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Note: Text has been edited for clarity.

Contents: **Transcript**
 Additional Questions [pending]

Implementing Guidance on Significant Changes: One Institution's Experience

Speakers:

Patricia Brown, VMD, MS, OLAW, NIH

Elaine Kim, BS, CPIA, Colorado State University

Lon Kendall, DVM, PhD, DAACLAM, Colorado State University

Susan Silk, MS, NIH, OLAW, NIH

Swapna Mohan, DVM, PhD, OLAW, NIH

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Slide 1 (Implementing Guidance on Significant Changes)

>> *Swapna:* Today is September 8th, 2016. I am Dr. Swapna Mohan, from the Division of Policy and Education, OLAW. And it is my pleasure to welcome Dr. Lon Kendall and Elaine Kim from Colorado State University to [OLAW Online Seminars](#) to present Implementation of OLAW Guidance on Significant Changes to Animal Activities. They will talk about how they implemented Veterinary Verification and Consultation, also known as VVC, at their institution.

We have selected them because they are using the VVC guidance effectively for their research program. You are free to use ideas presented in their discussion, but you are not required to do so. Implementation of OLAW's significant change guidance is optional. The only requirement, if you choose to implement the guidance, is that it be done in compliance with OLAW's guidance. OLAW's expectations are that any institution that chooses to use this guidance will tailor it to support their own research and animal use program. In today's webinar we will hear about how Colorado State did just that.

Dr. Kendall received his DVM from Colorado State University. He then completed the Comparative Medicine Training Program, and a PhD in Veterinary Pathobiology at the University of Missouri. He is currently the Attending Veterinarian and Director of Laboratory Animal Resources at Colorado State, where he is the director of the residency training program, has an active research program studying analgesic efficacy in rodent models, and serves on the IACUC.

Elaine Kim earned her bachelor's degree in biology at UC Berkeley, and recently earned her CPIA credential. Elaine is the Senior IACUC Coordinator at Colorado State. She has been an IACUC Coordinator since 2010 and manages protocol review, works with PIs and the IACUC on institutional policies and guidelines, and communicates with external funding agencies and collaborators.

And now it's my pleasure to welcome Elaine and Lon to the OLAW Online Seminar and share their experience with the implementation of significant changes.

Slide 2 (Objectives)

>>Elaine: Thank you Swapna.

Hello everyone. We are happy to be here to share with you what we have done at CSU to implement the Guidance on Significant Changes to Animal Activities, [NOT-OD-14-126](#). And during this webinar, we will reference this document as the Guidance or the Notice. First, let's go over the objectives of this webinar they are as follows: we will review the Guidance document from OLAW. In particular, we will review the definition of a significant change, as well as outline key components of a functional VVC. We will provide institutional and programmatic context for CSU's implementation of the Guidance, NOT-OD-14-126. We will outline how CSU IACUC chose to implement VVC at our institution, including an overview of our VVC policies.

Slide 3 (Objectives cont.)

We will also examine CSU's VVC review process, certain aspects of our VVC policies, and a comparison of protocol review metrics for amendments that go through Classic IACUC Review vs. VVC Review. By Classic IACUC Review, I mean DMR [designated member review] or FCR [full committee review]. We will review the revisions that the IACUC approved for our VVC policies and the basis of those changes. And then finally, we will apply VVC in specific situations using scenarios.

Slide 4 (NOT-OD-14-126: Definition of a Significant Change)

So now let's move to the Notice. Specifically, let's define what is a significant change? As it states in the Guidance, significant changes include changes that have, or have the potential to have, a negative impact on animal welfare. In addition, some activities that may not have a direct impact on animal welfare are also considered to be significant.

Slide 5 (NOT-OD-14-126: Paragraph 1)

We're going to go through the Notice paragraph by paragraph. This is paragraph 1. This is where OLAW defines the types of significant changes that must be reviewed by the IACUC via methods outlined in the PHS Policy [[PHS Policy on Humane Care and Use of Laboratory Animals](#)], what we are referring to as Classic IACUC Review, which is DMR or FCR. These significant changes include the following:

- going from nonsurvival to survival surgery;
- changes resulting in greater pain, distress, or degree of invasiveness;

- changes in housing and/or use of animals in a location that is not part of the animal program overseen by the IACUC;
- change in species;
- change in study objectives;
- change in PI; and
- change that impacts personnel safety.

Slide 6 (NOT-OD-14-126: Paragraph 2)

Paragraph 2 goes on and states the specific significant changes that may be handled administratively according to IACUC-reviewed and approved policies in consultation with a veterinarian authorized by the IACUC. These changes include:

- anesthesia, analgesia, sedation, or experimental substances;
- euthanasia to any method approved in the [AVMA Guidelines for the Euthanasia of Animals](#); and
- duration, frequency, type, or number of procedures performed on an animal.

The veterinarian is not conducting DMR, but is serving as a subject matter expert to verify that compliance with the IACUC reviewed and approved policy is appropriate for the animals in this circumstance. Consultation with the veterinarian must be documented. The veterinarian may refer any request to the IACUC for review for any reason and must refer any request that does not meet the parameters of the IACUC-reviewed and proved policies to a Classic IACUC Review.

Slide 7 (NOT-OD-14-126: Paragraph 3)

Paragraph 3 states that a significant change that may be handled administratively according to an existing IACUC-reviewed and approved policy without additional consultation or notification is an increase in previously approved animal numbers.

Slide 8 (NOT-OD-14-126: Paragraph 4)

And finally, paragraph 4 outlines the changes that may be handled administratively without IACUC approved policies, consultations, or notifications. They include:

- correction of [typographical errors];
- correction of grammar;
- contact information updates; and
- change in personnel, other than the PI. When non PI personnel changes are made, there must be an administrative review to ensure that all such personnel are appropriately identified, adequately trained and qualified, enrolled in occupational health and safety programs, and meet other criteria as required by the IACUC.

Slide 9 (Veterinary Verification and Consultation (VVC))

Now let's return to the VVC portion of the Guidance. In this slide we have presented another way to outline the key components of a functional VVC. First you see a veterinarian who is authorized by the IACUC is required. This veterinarian does not have to be the Attending Veterinarian and it can be more than one veterinarian.

Next we have IACUC-reviewed and approved policies; these are also required. Please note that the definition of “policies” provided during this presentation are as defined in the OLAW webinar from August 21st, 2014 on the [Guidance to Significant Changes to Animal Activities](#). Page 4 of the transcript for that webinar states: “We mean guidance documents, standard operating procedures, and drug formularies. These policies need to be reviewed and approved by the IACUC at least once every 3 years.”

Finally, to clarify, VVC is not the same as DMR. Rather, it is an IACUC authorized veterinarian who verifies what the IACUC previously reviewed and approved in their policies.

Slide 10 (Institutional Context: CSU Research)

Next we’re going to go over the institutional context of the research that we do here at CSU. This will help you understand why our IACUC chose to implement a VVC process in addition to why we did it in this particular way. Right now, CSU has over 600 active IACUC protocols, with about 200 different PIs. We have a veterinary school, which includes our Veterinary Teaching Hospital, where our researchers perform veterinary clinical studies. Many of our researchers also perform infectious disease studies, biomedical research, and we also have faculty who perform food and fiber research, as well as teach with [agricultural] animals. Lastly, an increasing realm of research at CSU is work funded by private sponsors that may be FDA regulated.

Slide 11 (Two Policies)

>> *Lon*: When this Notice came out in August of 2014, we knew that we wanted to implement VVC at our institution with the appropriate checks and balances as it was going to help facilitate the research. My staff and I began working on two documents: the first was an overview of our Protocol Review Process. This document outlines the entire protocol review process from pre-review, full committee review, designated member review, annual review, and we updated it to include a section on VVC and administrative review.

The other document that we put together was a Performance of Repeat Procedures and these were to outline what procedures can be changed under VVC. The IACUC office and I discussed how documentation of VVC would occur and how the authorized veterinarians would be able to confirm their verification and consultation. The IACUC discussed these documents in the administrative process in October 2014 and voted to approve.

We’ve provided copies of our policies, which are available in the [supplemental material](#) to the webinar and under the handouts section on the bar [of the webinar control panel].

Slide 12 (Implementation of NOT-OD-14-126 at CSU)

Our initial policies included all 3 options outlined in the Notice: changes in drugs, change in euthanasia methods, and change in procedures. For the drugs, we created guidance

documents and referenced formularies for anesthesia, analgesics, and sedatives for the species we commonly use. Our policy stated similar to what the guidance said that any AVMA approved method of euthanasia was acceptable for VVC approval. And then we identified through the Performance of Repeat Procedures policy the types of procedural changes that could be reviewed by VVC.

For example, the blood collection site and volume, routes of administration and volumes, and dosages. And we used a reference from Diehl in the *Journal of Applied Toxicology*, which is a pretty good reference that provides maximum volumes of administration and withdrawal of research animals. [Diehl et al., *J Applied Toxicology*, 21:15-23, 2001]

And we also included a number of procedures that could be performed on animals, excluding surgeries contingent upon them not exceeding IACUC guidelines, for example, the number of cystocentesis or arthrocentesis that could be performed.

Slide 13 (VVC Review Process)

When amendments are submitted for review, we look at them to see if they meet the criteria outlined in our VVC policies. If the amendment falls into one of the categories under VVC, then it gets assigned in our online protocol system for VVC Review. We verify the change is consistent with the policies, and document which sections within the verification is submitted through the online program. And then the IACUC office processes the amendment approval.

If I or the other vets don't feel that the amendment falls under the VVC process, even though it was assigned to VVC, then we leave a comment stating that it needs to be sent out for traditional IACUC review and usually provide a rationale for that. Then the IACUC office routes amendment for IACUC review in the protocol system.

If we ever have any questions about whether or not an amendment should go to VVC or not, then it goes to IACUC review. As an IACUC member, I have a good understanding of the policies and what the IACUC would want to review even if it is submitted via VVC. And if I identify one of those during the review process, then I will have it go back to the IACUC for review.

Slide 14 (VVC Review Process cont.)

As we progressed through implementation of VVC at our institution, we recognized that additional amendments could be handled by VVC Review. And to better serve our researchers, we evaluated ways to expand the VVC and administrative review of amendments based on OLAW's Guidance.

Slide 15 (Additional Considerations)

These changes resulted in modifications of our two policies which were approved by the IACUC. For example, we included additional mouse strains or vendors, as changes that could be done by VVC; or changes in the final disposition of the animal, including transfer

to other protocols, as long as the animals didn't undergo additional painful, distressful, or invasive procedures.

Slide 16 (Additional Considerations cont.)

Additional revisions also included some other procedures that we started to see more amendments for. So we included nasal swabs, buccal swabs, fecal collections in our Performance of Repeat Procedures document for the duration, frequency, and types of those procedures that could be conducted; the number of procedures as long as there was no increase in the pain, distress, or invasiveness; and we updated our reference material.

We also added change in locations to the administrative review process, allowing the IACUC office to approve a change in housing location as long as it was part of the IACUC reviewed current housing locations.

Slide 17 (VVC Review Documentation)

>>Elaine: Once it is determined that an amendment may undergo VVC Review, and the veterinarian submits their review, this is how we document the VVC Review in our online protocol system.

The veterinarian, in our case it is the AV or his delegate, submits their review online and includes their rationale in their review, usually by citing the section of our VVC policy that it falls under. Then the IACUC office includes this rationale in the monthly IACUC meeting minutes where we list all protocol actions since the last monthly meeting. And as we have stated previously, if there is any question as to whether the amendment should go to VVC Review or not, it gets sent to Classic IACUC Review.

Slide 18 (Communication of VVC implementation)

Here at CSU, we wanted to make sure that our researchers knew what the IACUC was doing to facilitate their research. Therefore we took advantage of the following venues available to us: Quarterly Lab Liaison meetings where Laboratory Animal Resources, the IACUC office, and PIs, including their research associates and lab personnel performing the animal work, could come ask us questions, learn about Laboratory Animal Resources, and learn about what Laboratory Animal Resources and the IACUC were doing for them, as well as learn about their research.

The IACUC office also provided short Q&A's at departmental faculty meetings. And the IACUC office and the AV continued to educate our PIs with one-on-one communications, whether it was through email, phone, or in person.

Slide 19 (CSU Protocol Metrics)

To show you how some of our amendment review turnaround times for 2016 have looked so far, we have DMR or FCR amendments currently have an average turnaround of about 24 days. While VVC amendments currently have an average turnaround of about 4.5 days. VVC amendments make up about 19% of our total amendments submitted.

In comparison to 2015, January to December: DMR or FCR amendments had an average turnaround of about 26 days. And VVC amendments had an average turnaround of about 6 days. They made up about 18% of our total amendments submitted.

So you can see that we have improved on both paths of amendment review in terms of turnaround time, without sacrificing the quality of the review, and the percentage of amendments that qualify for VVC has stayed about the same.

Slide 20 (Scenario #1)

>>Lon: At this time, we will apply VVC in specific situations using scenarios. And I'd also like to point out, if you have any questions please submit them at this time and we'll be able to review them following these scenarios. So the first scenario that we have is an investigator wants to expand the dose range of ketamine/xylazine anesthesia that they use in their approved protocol.

Slide 21 (Scenario #1: Result)

In this situation, veterinary verification is acceptable if the range in the reference formularies mentioned in the protocol review process policies – if it's listed in there. If the PI's requested a dose range outside of what is in those references, then the amendment would need to go to IACUC review. I'll also add on to this if the PI wanted to change their anesthetic to something that was within the policy, as long as it stated in the policy that the VVC could review that, that could be reviewed by VVC as well.

Slide 22 (Scenario #2)

In the second scenario, the PI is approved to euthanize their rats by cervical dislocation while under isoflurane anesthesia. They would like to amend their protocol to include euthanasia by exsanguination while under anesthesia.

Slide 23 (Scenario #2: Result)

In this situation, exsanguination under anesthesia is an AVMA approved method of euthanasia and as stated in our policy for VVC Review, we can modify euthanasia methods as long as they are in agreement with the AVMA guidelines. So this was acceptable for VVC Review.

Slide 24 (Scenario #3)

In scenario 3, the PI has euthanasia followed by tissue collection procedure included on their protocol. They want to amend it so that they can collect the tissue while the animal is under anesthesia and still alive, then euthanize after tissue collection.

Slide 25 (Scenario #3: Result)

In this instance, the investigators want to add an additional procedure. Additional procedures cannot be reviewed by VVC per the OLAW Guidance and therefore this is referred to IACUC review.

Slide 26 (Scenario #4)

In the 4th scenario, we have a PI that has blood collection in dogs approved at 1, 12, and 24 hours after test article administration. They would like to amend the protocol to include additional blood collection time points at 4, 16, and 20 hours.

Slide 27 (Scenario #4: Result)

At CSU this example would be eligible for VVC Review. Our Performance of Repeat Procedures policy outlines the volume of blood that can be collected in a 24 hour time frame, based on the blood volume of the animal. So as long as the total volume of the blood collected does not exceed the guidelines, then they can be reviewed by VVC. If it exceeds them, then it would need to go through Classic IACUC Review.

I think I'll also add on the previous scenario that if they were wanting to change blood site collection, as long as that is highlighted in our VVC policies, then they could do that. So if they wanted to change from cephalic to jugular vein collection then that would also be eligible for VVC Review.

Slide 28 (Scenario #5)

In scenario 5, a protocol is approved to perform cystocentesis in cats to evaluate biomarkers. The PI would now like to amend their protocol to include blood collection at 1, 6, and 12 hours to evaluate biomarkers in the blood.

Slide 29 (Scenario #5: Result)

Now, although blood collection guidelines are outlined in our Performance of Repeat Procedures policy, since this is a new procedure to the protocol, it's not eligible for VVC Review and must be submitted to the IACUC.

Slide 30 (Scenario #6)

And the last one, we have a PI protocol involves placing a vertebral disk fusion device in sheep followed by 8 week recovery period, then euthanasia. They would like to transfer the animal to another IACUC approved protocol for a terminal surgical procedure.

Slide 31 (Scenario #6: Result)

This is not specifically addressed in the OLAW Guidance; however, the CSU IACUC policy on VVC Review has included the disposition of animals as a component of the VVC Review process. In this example, since the animal is being transferred to a protocol that is not more painful, distressful, or invasive than the original approval, this would be eligible for VVC Review. However, if the animal was going to be transferred to another protocol to undergo an additional survival surgical procedure, this would require review by the IACUC.

>> *Swapna*: Thank you, Lon. We have some questions that we received prior to the broadcast, so we will address those now.

Slide 32 (Question #1)

Our first question is for both OLAW and CSU: My institution is concerned about increasing the likelihood of getting into non-compliant situations with VVC implementation. The potential risks appear to outweigh the benefits. Does OLAW have comments about this? How did CSU handle this issue and what did their IACUC say?

>>*Lon*: I think from the CSU perspective, we really studied the Guidance document and when we put together our policies and had that pretty firmed up in what we thought met the Guidance, we then contacted OLAW to see if we were in line with what they were thinking. And they were in agreement with that. And we've also heard them state at several conferences that they're not going to punish us for trying to do this the right way as long as we're not trying to do it with some sort of ill intent. So we took their word at that. And USDA has told us similar type of guidance. We felt that given our policies and what the IACUC reviewed and the Guidance, that what we were doing was in line with the Guidance then it really helps facilitate our research.

>>*Pat*: Hi, this is Pat Brown from OLAW and I'm going to confirm what Lon just said. It was OLAW's and USDA's intent on issuing the Guidance to give IACUCs flexibility in using their professional judgement to develop policies for handling some significant changes and also to reduce the burden on the investigators and the committee. Noncompliance should not be a concern because during the renewal of an institution's Assurance, OLAW Assurance officers will assist and guide the process. If you have a specific question regarding implementation of IACUC policies for VVC, we would be happy to help you address them.

As we have seen from Elaine's and Lon's example, they implemented VVC in steps focusing on policies for changes to anesthesia and analgesia using drug formularies. They then focused on changes to routine procedures, such as blood collections. An institution could do something similar by starting with a procedure that is very helpful to your institution's research program, and then implementing VVC step-by-step.

Slide 33 (Question #2)

>>*Swapna*: Thank you, Pat and Lon. Our next question is for Elaine. How has CSU navigated the documentation requirements of VVC implementation with their online protocol system?

>>*Elaine*: Here, at CSU because we already use an online protocol system, we chose to include VVC Review in that online protocol review process. This means that we were constrained by the limitations of our program, including the language the system uses during protocol review. But the language we use to document the VVC Review and the notes that we attach to the protocol are all taken from our policies and from the Guidance. We wanted to make sure that the administrative end of the VVC process was not overly burdensome for the IACUC office and also for our veterinarians, and by integrating it into our existing system it has helped to create a smooth transition.

Slide 34 (Question #3)

>>*Swapna*: Thank you, Elaine. This next question is about the process of VVC. Could you please explain how the VVC process is different from veterinary care? Or are they the same thing?

>>*Lon*: Did Pat want to take that?

>>*Pat*: I'm sorry, I was looking at some more questions coming in here. So when it comes to veterinary care, the veterinarian rules, basically. When an animal unexpectedly needs immediate clinical care, that is the veterinarian's duty and responsibility to provide that. VVC would then become applicable for other animals that were going to be used in the same experiment or listed on the protocol for future activities as that will need to be addressed as a change to the protocol. So the PI would be expected to submit an amendment and VVC would then handle that request. Of course, as long as the IACUC has a VVC policy that covers that change. The change must be documented and associated with the protocol according to the IACUC's recordkeeping process.

>>*Elaine*: And here at CSU, our IACUC office often gets phone calls from Lon or his delegate or from the PI themselves saying they were told by the AV to call us to submit an amendment for VVC. And then at that point, we can help them submit the amendment online, and depending on the time sensitivity of the situation, we just assess what needs to be done and the timeline.

Slide 35 (Questions?)

>>*Swapna*: Thank you, Elaine. We have some really good questions coming in from the community. I'll start reading those out.

[Question 4] Our first one is for Pat. It's about 1.c in the Guidance, in housing and/or use of animals in a location that is not part of the animal program overseen by the IACUC. Our IACUC would like clarification of whether any change in housing, that is cage type or from one IACUC approved room to another, is significant or whether this just means that changing the housing from a program overseen by the IACUC to one not overseen by the IACUC is significant?

>>*Pat*: We are focused on when an investigator decides to take animals outside of an area that the IACUC is already aware of. It's the location issue here. We're not concerned about moving animals from one room in a facility to another or using one different cage type to another. This is really a significant change would be when your investigator is taking the animals to some previously unapproved location in the greater institution.

>>*Elaine*: And if I could just add here too that when we get these types of VVC requests, we do look at the bigger picture, not room numbers. For example, I said we had infectious disease work going on here, so we have bio safety [level] 2 and 3 here for animal

housing. So basically that's one aspect that we can look at. We also look at what gets inspected during our semiannual facility inspections. Is it included on that list? Basically if it goes from one building to another, which is typically what we see, that is the level of scrutiny where we are not [looking at] the room numbers, but the buildings.

>>*Swapna*: Thank you, Elaine and Pat. [Question 5] The next question we have is about euthanasia methods. Did the euthanasia methods covered under the VVC include only acceptable methods in the AVMA guidelines or are also methods listed as acceptable with conditions?

>>*Pat*: The VVC can include acceptable methods or acceptable with conditions methods, as long as those conditions are being met.

>>*Elaine*: And if I could comment here as well, depending on the level of comfort your IACUC has, for example, here at CSU with our culture of compliance we knew that our IACUC would be most comfortable following the Guidance language, so we are following the AVMA euthanasia guidelines in our VVC Review process. If something should shift or if our wildlife research community asks us to consider a revision, then we'll take it to the IACUC for review.

>>*Swapna*: Thank you. Elaine, the next question [Question 6] is also for you. It's asking how you address this issue at Colorado State. If increases in animal numbers can be approved administratively and in accordance with IACUC policies regarding allowable limits, who must ensure that the original rationale for the proposed animal numbers still stands?

>>*Elaine*: That's a good question. In our VVC policy, the increase in animal numbers is limited to within 10% for non USDA regulated animals. Primarily when this comes in for VVC, it's mice or rats, *Mus* or *Rattus*. And my assistant coordinator and I look at the protocol and we do look at the rationale and we also look at the overall project overview to make sure that the additional animal numbers have been incorporated there as well. So we do do a pre-review in a sense on these amendments and at any point during that process if either of us have a concern, we mention it to the AV and we basically do kind of an offline email or phone call conversation. We never feel constrained by the VVC. It's there as an option. And if we feel that there's some other issues that need to be resolved and that the IACUC wants to see, then it gets sent to Classic IACUC Review.

>>*Lon*: And those rationales are typically included in the amendment – in the request to increase the animal numbers. So it's not that the ordering – the people doing the ordering just automatically say okay, you can do 10% more animals that gets approved by VVC first before they can order.

>>Elaine: Yeah. What Lon is mentioning is that our animal ordering system is tied into the protocol approval. If they don't have that protocol approval then they can't order it in our online system.

>>Swapna: Okay. Thank you. [Question 7] Lon or Elaine, could you give some examples of the types of procedures that you make allowable by VVC at your institution?

>>Lon: Yeah. Blood collection is one. We've actually got a number of them. It just depends based on what people were doing at the time. Examples that we have are: oral gavage, the frequency and how much you can give, how often, and in various species; blood collection, sites and volumes of where you can get blood. How much blood you can collect from an individual animal over a given period of time. Injection volumes and the max, for example, the amount – the maximum volume that you can give intraperitoneally or intramuscularly. We do a bit of orthopedic work, so arthrocentesis is pretty common. We have guidance on how often and how much fluid you can collect from a joint. Those are examples of it. And if you go to that Repeat Procedures document, that has them outlined as to what we have included.

>>Pat: And OLAW would like to just comment that it really is going to vary depending on the institution, as Lon has given in this example, on the types of procedures that are typically, routinely done by the investigators where there's already kind of a confidence on what would be the range of how frequently you could do something. And, the experience of the investigator is also a consideration.

>>Swapna: Thank you. [Question 8] Elaine, it stated that the VVC Review is contained in the IACUC meeting minutes. So they're asking that – the VVC Review contained in meeting minutes – are the results of the review? How are these results handled if an IACUC member states they want a committee review of the protocol or what was approved by the VVC?

>>Elaine: Okay. That's a good question. And this has happened before in terms of the IACUC asking: If I see something in the minutes that happened in the past month that I have a question about, when and how can I get this question answered and can the IACUC review it again? So we've made it clear to our IACUC that they have the right as a member to call any protocol to review for any reason. And so if they see that under the amendment section and have a question, and if they still want additional questions answered by the PI after Lon and I fill in the blanks on the review and what the amendment was for, then I'll notify the PI that the IACUC is going to review their recent amendment again.

Since they have the approval in place they can still proceed, but if there is something that the member is asking that's related to the actual procedure itself, then we'll just work with the researcher on that. But definitely if that happened, because that was something that I anticipated happening in the early months of implementation, so that's why it was

so important to make sure the IACUC felt comfortable with the various modes of transparency that we're trying to establish. And so far they've really – this issue hasn't actually come up, and that's I think partly because Lon has a good handle on what our IACUC is comfortable with here at CSU.

>>*Swapna*: [Question 9] And at CSU regarding the turnaround time for amendments, do you send your amendments to FCR?

>>*Elaine*: No, all of our amendments typically get automatically sent out for – what we do here for a DMR determination time period is 3 business days. So they all usually get sent out for that unless we know that it falls under our VVC Review process.

Previously our protocol review turnaround times were less, essentially, but what we also found out was that there were some issues that were not getting resolved during the protocol review process that should have been addressed. To address that, we've implemented some DMR and veterinary pre-review processes. And of course when you do that, it does add some time to the review, but it added a quality review, and the IACUC and the PIs here understood what we needed to do and why [in order] to address the potential risks and the animal welfare issues. That added some time to our overall review, but so far nobody's complained because if they really have a time sensitivity and need something right away, they call us directly and we just work with them on it.

>>*Swapna*: I see. [Question 10] There is a question about your online system that you use. They're asking if it's with one of the commercial systems or it's a custom program that you developed and use only at your institution?

>>*Lon*: It's a commercial product.

>>*Elaine*: Yeah.

>>*Swapna*: I see.

>>*Lon*: They were able to modify it to add the VVC process into the review.

>>*Swapna*: I see. [Question 11] So when you added this did you have to include it as a note in your annual report to OLAW?

>>*Lon*: I'm not sure I understand the question.

>>*Elaine*: Yeah.

>>*Swapna*: So when you started using this process of VVC, did you have to include it in your annual report?

>>*Elaine*: Lon added the VVC Review process to our Assurance language. So I guess you could say he amended it when he submitted the annual report one year.

>>Pat: So that's concurring, yes, that you indicated that you made the change in the next time your annual report came due.

>>Elaine: Yeah.

>>Pat: Okay. And that would be the expectation for an institution. But we also will be – when you're going through your next renewal process, we would expect it also to be described in your Assurance document at that point too. We're kind of playing catch up with some institutions in actually having it documented in their Assurance as they come up for renewal.

>>Swapna: Thank you. [Question 12] Lon, this next question is for you. It's asking when an investigator adds a new strain and the protocol is routed to VVC, does the veterinarian also review the statistical analysis justifying the additional animals or does the IACUC admin review the statistics?

>>Lon: Usually the change in strain is not associated with a change in animal numbers. It's usually a change in strain. If they do add a strain and it doesn't increase their numbers, then the statistical justification holds. If they are increasing their numbers with that additional strain, it's usually justified in their description as to why they need this strain. And the numbers, at least here, typically they follow the same group numbers as what was approved.

>>Elaine: Yeah. Usually when we see that, we clarify and verify that they don't need more animals, they just want to add another strain. And then if they do want to add numbers, like Lon said, we go through our usual review of the information.

>>Swapna: Okay. [Question 13] We have an interesting question about wildlife protocols. It's asking: Have you applied VVC to any wildlife protocols? And if so, what IACUC policies have been useful for that?

>>Elaine: Have we done that?

>>Lon: I don't think we have.

>>Elaine: No. I don't think the circumstances have lined up quite right to use VVC in a wildlife situation. And of course we have our wildlife researchers who are in the field doing work in the field and they don't bring the animals back versus collecting animals and bringing them back here to house. So none comes to mind.

>>Lon: I can see it being applied to the wildlife situation if they were needing to change a euthanasia method or to change a blood collection site, something like that would fall under our VVC process.

>>*Elaine*: From what I remember for National Park Service, if a researcher calls them and says I'm in the field and I have a question, I think I need to change the anesthesia I'm using or – I could imagine this being useful in that context because then the entire IACUC doesn't have to meet. It could just be the veterinarian that they've chosen to do VVC.

>>*Swapna*: Right. [Question 14] The next question is asking Lon's comment on something. So this person says: I do not agree with the VVC Review for increasing number of blood collections, only based on blood volume, since theoretically you can collect 50 milliliter from a dog. So if you collected one ml per time point, CSU would allow the dog to be bled 50 times in a 24 hour period. So this would be excessive in an uncatheterized animal. Do you have any comments on that?

>>*Lon*: We definitely take that into consideration, but it's the way our policy is written. The way it's written, we could review that and approve by VVC. I think that's up to the IACUC to decide. Obviously that's also one of the situations where we would say that's a bit of an excessive number without a catheter and would suggest a catheter or send it back to the IACUC.

>>*Elaine*: Yeah. Again, here's where our culture of compliance steps in. Even though technically it might be allowable by our policies, because we're trying to facilitate research, Lon knows our committee and he knows that we have eyes on this, and we know about – he does work like this, so he knows the realities of doing something like this in an uncatheterized animal. I feel that our documents have, I guess you could say, a flexible range, but it is within a realistic context that is unique to us here at CSU.

>>*Swapna*: Great. So I guess it's at the discretion of the vet then?

>>*Lon*: And the IACUC. I mean, your IACUC has to review those policies. And I think there's always the extremes and I think you've got to take those into consideration when you're making these decisions.

>>*Swapna*: Yes. So the next question is for Pat. [Question 15] This person is asking: Does the USDA accept this policy of VVC or administrative approval?

>>*Pat*: Yes. This guidance was developed in concert with USDA and they support it and it is described in their – the APHIS Inspection Guide does talk about the significant changes guidance.

>>*Swapna*: Thank you. [Question 16] So the next question is to CSU. This person says: Four and a half days seems long. At our institution we allow the change to be implemented immediately following the consultation with the veterinarian. Do you require the study team to wait until the paperwork changes to the electronic protocol and is finished to implement the changes?

>>Elaine: I should have pointed out earlier that those are average numbers. There are some people who submit and their amendment can go to VVC, but they're not in a rush. And those will take a couple of weeks based on the circumstances. But there are lots of cases where they call and I help the PI submit it online and the approval is done immediately after talking with Lon and he submits his review.

I should point out that is an average because it ranges from zero days, like within the hour, to 20 days or something. So that was the number that was generated. And basically based on our program here and what the IACUC is comfortable with in terms of documentation, we always include it in the online system. That is how we document it. If the PI – they know what is possible with our IACUC – if they want something within the hour, they know it's a slim to none depending on the type of change. If it's kind of complicated, they know that maybe I can get it done in a day or two. We kind of have set the limits on what's allowable and what's reasonable here. I hope that answered the question.

>>Swapna: Do you make them wait until the electronic protocol goes through before they implement the changes?

>>Elaine: Yeah. And basically everyone here seems to have email on their phone, and the online system sends them an auto generated approval email so they know right away. If they're waiting at the hospital and then they see it on their phone, then they proceed.

>>Swapna: I see. [Question 17] The next question is for Lon. If a request to add additional blood sampling requires additional sedation in non-human primates, would that still fit within the VVC at your institution?

>>Lon: We don't have non-human primates, so it's a difficult example for me to follow.

>>Swapna: Any other animal, let's say?

>>Lon: Yeah. If the sedation – I think I'd have to answer it by that if the sedation isn't in the original protocol – it might be – it would probably be considered an additional procedure and would need to go to IACUC review.

>>Swapna: I see. [Question 18] The next question is for Pat. Can you give us an estimate of the OLAW facilities that use VVC?

>>Pat: I can't give you an answer. We have not been capturing that information as we do our reviews and renewals of Assurances, but we are encouraged because there seems to be more interest when we have been presenting VVC and having questions come into us. So it's our expectation that there are more and more programs that are becoming comfortable with it and using it.

>>*Swapna*: I see, thank you. [Question 19] The next question is asking about the scenarios we presented. It's asking about scenario 6. Let me go back to that. So it's saying: How is scenario 6 different from scenario 3, where 6 is ok for VVC and 3 is not ok for VVC? Six would be a PI protocol involves placing vertebral disk fusion device followed by 8 week recovery, then euthanasia. And then, they would like to transfer to another protocol for terminal surgical procedure. Let me just see what 3 is.

>>*Elaine*: Three was extending the anesthesia, I believe.

>>*Swapna*: Euthanasia followed by tissue collection and they want to amend it to tissue collection while the animal is alive.

>>*Lon*: The difference that I see is that in scenario 3, you're working on the individual animal and you're adding a procedure to add anesthesia so that you can collect the tissues. And in the other scenario [6], the procedures have all been approved. The procedure on this sheep in the original protocol was approved and the procedure in the second protocol that you want to transfer it to was approved. So all of the procedures are approved in 6, you're just transferring the animal. And in scenario 3, you're adding a procedure.

>>*Elaine*: Yeah. And if you also think about the increase in pain, distress or invasiveness, I believe for scenario 3 there was an increase in distress, right, because of the extended anesthesia?

>>*Lon*: Increase in invasiveness.

>>*Elaine*: Yeah. That's why that one went to Classic IACUC Review.

>>*Silk*: Hi, everyone. This is Susan Silk. We have reached the end of our time, however really good questions are continuing to come in. So if Lon and Elaine are willing, we're going to run long. We understand that some of you will have to leave because the hour is over, but we are going to go forward with these terrific questions. Lon and Elaine, is that okay?

>>*Lon*: Yeah.

>>*Elaine*: That sounds good.

>>*Silk*: Thanks, terrific. Bye, everybody.

>>*Swapna*: [Question 20] The next question is for Pat and it's asking about the example given for adding blood collection time points. I have heard conflicting guidance on this topic. Couldn't this be considered more painful or distressful to the animal? Similarly any change that could potentially increase the number of injections or dose administrations that an animal may undergo?

>>Pat: Here we're looking at the policy that the IACUC has in place and the expectation is that the same individual that was approved to collect the blood once is going to be using that same skill set to collect the blood again. It should not be considered a more painful or distressful procedure to the animal. And the same would go along with injections or dose administrations, that if it's already been approved as an activity and you're just changing the number of times it's occurring, as long as it meets the parameters the IACUC has set up for that particular procedure, we would say it was meeting the intent of our guidance.

>>Swapna: I want to note here that our captioner may not be able to stay beyond time. So if this is not captioned, you can still see the [questions and the answers] in the transcript when we post it on the OLAW website.

>>Swapna: Lon, you can answer this next question [Question 21]: If the Chair is a vet but not the attending vet, can the attending vet designate him as someone who can perform VVC?

>>Lon: I believe that the Guidance says that any veterinarian that the IACUC approves. So I think it would be up to your IACUC to make that decision.

>>Pat: And OLAW would agree.

>>Swapna: Thank you. The next question [Question 22] is for OLAW: Wouldn't an additional procedure be covered under the language "duration, frequency, type, or number of procedures performed on an animal" provided it did not change the level of distress or pain?

>>Pat: No, because what we're saying is if you're adding a procedure, that is not the same as changing a procedure that's already been approved on that particular protocol. The duration, frequency, type of a procedure that's already approved on the protocol is different than adding a new procedure to the protocol. So it's not the same and it does not meet the list of topics that's available for VVC consideration.

>>Elaine: And actually, if I could make a note here, thinking about that last scenario where the animal is being transferred from one protocol to another. There the VVC Review is the disposition of the animal in transferring it. But also, it has different procedures on each one that have already been approved. So that's how I think of it. It's not a new procedure but, like Pat said, it's already been approved but the animal is being moved to that protocol.

>>Swapna: Thank you. The next question [Question 23] is also for Pat, this person is asking: Do I understand correctly that the change in route of administration of an experimental substance would be ok for VVC approval whereas a change in the actual substance given would need IACUC approval?

>>Pat: We have recognized that there are some institutions that have IACUC policies that cover a collection of substances that are all within the same type of substances, for example some chemotherapeutic agents or whatever. And it's our understanding that the IACUC could have a policy that would allow a change within that group as long as it meets the parameters that the IACUC has established. So that's an example where you could potentially change the substance within a certain type of substance. And it's similar to the anesthesia/analgesia examples too where there's a formulary of anesthetics that are available with a certain dosage range that the IACUC has approved as being acceptable for a particular species; and if an investigator wants to change from one to the other, that would also be an example of where that would work.

>>Lon: We've included in our policy changes in vehicles. So if vehicle A for the substance being administered doesn't work and they want to try vehicle B, then that's something our IACUC has said is ok by VVC.

>>Swapna: This word "type" of procedures – we are getting some questions about that. [Question 24] This one is asking: What does change in "type" of procedure mean in paragraph 2 of the Guidance? If you interpret it broadly then it could be anything. So should it be interpreted in a more narrow sense?

>>Pat: Again, this is where we are deferring to the IACUC to come up with what are the procedures that typically happen at their institution that they routinely approve where they have established policies on how frequently you can, say, do a cystocentesis or arthrocentesis. It really is tied to the institution's research focus and it's not OLAW's purview to be getting down to that level of detail about which type of procedure is ok and which isn't. We really want the IACUC to be making their professional judgement on what they consider within a reasonable change that could be handled this way, with appropriate policies in place that define those procedures.

>>Swapna: Does CSU have anything to add?

>>Lon: I guess I would just go back to the new procedure, because I struggled with that as well and got the guidance from OLAW that if it's a new procedure on the protocol that isn't approved then it can't be reviewed by VVC. So we have just kind of accepted that.

>>Elaine: Yeah, I guess for the type of procedure – I remember during discussion at a meeting once, we talked about blood collection and then urine collection. Those are both – you could consider them and label them as fluid collection. So what if your protocol said fluid collection? And then the PI said that they are going to collect blood and urine, and then they want to add saliva or tears. I am just putting that out there in terms of that could be a type of procedure, but that was something that was discussed. Depending on your IACUC, the trust that is there between the veterinarian and the IACUC office, and the IACUC itself, they can have their policy state what parameters need to be met to have it go through VVC Review.

>>*Swapna*: This next question is for Pat. [Question 25] Can an institution have in their VVC policy that the vet can use any current IACUC approved protocol that uses the species and procedures as a reference document? This would only apply if the significant change being considered for VVC involved the same species and procedures that are in the other current IACUC approved protocol.

>>*Pat*: Well, this is again an example where someone is saying they want to add a procedure to another protocol. We are not saying you can add a procedure. You must be changing an existing protocol by modifying what has already been approved by the IACUC regarding that particular procedure. As we have been giving as example, blood collection is a typical procedure that we've seen IACUCs use. Other types of samples that might need to be collected, that type of thing. But to just say "we are now going to add anything we want"; no, that doesn't mean the same thing. When you are adding one procedure to an existing protocol, you're adding a procedure that needs to go through DMR or FCR.

>>*Lon*: Correct me if I'm wrong though, but you could use those parameters within your policy that you develop for VVC. So for example, you could list in your policy that references other previously approved protocols to make those changes. So for example, if I'm collecting blood at multiple time points that's been approved in one protocol, and another protocol has blood collection and they just want to increase the time points. If your policy stated other IACUC protocols as reference material, that could be done by VVC, as long as it's not adding a new procedure.

>>*Pat*: Right, so in essence, it's a standard operating procedure [SOP] or policy that the IACUC has approved and said "ok, here's the way we recommend that this particular thing happen". Then yes, based on a particular lab's multi-year experience doing this particular thing, then it would become a standard operating procedure that the committee has approved, absolutely. And then it could of course be referenced in future protocols as an SOP.

>>*Swapna*: Thank you. Lon, this is going back to something you'd addressed earlier, but I think a lot of people are having this question [Question 26] about the change in type of procedures and how it is distinct from a new procedure, which CSU does not allow to go through the VVC process. How is change in type of procedure distinct from a new procedure?

>>*Lon*: The change in type of procedures, usually relates to something within that Repeat Performance document. For example, if they are changing the amount of blood that they are collecting or if they are changing the frequency of blood collection, changing the frequency of joint fluid collection, changing the route of substance administration, those are all outlined in our Repeat Procedures document. As long as they have that procedure described and approved in their protocol, then how they go about doing it and the details

of it are what we look at by VVC. We don't approve anything by VVC that doesn't already have a baseline in the protocol.

>>*Swapna*: Thank you. The next question is about increase in animal numbers. [Question 27] If a PI requests an increase in 10% of animal numbers and it's approved by VVC, can the PI request another increase in 10% or does that second request have to go to committee review?

>>*Elaine*: Well, I'd say if, hold on let me think. Our initial response would be to look at this and see that it happened recently and we'd ask them "What are your plans? Are you finding that you are needing to do an experiment"? Basically, get more information because we don't want to abuse the process and so basically, find out from the PI "Do you anticipate needing another 10% next month?" If so, we recommend handling this another way. Lon, do you have anything to add?

>>*Lon*: I would agree with that. And most of our animal number increases by 10% is actually part of the administrative review process. So from the IACUC administrator's side, if they see that change then they would start to question, as Elaine indicated, and start to go through an amendment process.

>>*Swapna*: We have so many good questions today but we don't have time to answer them all. The other questions that are coming in now, we will collect those questions and add them to the webinar transcript and provide written answers. At this point I'd like to thank everyone who sent in questions and are continuing to send in more questions. And these questions and their answers, you can access them at the OLAW webinars webpage. You can send in more questions by email [olawdpe@mail.nih.gov]. Our speakers will address them and the answers will be posted with webinar transcript.

Slide 36 (Next Webinar)

Before we go, I wanted to point out that the next OLAW Online Seminar will be on December 15 on Self Evaluation and Reporting: Always let the *Guide* be your Conscience. Thank you to Dr. Lon Kendall and Elaine Kim for a wonderful talk. And I thank all of you for participating in our webinar, and with special thanks to those who sent in questions. Good-bye and thank you for joining us today.

Additional Submitted Questions Not Addressed During the Webinar

[pending]

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