also want to ensure however that the most recent consent form is being used and decide whether it needs to be revised given any new information obtained.

**Information that may impact on the risk benefit ratio such as adverse events and complaints:**

Again, this is actually one of the most important because there is a continuous need to assess if serious adverse events are occurring at a greater than expected frequency. If the IRB finds that a number of SAE's are related to the intervention, does the consent form need to be changed to describe the new risks? These are some of the questions they are asking or after. Should the new risks be considered expected and the protocol revised so that subjects can be adequately apprised of the risks they are entering and make an informed decision as to whether they want to participate in the research? How does this information impact the risk benefit ratio? If any new unanticipated risks to subjects or others of a severe nature are reported, the IRB may require changes to the protocol to safeguard research subjects. Some of the questions the IRB is going to be trying to determine are, "was the unanticipated problem attributed to the product or to investigator non-compliance with the protocol". If so, they are going to recommend changes or rather require changes in order to reduce the risk to subjects.

**Summaries, recommendations or minutes of the data monitoring committee meetings or findings based on information collected by the data safety monitoring plan.**

The data monitoring committee is comprised of a group of independent experts that convene to monitor the progress and outcomes, both benefits and risks, associated with the study. They are convened in both single site and multisite research but they play a significant and unique role in multisite research because they have an advantage over the single local IRB who is not able to observe information to the extent that the data safety monitoring board can. They see all the information from all the study sites that are participating and so they are able to observe accrual rates and outcome data from all sites participating in the study. They also have the benefit of being able to review unblinded data which is invaluable in assessing adverse events and attributing them to specific arms of the study. And so for multisite studies, the data monitoring committee is in a much better position to be able to identify trends that a local IRB may not be able to see and thereby advise them. One of the things the IRB will be trying to determine from these reports is whether any information provided in these reports raise the level of risks to the point where the consent form needs to be changed or subjects need to be informed of new findings. The data monitoring committee will also come up with recommendations - whether a study needs to be stopped earlier than planned because of some of the risks they see.

And finally these last points all come hand in hand, **research findings to date and multicenter reports.** We have kind of touched on a number of them. All of these items are really to help the IRB assess the risk/benefit ratio. Sometimes the investigator is aware of scientific findings in the literature and it is his or her responsibility to provide this information to the IRB if it may affect their research and the risk assessment. Other times a member of the IRB may come across relevant new information either during the course of his or her clinical duties using a similar class of product or through review of the literature themselves. All of this information the IRB takes into consideration when continuously monitoring the risks and benefits associated with a research study.

So how can continuing review be conducted? Similar to initial review, it can be conducted by either the convened IRB or if eligible, by expedited review. We will first touch on convened board review very briefly. I am going to cover this section pretty fast. If the study was originally approved by the convened IRB, and does not qualify for any of the expedited review categories, then it must continue to be reviewed by the convened IRB and in such cases, once the continuing review materials are submitted, it is scheduled for the IRB meeting and all IRB members must receive and

review the protocol summary and status report that we already talked about. At least one voting member of the IRB needs to receive a copy of the complete protocol including any modifications previously approved by the IRB, and all IRB members should have access to the complete protocol file and relevant IRB minutes in case they want to review them. For continuing review, the convened IRB has the same options for determinations as during initial review. They can elect to approve the study, they can approve the study with minor modifications, or they can defer approval because of substantive conditions. If the convened IRB elects to approve the continuing review or approve the continuing review with minor modifications, then the continuing review approval date is set as the date of the meeting at which either of these two determinations is made. It is important to remember that it is not the date that the conditions are verified, those documents may come in a few days later, they may come in a few weeks later and so that raises another problem if it goes beyond the approval period. It can be that the IRB elects to defer approval, well then the continuing review approval date would be set as the approval date which the protocol is finally approved or approved with minor modifications.

I just want to make sure, we are still having problems here...

Alright so establishing the renewal date. The renewal date or continuing review expiration date, however you want to refer to it as, must occur no later than one year after the last approval date. This is per the regulations. There is a caveat which we will get into in a second, but if the IRB last granted approval on May 1<sup>st</sup> 2012, then the next review has to occur latest on or before May 1<sup>st</sup>, 2013. We are going to go over an example in a little bit on calculating dates.

The 30 day rule that I mentioned, sometimes referred to as the anniversary date rule, allows continuing review to occur - well in cases when continuing review occurs annually and the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the subsequent continuing review must occur. So let's go back to that previous example. If the convened IRB last granted approval on May 1<sup>st</sup> 2012, then the IRB can conduct its next review anytime between April 1<sup>st</sup> and May 1<sup>st</sup> 2013, up to 30 days before the expiration date, and still reapprove the research for another one year period that expires on May 1<sup>st</sup>, 2014. We'll go over this again, and I have a case study to make sure we all get this point.

So let's turn briefly to expedited review. If a study was originally deemed minimal risk and it qualified for expedited review categories one through seven and nothing has changed that would affect its ability to be reviewed by expedited review, then it can continue to be reviewed by expedited review at the time of continuing review. The expedited reviewer is responsible for making the determination that the study remains minimal risk and nothing has changed that would kick it out of one of those categories. It is important to allow sufficient time for the reviewer to make this assessment because there is always a chance that once he receives the information and reviews it he realizes that the study no longer qualifies for expedited review and has to go to the convened board. Therefore then you would have to schedule it at the next meeting of the convened board which for some people could be a month later. So you really want to make sure you allow sufficient time for that last minute decision to be made and don't run the risk of your approval expiring as a result of poor planning. If the study was originally approved by convened board review, but it now qualifies for expedited review categories 8 or 9, then it can be reviewed by expedited review at the time of continuing review. We are going to talk about and focus on expedited review categories 8 and 9 in a few minutes.

Who can perform continuing review by expedited review? Same thing as initial review.

Continuing review by expedited review can be conducted by the IRB Chair or an experienced IRB voting member designated by the Chair. In this case the expedited reviewer would receive and review all documentation and the complete protocol. In the interest of time we are not going to delve into all the particulars of expedited review, however those needing a refresher can please refer to the training that I gave in June on Expedited Review as that covers all the nuts and bolts of it.

So what determinations can the expedited reviewer make? They are allowed to approve the protocol; approve with modifications; or defer to the convened board. Remember expedited reviewers cannot disapprove a study; that applies to both initial and continuing review. So in establishing the continuing review approval date, if the expedited reviewer approves the continuing review of the study outright, then the continuing review approval date is set as the date the expedited reviewer completes his or her review. If they require modification in order to secure approval, this is where it differs from convened board review, the continuing review approval date is not set until the investigator submits the modifications and the expedited reviewer determines that all required modifications have been addressed. And so that is one of the key differences between continuing review by convened board versus expedited review. Finally if the expedited reviewer defers approval to the convened board then you would follow the procedures for convened board review.

In terms of establishing the renewal date for expedited review, very similar to convened board review. If the last approval was granted on January 15, 2012, then continuing review approval must occur latest January 15, 2013, one year later. And so we have a case study where I am going to go over expiration dates and we are going to hope that the polling feature works correctly this time. So let me go ahead and read out the case study and then we will work on the poll.

So in this case we have a protocol that expires on January 15, 2013, submitted for continuing review. The study continues to qualify for expedited review we are told. On December 10, 2012 the expedited reviewer reviews the study and requests a number of clarifications from the investigator. The investigator submits the requested information and on December 29, 2012 the expedited reviewer confirms that all issues have been addressed and the study is approvable for another one year period. And so our poll question involves when the next expiration date for the study should be. I am going to open the poll while you get the answer. Polls should be open and votes are coming in, the options are the expiration date for the study should be A) December 10<sup>th</sup> 2013, B) December 29<sup>th</sup>, 2013, C) January 15<sup>th</sup>, 2014 D) Either B or C or E) None of the above. I will give everyone some time to answer that, take your time. Alright I am going to end the poll, hopefully this time everyone will be able to see the results, we are going to cross our fingers here. I am not quite sure if you guys can see it but it looks like the answers are about 33% of you responded December 29, 2013, and then we have a split between January 15<sup>th</sup>, 2014 and D) either B or C, and that is correct. Essentially the answer could be either B or C and the reason being that if the facility elects to use the 30 day rule, if they have that in their SOP, then they could set the expiration date as January 15<sup>th</sup> 2014. If they do not elect to use the 30 day rule then the expiration date would be the date that the expedited reviewer confirmed that all modifications were met and that would be December 29<sup>th</sup>, 2013.

Alright let me close the file. So now we are going to move into expedited review categories 8 and 9. I remembered you all asked for this and we promised that we would cover this during the continuing review lecture so thank you for your patience. So expedited review 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 **and** the only remaining research related activity is long-term follow-up of subjects. Now OHRP's 2010 continuing review guidance considers long-term follow-up to include minimal risk interactions, for example surveys, and the collection of follow-up data and procedures or interventions that are being done as part of routine clinical practice. Essentially record review. If interventions for research purposes are still occurring then expedited review Category 8 cannot be used, that is the key there. Category 8 can also be used for studies where no subjects have been enrolled at your local facility and OHRP interprets that to mean no subjects have ever been enrolled at your facility **and** no additional risks have been identified by the investigator, or if it is a multisite study and other sites are enrolled, by any of the other facilities where subjects have been enrolled. Keep in mind if new risks have been identified since the last IRB review, perhaps even in the literature, then this category would not apply as the convened IRB would need to review this new information to determine if the study or consent form needs to be revised as a result. So even if subjects have not been enrolled at your facility, if there is any new information out there, then this category cannot be used because it is important that the IRB always take this information into consideration in order to protect future participants in this case since there are no participants enrolled. Finally Category 8 can also be used in cases where the only remaining research activity involves the analysis of identifiable data. Remember if the analysis of identifiable data is ongoing, the study must remain open and therefore subject to continuing review. And in such cases you can use expedited review Category 8 to conduct your continuing review.

And so administratively how is this done? Well when the continuing review materials are submitted, an administrative review can occur to determine if a study last reviewed by the convened board is eligible for expedited review Category 8 or 9, but we will get to that. If it appears so then the materials can be routed for expedited review. Now remember it is always the expedited reviewer, the IRB member, who has to confirm that all criteria are met and that the category applies. If he or she confirms it, then she can proceed and conduct the continuing review by expedited review.

Expedited review Category 9 is a little trickier and that is because it requires that the IRB have previously determined and documented at a convened meeting that either the research as a whole or the remaining research activities involve no greater than minimal risk. This is where people get tripped up.

So let's go over all the criteria that must be met. First the research must not be subject to an IND or an IDE, that is an investigational new drug application or an investigational device exemption. Secondly, Expedited Review Categories 2 through 8 do not apply. Thirdly as I mentioned, the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk. And then finally, similar to what we saw for expedited review category 8B I believe, no additional risks have been identified by the investigator or in the case of multisite studies by any institution involved in the research since the last review.

Let us go over this in more detail. The first two criteria I think are fairly straight forward: Does it have an IND or IDE, if it does Category 9 is not an option. If it does not you go on to determine do expedited review Categories 2-8 apply? If they do not then we are looking good. Number three is has the IRB determined and documented at a convened meeting that the research involves no greater than minimal risk? Now for those studies determined to be minimal risk by the convened IRB at the initial review, this determination should be documented already in the meeting minutes

and in that case you are covered. The problem is those studies that were not initially deemed minimal risk but as the study progressed the IRB determined that the remaining research activities represent no greater than minimal risk to subjects. This is the determination that would have had to have been made and documented at the convened meeting of the IRB prior to the subsequent use of this expedited review category. There is one more criteria, number four which we talked about already and that is that no additional risks have been identified. But this requirement to document that the IRB, the convened board has determined that the study or all remaining research activities involve no greater than minimal risk is very important, this is where people have problems with this category.

When the study comes in and lets say an administrative review is done, and it looks like all those criteria have been met, it is very important that a review of the initial approval minutes as well as the last set of meeting minutes has occurred to make sure that the current status of the study is minimal risk. The expedited reviewer, if you had an expedited review, would then once again confirm that. If that determination has not been documented in any of the IRB meeting minutes, then that project has to go to the convened board for such a determination to be made and then after that you can subsequently use this category as long as all four criteria continue to apply. You really have to reassess the project at each and every continuing review because things can change as the study progresses.

So we have two case studies on these expedited review categories that we are going to go into. Case study one involves a research study evaluating cytokine levels in subjects diagnosed with rheumatoid arthritis. In this case, 50 subjects will be enrolled per year over the next five years. 20ml of blood will be collected by venipuncture four times per week for six weeks. The research study we are told is not conducted under an IND or IDE. The meeting minutes from the initial approval note that the IRB determined that the study was no greater than minimal risk and we are told that no additional risks have been identified during the approval period. So we are going to go ahead and open the poll. I am going to read out the options. One of the handouts we included was the list of expedited review categories so that is something you might want to pick up and refer to. Thank you. Open the poll, give you all a minute or two to answer, the options are: at continuing review the study is eligible for review by A) the convened IRB, B) expedited review, based on Category 2, C) expedited review but based on Category 8, or D) expedited review Category 9. I will give you all 30 more seconds or so as the results come in. Alright I think the majority of the results are in..give people just a few more seconds. I am about to the end the poll. The answers are changing, maybe that is more people sending in their answers.

I am going to broadcast the results and you should be able to see them. Apparently it is a little grayed out so let's see if we can get it crystal clear. The results are displayed and the majority of you, about 40%, said that you believe that the protocol is eligible for expedited review Category 9 and that is correct. A number of you, the next highest about 25% said expedited review Category 2 and I am glad, I am glad you went there actually because it almost is, almost but not quite unfortunately. Expedited review Category 2 cannot be used because of the frequency of the blood draws. It really limits the frequency of blood draws to no more than twice a week and in the case we gave they were doing four blood draws a week. I realize that was a bit of a trick question because we did not really focus on all the other expedited review categories, so shame on me but thanks for playing along. Sixteen percent of you said expedited review Category 8 and I want to go over why that is not relevant: Research procedures are still ongoing. Remember one of the keys to Category 8 is research is permanently closed to the enrollment of new subjects **and** all subjects have completed

all research interventions **and** the research remains active only for long-term follow-up of subjects. So that is the reason why Category 8 would not apply – this is very key. Lastly, about 18% of you said the convened IRB and in truth you are not wrong, a protocol is always eligible for review by the convened board so you are not wrong there. Kudos to you. An IRB can always elect to review any protocol, any continuing review, by convened board should they choose.

Alright I am going to close that and we have one more case. Our second case also focuses on expedited review. This case involves a research study evaluating the effects of urban pollution on pulmonary status in healthy adults. In this research study, subjects will undergo monthly surveys regarding exercise and pulmonary symptoms and a single chest x-ray five years after enrollment. The IRB meeting minutes indicate that at the initial review the IRB determined that the study involves no greater than minimal risk. I am going to open up our poll and I will read out the answers once the poll is open. Alright so it is open, our options here are for this case: at the time of continuing review the study is eligible for review by A) the convened board - okay people do not go for that again, come on work with me, B) expedited review Category 4, C) expedited review Category 8, D) expedited review Category 9 or E) additional information is needed. I will give you guys some time.

Alright I will give you all about five more seconds and I am going to end the poll and broadcast the results. Alright here we have a bit more of a split. About 34% of you felt that the correct answer is E, additional information is needed and that is correct. We did not provide you with information on whether the study was conducted under an IND or an IDE, the likelihood is not but you never know, we did not say. We also did not provide you with information on whether any new additional risks had been identified since the last review. And so for that reason Category 9 could not automatically be cited based on the information we gave. For those who selected Category 8, again remember as long as research procedures are ongoing, the surveys would not be a problem but the x-ray would. The surveys would be considered long term follow-up, if that is what you were thinking you would not have been necessarily wrong there but there is that single X-ray that occurs five years after enrollment. Those who selected Category 4 - x-rays are the one thing, well not the one but one of the things that is excluded from expedited review Category 4 and so unfortunately the study would not have been eligible for expedited review Category 4 because of the inclusion of that single X-ray again.

So I am going to hide this and proceed to the last section of our training which is lapses in IRB approval. Now since we are almost at the end of our presentation I thought it was a good time to reiterate there is no provision for any grace period to extend the conduct of research beyond the expiration date of IRB approval. Also there is no provision to grant approval for greater than one year and so if approval expires, the local research office must promptly notify the investigator. The investigator in turn must stop all research activities, including but not limited to enrollment of the subjects, continuation of research interventions or interactions with currently participating subjects, and data analysis. The investigator must immediately submit to the IRB Chair a list of research subjects who could be harmed by stopping study procedures and the Chair, in consultation with the Chief of Staff, will determine if subjects on the list may continue participating in the research interventions or interactions.

I want to just comment a little bit on the term lapses in IRB approval because many of us often refer to halting a study because of a lapse as a study suspension. Please remember OHRP, ORO, FDA, none of them consider an expiration of IRB approval to be a suspension or termination of approval

and so none of these agencies, or entities rather, require reporting of these activities as they do for other study suspensions. Now an IRB may determine that a pattern of lapses in IRB approval, perhaps due to the investigator not submitting materials in time or responding to requests for more information in a timely manner, an IRB has the right to determine that that constitutes serious or continuing non-compliance and if they do, at that point the reporting requirements for serious or continuing non-compliance would be followed; but on its own, a lapse of approval is not a study suspension.

What do you do once the study has lapsed, well as I mentioned all the activities have to stop and IRB re-review and re-approval must occur before the study can resume. The IRB cannot retrospectively grant approval to cover a period of lapsed IRB approval. Your local policies will dictate the procedures you follow to restart a study after a lapse of IRB approval. Your local policies and procedures should specify how long after expiration you will allow the IRB to perform continuing review using the continuing review application materials already submitted, versus requiring them to submit a new continuing review application. Just because approval lapses it does not automatically mean that the study has to be closed and new protocol material submitted for review. Please, local policies again will dictate at what point in time following study expiration and not hearing from the investigator at all, the IRB will resort to closure of a study. This is totally up to your local procedures. We do suggest that you be pretty clear in your local procedures to avoid any problems from auditors, but it is not automatic.

I am about to wrap up, but I just want to briefly comment on a question I received from the field in preparation for this training regarding study closure forms. Specifically the question was whether a study closure form is required and if it has to be a separate form. I think this facility was including it in their continuing review form. We do not have time today to go over study closures, that is really a mini topic in and of itself, but I wanted to acknowledge the question received and say that really there are no regulatory requirements that apply to study closure. So again it is up to your local policies to specify which format you ask investigators to follow to indicate closure of a study. Many IRBs do use a separate study closure form to document study closure requests but it is up to you and your IRB. I will say a separate form can be used as an opportunity to ensure that the investigator understands what it means to close a study and what his or her responsibilities are with respect to data protection once a study has closed. But again how you proceed is based on your local policies.

And so that brings us almost to the end. I thought we were there sorry. This is a quick FAQ on two questions we often get here in ORD. I will go over it very quickly. First question is does the informed consent form have to be reapproved at your continuing review, and the answer to that is if nothing has changed on the form, nothing has changed in the study procedures that require the form to be changed then no, re-approval is not necessary. However there is a caveat and it leads directly to the second question. Does the IRB have to restamp the informed consent form at each continuing review? And the answer to that also is no. However if an IRB includes an expiration date on the consent form, then of course you would need to issue a new consent form. However, the Common Rule nor VHA Handbook 1200.05 require an expiration date be included on the informed consent form. So again you want to look at what your local SOP's say and proceed accordingly.

These are just some comments on compliance findings. I am not going to go over them, you can read them at your leisure, but these are some common compliance findings from ORO that relate to continuing review.

Included are references that we covered in today's lecture and also our contact information. We have a website where this presentation will be archived as well as our previous presentations. Also we have included the email address for the ORD regulatory group where you are encouraged to submit any regulatory questions you have, and all of our contact information.

So before we go into the Q&A session and open up the floor, or go into the box, I did let you all know at the beginning that we received some questions from the field in advance and so I have asked Dr. Karen Jeans to come on and she is going to go over some of those questions and answer them, so I am going to pass the torch to Dr. Jeans.

Karen Jeans: Okay well thank you very much, and first of all before I start answering questions I would like to truly thank Soundia and Theresa and Lucinda and Lindsay for the outstanding presentation that was done today. This is a very complicated topic and this was presented extremely well, with some very credible nuances in there emphasizing the devil's in the detail, so excellent job and I hope that this is extremely useful to all of you on the call today. There were some questions that were sent in to ORD prior to this call and so I am going to address those four questions, and these questions deal with conflict of interest forms, scope of practice, the privacy officer-information security officer checklist and actually an R&D committee issue concerning notification of continuing review by the ACOS for R&D.

So I am going to start with the first one. The question was, "is a new conflict of interest form needed if the principal investigator attests on the continuing review form that nothing has changed since the last review period with regards to conflicts with the PI or study staff". So this is actually an interesting question because the context of this question is that VA has no handbooks on how we are supposed to do conflict of interest. We have been working on one for a number of years and we do think one will come out and the office of general council, the office of research and development, multiple program offices, privacy are working on this handbook.

So when it comes to is there a handbook that mandates the use of a conflict of interest form by VA or VHA, the answer is no but here is the issue. Because there were, across the VA system, we have right now 109 VAs that have assurances to enable them to conduct human subjects research, each of these different institutional review boards and institutions were capturing financial disclosures in different ways. And we as an agency are subject to multiple regulations and laws regarding conflict of interest including the standards of conduct for employees of the executive branch of the government. So the Office of General Counsel developed a form and it does not have an official OND form number yet but it is on the technology transfer site and this is the conflict of interest form that is being referenced in this question. The Office of General Counsel has basically asked that that is the form to be used whenever your institutions are reporting financial disclosures for researchers. So when it comes to "is a new conflict of interest form needed", the answer should be follow your local IRB and institutional policies and procedures for reporting disclosures. If your local institution does not require a new conflict of interest form every year, then that is fine because there is no VA or VHA policy requirement regarding the use of that form, so default to the local policy. So with that are there any questions regarding that before I move on?

Soundia Duche: You might want to submit it to the Q&A box since Theresa is monitoring that.

Karen Jeans: I know that we are very short on time, and I tend to talk a lot. So the second question involves a really good question, about scope of practice, and I am really glad the person who asked this did this. The question is as follows, “does the study staff need to complete a new scope of practice form if their duties have not changed during the last review period” and I am assuming for purposes of this question the last review period is the last continuing review period by the IRB. So the first thing I want to emphasize is that it is not within the IRB’s scope of authority to be reviewing the scope of practice; that is really not the role of an IRB. So that is the first statement I want to make. But in regards to scope of practice forms, so that everybody on the call is on the same page, in VHA Directive 1200 the Office of Research and Development, we basically require the Facility Director of the VA Medical Centers to ensure that every single employee who is involved in research practices, research staff services, that they either have a scope of practice, they have a functional statement or if they have clinical privileges, that if those are the same as what they are doing for research then those clinical privileges can indeed be the same thing as a scope of practice, they do not need a separate scope. Now there is nothing in VHA Directive 1200 that states when it has to be redone, however every year as part of VHA Handbook 1200.01, the ACOS is responsible for ensuring that everyone who has a scope of practice is operating within their scope of practice and that if they are not, their scope of practice is changed. So the question again is does the study staff need to complete a new scope of practice form if the duties have not changed during the last review period, the answer is no, there is no need to complete a new scope of practice, but the ACOS is responsible every year for reviewing that scope of practice of all the research employees to ensure that they are operating currently within what is on file. Okay that is question two.

Question three is also a brilliant question, wonderful questions by the way. “I would like to know if the new privacy officer/information security officer checklist is needed at continuing review”? This checklist, the privacy officer/information security officer checklist is a form, that is a worksheet, that is all it is. It is a tool. It is like an IRB reviewer tool. It is like something that when you are taking notes at a meeting you can choose to use it or not. There is no handbook, we always go back to policy here that mandates the use of that checklist, and it is there for the privacy officers and information security officers’ convenience because there was a need verbalized to the program offices that are responsible for this checklist, “Hey can you give us a tool that will help us in terms of looking at those things we need to look at for research studies” because the job of the privacy officer and the information security officer just like everyone else who is involved in research is so complex and we have the utmost respect for these roles because you are doing, not only as privacy officer and information security officer for research, most of you also are involved in the clinical side of the house as well. So the answer is it is not required, the form itself is not required. It is one of those that if you want to do it again at continuing review so be it, if not there is no requirement because it is to be used at your discretion.

Now the fourth question is actually very important as well because I could actually spend 20 to 30 minutes on it alone. I am going to present the question first and then present the requirement and then discuss what ORD’s position is on this. And the question that was sent in is, “Currently at all medical centers Principal Investigators are not allowed to continue any research without the ACOS/R&D approval letters being issued. However according to guidance that was issued by the Office of Research and Development, Principal Investigators can continue research after the IRB has approved and before the ACOS/R&D letter is issued. Can you please talk about this.

So let’s talk about this. Going back again to what is required by the Office of Research and Development in VHA Handbook 1200.01. When we issued VHA Handbook 1200.01 and that is

the handbook on the R&D committee, at that time and what drives policy many times is a need, we put a requirement in not just because we are all sitting around a table and thinking let's just see how we can make a lot of people miserable, it is to address an issue. And so at the time that we came out with 1200.01 there was a real big issue going on with research being initiated without all the approvals in place, without the R&D Committee in place. So in VHA Handbook 1200.01 we put a requirement in as the Office of Research and Development that even though an investigator gets their IRB approval letter, gets their biosafety letter, if it involves biosafety, they get their R&D Committee approval letter, they cannot start that project, initiate that project, until they get the ACOS/R&D letter saying okay as the ACOS/R&D I see all your approvals are in place for the study to begin. I do not think there is an issue with that, but this question is asking about the second part of it.

Within VHA Handbook 1200.01 we also put in a requirement that the ACOS is responsible for notifying the investigator of approval after continuing review by the R&D committee and subcommittees. Now again remember that in VHA Handbook 1200.01 there is no requirement for R&D continuing review if a research activity is already being reviewed by another subcommittee. So for all these studies that are being reviewed by the IRB there is no requirement by the Office of Research and Development to have it go through an R&D continuing review approval. So then continuing on here, why do we put this into place? We put this in place so that somebody, because the R&D Committee is not responsible for conducting continuing review of these protocols in which another subcommittee such as the IRB has oversight the project, that someone at the research institution, and the ACOS is responsible for day to day management of the research that is conducted at the facility, is aware, hey, everything is fine because many times particularly after the study is approved initially, and lets say it goes through biosafety and it is going through the IRB, those approval times, those times it goes through committee are not concurrent, they may be two to three months apart.

So it is not the intention of ORD to state or to require that when the IRB approves the study, that one has to wait until the ACOS generates a letter stating to the investigator, oh by the way the IRB has approved your study because that is not what ORD intended and it actually has implications. Because as Soundia did an outstanding job presenting at the beginning of this, and it was very important when she was doing the poll of when did you do your continuing reviews, for the IRB approval letters in terms of how to make sure that you get the application data in prior to the expiration so it does not lapse. So now you have all that going and you have done that and then the study stops because the ACOS has not issued a letter that the IRB has approved the study as they were supposed to do. That has implications for data integrity, it has implications for the subjects themselves because one of the questions that of course I would be asking was what is happening? Okay what is the IRB doing when this is happening? Are they notifying subjects because you may get in that situation where you are raising ethical issues. Subjects need to be told, " oh by the way we are having to stop your study". This is not the intention of ORD and so when I read this I am going to be contacting the site that sent this question so that we can address this and help the site out directly because I want to emphasize again on this conference call, I am grateful this question was asked, to let everyone know on the call "no", it is not ORD's intention, it is not required that you stop the study at continuing review until the ACOS issues the letter and we have issued guidance on this topic, that is ORD's formal opinion on VHA Handbook 1200.01 requirements.

So I hope that I clarified that and I really want to thank the four people that sent these questions because they are really good questions and I think they are beneficial for all the group that are on the call today. Okay and with that I will turn things back over.

Soundia Duche: Excellent, thank you so much Dr. Jeans and for those who sent in the questions or if others have follow-on questions for Dr. Jeans please email her directly on this. As she mentioned this is an important topic and we want to make sure that it is very clear what ORD policy is on this. And we have I think three or four questions.

Theresa: We have four questions in the queue right now. This is Theresa, I am going to read off the questions and then other folks are going to answer. Our first question is if a study with moderate risk is no longer recruiting subjects, and is limited to data analysis and thus qualifies for expedited review, does the risk become minimal?

Soundia Duche: And the answer to that is effectively yes, the whole goal behind Expedited Review Category 8 is if the research now meets all of the many criteria provided, then the risk to subjects at that point is minimal. And so if you are in the data analysis phase you are no longer recruiting subject, subjects are no longer going through any interventions, and remember you are not going back and forth, you are not one minute in data analysis and then back to recruiting no, the study research activities are over and so risk to subjects effectively are minimal. But more importantly you will be able to use Expedited Review Category 8 for subsequent continuing review.

Karen Jeans: This is Karen, that is an excellent way to present it because again it is not getting caught up into this categorization is it now minimal risk because in the Common Rule we have minimal risk and then everything else. Okay so let's talk about a drug study, if you have a drug study where the remaining activities are those that are limited to Category 8 as Soundia had pointed out, the study's remaining activities have now moved beyond those that are greater than minimal risk so it now qualifies for Category 8. So that is exactly where we are at with this, so excellent question, good question.

Theresa Straut: Okay, our next question is can local policy determine how long a lapse in continuing review can be done before a full initial review submission is required?

Soundia Duche: And I am going to say yes and I am going to ask Karen to comment on that because I think that she has some strong thoughts on this.

Karen Jeans: I have very strong thoughts on this thank you, because this is all very, it is really unique to every IRB. What do you do when you have a lapse and how long do you let it go? How long do you decide before, and again the regulations are basically that it has got to meet approval criteria in order for it to be reactivated. The study has to meet approval criteria at all times in order for it to be approved by the IRB. So you now have a study in which it has lapsed for reasons unknown. It could be because the submission materials were not submitted in time, it could be because you have a lapse because it was submitted in time, but when the IRB reviewed it there were issues that required returning to the convened IRB and again that is just something that happens, so it has now lapsed. So you have to look at the scenario that has happened. You will see a wide variety across the system whether it be VA, academia, commercial, private in terms of how this issue is handled. ORD does not have a specific position on this except for the fact that when it

lapses, in order to bring it out of lapse it has to meet all the approval criteria. So the long answer to your short question is that your own local policies will drive this answer.

Theresa Straut: We have another question, if a study met expedited categories for example four and seven at time of initial approval, at continuing review if the status is identifiable data analysis only, is it best to use Category 5 at the time of continuing review re-approval?

Soundia Duche: I think maybe you meant Category 8 or 9?

Theresa Straut: No it is written as Category 5.

Soundia Duche: Okay well let me answer your question, if a study initially is eligible for expedited review, whatever category, then at continuing review if nothing has changed so that it is no longer eligible for expedited review, then just stick with the original defined category. Category 8 and 9 deal with projects that were initially reviewed by the convened IRB and how can they now become eligible for expedited review, and so that I think is really what you are after and so for them one of the only ways to now be reviewed by expedited review is if they are in the data analysis phase. But for studies that were originally reviewed by expedited review, as long as they continue to qualify for it even as the study progresses up until closure, continue reviewing it by expedited review according to your initial category.

Theresa Straut: We have another question, what happens if an investigator retires, the investigators submitted a request to have a co-investigator take over as the PI, the IRB approve his protocol change this week, and the R&D does not meet until the end of October. Does the protocol need a final approval from the R&D or can the research continue?

Karen Jeans: Can you read that again Theresa?

Theresa Straut: Yes.

<Cross talk>

Theresa Straut: What happens if an investigators retires, the investigator submitted a request to have a co-investigator take over as the PI. The IRB approved his protocol change this week; the R&D does not meet until the end of October so I am assuming that they retired prior to the R&D committee meeting. So the R&D committee does not meet until the end of October, does the protocol need a final approval from the R&D committee or can the research continue?

Karen Jeans: Well again this is going back to something about that fourth question, and I actually want you to send this question to me personally but here is the issue here, so I am assuming and this is where again the devil is in the details. I am assuming that this is a study, because it is an investigator that has retired, that has been initially approved. So again VHA Handbook 1200.01 R&D committee, we do not require continuing review to be conducted by the R&D committee for studies that are under oversight of a subcommittee. Nor is the R&D committee required to review and approve an amendment when again it is under the oversight of another subcommittee and this is one of the reasons why we do not require it because you get into these kinds of situations. The R&D in these types of studies is really looking at institutional issues, it is not looking at the actual conduct of the study because that is the role, in this situation, of the IRB. So I do not know which

facility this is, I do not know what your local R&D policies are because when I hear that phrase I think the phrasing was can it continue, the last part of that was...

Theresa Straut: Can the research continue?

Karen Jeans: Can the research continue so I am going to need to ask you offline what your local policies are but if you do exactly what is required by ORD then this is a non-issue because it does not go to the R&D committee anyway. Because our policies in ORD do not require this type of protocol to come before the R&D committee to approve a change in investigator because that is a modification to previously approved research which is under the oversight of the IRB. Again this individual of course who is taking over for the investigator has been approved by the IRB based upon the information in your question, they have to have the appropriate credentials to do the research and if privileging is required, but otherwise this actually is a non-issue unless you have local SOP's which are more stringent than that required by ORD. Excellent question.

Theresa Straut: We have a few more that have come in and we still have a little bit of time so I will go ahead with them. Going back to the very first question that we had which was the moderate risk switching to the minimal risk if you recall, this goes back to that question. Should this change in risk level be documented in the IRB minutes?

Karen Jeans: You have to document, I am assuming here that and I think this is expedited all the way through anyway.

Theresa Straut: No, it was a moderate...

Karen Jeans: Oh it was moderate, so it went to the convened IRB okay, so you do want to document why is the study now eligible for expedited review and by doing that, that is the answer to the question because now that the remaining study activities meet Category 8, I think that is the question I think we got. Then that is the answer because the study was originally greater than minimal risk, now because of this phase of the study it was initially approved as greater than minimal risk, now the studies activities fall into Category 8 which are as Soundia described, so that is what you need to document because that is what your convened IRB is deciding upon.

Theresa Straut: I think this will be the last two questions I think we can fit in. So anybody else needing to send a question, you have the slide information but we are just going to do the last two. For R&D review of projects not being followed by an oversight subcommittee, does the R&D committee establish an expiration date?

Karen Jeans: Okay, that needs to come to me offline, I want to keep this on IRB continuing review, so I want to answer the questions for IRB. So we will stay with IRB continuing review.

Theresa Straut: So with this the same person had a question kind of a part two of the question. For projects followed by SRS...

Karen Jeans: Yes, I will answer those questions offline; I really want to keep this on IRB continuing review.

Theresa Straut: Alright, and this will be the last one then, what about review and approval during continuing review of a Central IRB study taking place at your site, does it need to be reviewed and approval by the local R&D committee?

Soundia Duche: I think that follows what Karen was saying, the Central IRB is the IRB of record for that particular study. The Central IRB then is what you call a component/subcommittee or...

Karen Jeans: That is right and this is actually a really good question because there is confusion about how to use the Central IRB. The Central IRB is one of the IRB of records for a VA facility so at initial approval the Central IRB serves the IRB role, your R&D committee at your VA facility is still responsible for reviewing that for initial approval. Then it follows through as we talked about on some of these questions, the R&D committee does not need to conduct a continuing review when the Central IRB has conducted continuing review because they are the IRB of record. Unless you have a local R&D requirement which is not required by the Office of Research and Development to conduct continuing review then there is no special need to conduct an R&D continuing review approval solely because the Central IRB is the IRB of record for some of your studies and they are conducting the continuing review.

Theresa Straut: Okay that is the last question.

Soundia Duche: Well thank you everybody great questions, great participation. I hope you all enjoyed the material and benefited from it. As Heidi mentioned in about, she said a few days, I know in about a week or two the transcript will be up but in the meantime she will get the audio archived recording of this presentation and the slides so that will be on the PRIDE website. You have all of our contact information if you need to get in touch with us. I want to give a special thanks to Heidi as always in the HSR&D Team for helping us out and special thanks to my colleagues Lucinda Shouse and Theresa Straut and Dr. Karen Jeans for reviewing the slides and participating in the Q&A sessions and just really helping make this training hopefully relevant and beneficial and applicable to you all.

As always a brief evaluation is going to pop up once you exit, it only consists of about four to six questions, please take a moment to answer the questions as we really rely on it to get feedback from you all on the training that we conducted, the strengths, the weaknesses as well as the importance of this training to you as ORD continues to evaluate its services. Thanks again everyone and have a wonderful evening.