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Note: Text has been edited for clarity.

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

The 2016 Vertebrate Animals Section, Grants Policy, and Congruence

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Slides 1-2 (The 2016 Vertebrate Animals Section, Grants Policy, and Congruence)
>>*Silk:* Today is March 10, 2016. I am Susan Silk, Director of the OLAW Division of Policy and Education. It is my pleasure to introduce Dr. Swapna Mohan, the newest member of my Division. Swapna and I will be sharing the moderator role for today's webinar. It is also a pleasure to welcome Sam Varghese who will join OLAW Director Pat Brown in presenting the OLAW Online Seminar, **The 2016 Vertebrate Animals Section, Grants Policy, and Congruence.**

Dr. Samuel Varghese is the Director of the IACUC and the Institutional Biosafety Committee in the Office of Research at the University of Massachusetts Medical School. Sam earned his BS degree in chemistry, Master's degree in organic chemistry, and PhD in biochemistry at Rutgers University. He completed postdoctoral training in cellular and molecular biology and molecular endocrinology at Harvard Medical School and Massachusetts General Hospital. He joins us today to share his wisdom about congruence and to explain how they conduct congruence reviews at U Mass Medical School. OLAW Director, Dr. Pat Brown, will start us off with a review and updates about The 2016 Vertebrate Animals Section, Grants Policy, and Congruence.

Slide 3 (Webinar Objectives)
>>*Brown:* Hi Everyone. Thank you for joining us today. Sam and I have designed and organized our presentation to meet the 4 objectives listed on your screen. I'll remind you of each objective as we begin that section.

Best practices are not required. Sam will share best practices used at his institution and you can determine if they might be helpful at your institution. This is important, so I will

repeat it. The best practices that Sam will provide to you are examples of how U Mass Medical School fulfills the requirement for congruence between grants and IACUC protocols. You may use these methods or other methods that you devise to meet the requirement for congruence.

Slide 4 (Webinar Objective 1)
During the first part of my talk, I will explain why it is important and necessary to have congruence between the grant that funds an experiment and the approved IACUC protocol that verifies that the experiment has been reviewed and approved by the IACUC.

Slide 5 (What is Congruence?)
What is congruence? Wikipedia tells us that, "Congruence is the state achieved by coming together, the state of agreement. Congruence, as opposed to equivalence or approximation, is a relation which implies a kind of equivalence, though not complete equivalence." Each institution should determine the extent of agreement between grant and protocols that they require for congruence. For our discussion today, congruence is agreement between the animal activities, as described in a grant application, and the animal activities reviewed and approved by the IACUC.

Slide 6 (Why is Congruence Required?)
An institution must meet the terms and conditions of NIH grants policy to receive an NIH grant. The NIH Grants Policy Statement [NIH GPS Part II, A, 4.1.1.2] provides the policy requirements that make up those terms and conditions. Compliance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals [PHS Policy] is one of the terms and conditions of the Grants Policy Statement. More than just a set of rules, the Grants Policy Statement defines contractual and legal obligations between the grantee institution and NIH. If an institution accepts Public Health Service funds and fails to meet the terms and conditions, there can be fiscal, civil, and possibly criminal penalties.

Slide 7 (Why is Congruence a Requirement?)
Why is congruence a requirement? The NIH Grants Policy Statement requires that grantee organizations establish appropriate policies and procedures to ensure the humane care and use of animals. The NIH Grants Policy Statement also states that it is an institutional responsibility to ensure that the research described in the application is congruent with any corresponding protocols approved by the IACUC.

Here is why congruence is important. During peer review, the scientific review group, also called a study section, evaluates the scientific merit of grant applications to determine the most promising basic or applied research for NIH to fund. By accepting the grant award, the institution agrees to conduct the research that was described in the application. When the researcher writes his or her IACUC protocol they provide a detailed description of the animal activities. In addition to providing a way for the IACUC

to ensure humane animal care and use, congruence review enables the institution to keep its promise to NIH that the research being conducted in their institution is the same research that NIH determined to fund.

The PHS Policy and the NIH Grants Policy work together to ensure that public funds are used to promote the highest level of scientific integrity, public accountability, and social responsibility as reflected in humane animal care and use in the conduct of science.

Slide 8 (When May Congruence Be Determined?)
When may congruence be determined? Any time before the institution receives the money to conduct the animal activities. To meet NIH Grants Policy and PHS Policy requirements, congruence must be determined prior to grant award. Keep in mind, irrespective of when congruence is determined, the signature of the Authorized Organization Representative (or AOR) on the application indicates the organization's intent to comply with the laws, regulations, and policies to which the grant is subject.

The AOR is also attesting to the fact that the information contained in the application is true and complete and conforms with federal requirements and the organization's own policies and requirements. The signature block makes it very clear that there are potential civil and criminal penalties for submitting false statements.

Slide 9 (Webinar Objective 2)
In October 2015, NIH released an update to the Vertebrate Animals Section [VAS] of grant application forms [NOT-OD-16-006] for applications due on or after January 25, 2016. During the next part of my talk, I will explain the changes that were made to the VAS and discuss the impact of those changes on the requirements that we looked at a few moments ago.

Slide 10 (Why Change 2016 Grant Application?)
If live vertebrate animals are to be used, NIH requires that certain criteria are addressed in the Vertebrate Animals Section of the application. Changes in the 2016 applications were made to remove redundancy with IACUC review while still meeting the requirements of the Public Health Service Policy. The changes were also made to simplify the Vertebrate Animals Section criteria and reduce burden on applicants.

Slide 11 (2016 Grant Application Changes)
What were the changes that were made? The justification for the number of animals is now described in the Research Strategy Section of the application as part of the experimental design. This change was made due to new NIH grant application requirements concerning rigor and reproducibility. Applicants must state only the total number of animals proposed in the Vertebrate Animals Section. A description of veterinary care is no longer required in the Vertebrate Animals Section as this is not required by the PHS Policy and is redundant to IACUC review.

Also, only if the euthanasia method is not an AVMA Guidelines [American Veterinary Medical Association Guidelines for the Euthanasia of Animals] method, must the PI describe the method and provide a scientific justification. NIH expects that more than 90% of applications will propose methods consistent with the AVMA Guidelines. Beginning with applications due on or after May 25, 2016, the euthanasia criteria will be addressed by a series of Yes or No questions on the Cover Page Supplement Form and this will further reduce the burden to applicants and to congruence reviewers. This change is being made to meet the intent of the PHS Policy but in a streamlined manner. [For more information, see FAQs on Forms Updates 2016.]

Slide 12 (2016 PHS 398 Section 8 Vertebrate Animals)
This slide shows the new language in the application instructions describing the new Vertebrate Animals Section which now has only 3 criteria. As you can see if you were familiar with the previous VAS 5 points, many of the criteria are similar to the 5 points or ask for less information. We in OLAW think that this will make congruence review easier as there is less overlap between the IACUC protocol and the VAS, where inconsistencies could arise. [For more information, see VAS Worksheet.]

Slide 13 (Webinar Objectives 3)
Now we will discuss the roles, relationships, and responsibilities of the IACUC, the institution, and PIs in ensuring congruence.

Slide 14 (Who Must Meet the Contractual Obligations of the Grant?)
The NIH Grants Policy Statement defines contractual and legal obligations between the grantee institution and NIH. Who at the institution must meet the contractual obligations of the grant? The Authorized Organization Representative, or AOR, sometimes called the Signing Official, represents the entire institution. His or her signature on the application verifies to the NIH that the institution's commitment to the Grants Policy terms and conditions, including IACUC approval of all PHS-funded animal activities, is occurring.

By signing the grant application, the PI is also promising the NIH and the institution that he or she will conduct animal activities according to the PHS Policy. Included in the PI's commitment is conduct of PHS-funded animal activities according to an approved IACUC protocol.

Slide 15 (Is the IACUC Required to Review the Grant Application?)
What about the IACUC? Is the IACUC required to review the grant application? Well, OLAW has answered this question as one of our Frequently Asked Questions, OLAW FAQ D10. There is no explicit requirement for the IACUC to do a side-by-side comparison of an application and the IACUC protocol. However, the institution is responsible for ensuring that the information the IACUC reviews and approves is congruent with what is in the application. Institutions are free to devise workable mechanisms to accomplish this end.

Slide 16 (Who May Review for Congruence?)
Who may conduct the congruence review at an institution? It is important that whoever conducts the comparison is qualified to identify inconsistencies and has access to the IACUC protocol and grant. Someone who understands the IACUC protocol review process at the institution is a good fit for this review, such as a member of the IACUC office, the sponsored programs office, or compliance oversight personnel. At many institutions, an IACUC administrator acts as the liaison between the IACUC, the sponsored projects office, and the PI. They are familiar with PIs and the scope of their research and this can minimize the time spent in assuring grants are congruent with protocols.

Slide 17 (Who is Responsible?)
Here is a summary of who is responsible for what. The institution verifies that there is congruence between the grant and the IACUC protocol when it provides the IACUC approval date, usually as part of the Just-In-Time pre-award submission to NIH. The institution, through the AOR and the PI, are required to notify NIH of a change in scope of the project or any IACUC-required modifications before conducting the research. If, as a result of NIH peer review, the PI is asked to modify the project scope or animal use, he or she must promptly inform the IACUC. The PI is also responsible to provide an accurate description of the animal activities for review and approval by the IACUC.

Slide 18 (Responsible for Documentation)
What documentation does OLAW expect for the congruence review? The institution must document the IACUC's approval of the animal activities proposed in the grant. The institution, when asked by NIH, must be able to associate each grant or grants with a relevant protocol or protocols. If the institution uses a protocol numbering system, it must be able to link protocol numbers to grant numbers. But a 1:1 ratio is not required.

The most common method to prevent inconsistencies between the information submitted to NIH and that on the IACUC protocol is to implement a procedure for direct comparison. It is up to the institution who is given this responsibility for the comparison review. Having the department Chair or PI attest to consistency is a minimal approach and subjects the institution to a high level of risk.

Slide 19 (What About Other Agencies?)
What do other agencies require when it comes to congruence? I reached out to several of the other grant making agencies to find out what they expect.

Slide 20 (Department of Veterans Affairs)
The Department of Veterans Affairs [VA] has a memorandum of understanding with OLAW and agrees to follow the PHS Policy. If the VA makes awards involving research with animals, then congruence between the protocol and the grant or contract are required.

Slide 21 (National Science Foundation)
The National Science Foundation [NSF] requires that the IACUC approval be obtained

before an award is made. If IACUC approval is pending at the time of grant submission, then NSF will not make an award until an approval letter that confirms congruence is provided by the institution. In addition, the institution must have a PHS Animal Welfare Assurance. The approval letter must explicitly list the grantee's name, the title and number of the NSF proposal, and the date of IACUC approval. A link to the NSF grants policy guide is provided at the bottom of the slide.
[http://www.nsf.gov/pubs/policydocs/pappguide/nsf16001/gpg_2.jsp#IID7]

Slide 22 (Department of Defense)
For Department of Defense [DoD] grants, no specific congruency review is required. Instead, the DoD conducts an administrative review of the protocol. Department of Defense regulations require that any animal study either conducted or sponsored by the DoD be reviewed by a DoD veterinarian trained and experienced in lab animal medicine. There are 3 offices within the DoD that conduct this review. The Air Force's oversight office reviews Air Force animal use protocols from extramural sites. The Navy's Bureau of Medicine and Surgery, and called BUMED for short, reviews protocols funded to non DoD locations by the Office of Navy Research and other Navy entities. The Animal Care and Use Review Office, or ACURO, reviews protocols funded by the Army, the Defense Advanced Research Projects Agency (also known as DARPA), and other Army funding activities. The ACURO review entails a review of everything the IACUC reviews except annual reviews. A link to the DoD regulation is provided at the bottom of the slide.
[http://mrmc.amedd.army.mil/index.cfm?pageid=research_protections.acuro_regulations]

Slide 23 (USDA National Institute of Food and Agriculture?)
At the National Institute for Food and Agriculture, or NIFA, the research grant component of USDA, grant applications recommended for award are sent to NIFA's Awards Management Division (AMD) who perform an administrative review of the application and they process the award. As part of the administrative review, AMD determines if there are special considerations such as the use of vertebrate animals associated with the project. If the project involves vertebrate animals, AMD checks for IACUC approval and verifies that the approval date is current.

If the IACUC approval is not provided or the approval date is out of date, award funds are restricted or withheld until the information is provided and verified. In such situations, the institution often provides the IACUC approval document in order to release the award funds. In these instances, the AMD verifies that the approval document relates to the particular project and that the approval is current before releasing funds. A link to the NIFA grants guide is provided at the bottom of the slide.
[http://nifa.usda.gov/sites/default/files/resource/NIFA_policy_gde_Oct_2014.pdf]

Slide 24 (Where to Look in the Grant)
Where in the application should one look to determine congruence with the IACUC protocol? There are two primary areas in the grant to concentrate on when conducting grant congruency review: the Vertebrate Animals Section and the

Approach part of the Research Strategy Section. Has this been your experience Sam?

>>*Varghese:* Yes, exactly. That's what we do.

Slide 25 (What Content Should Be Compared?)
>>*Brown:* What content should be compared between the application and the IACUC protocol? The review should confirm that the species are in agreement, that the procedures described in the grant are what the IACUC has approved, and that the total number of animals proposed is similar. It's not necessary to use a microscope to make this comparison. While there are some requirements to provide certain details in grant applications, generally the protocol provides much more detail on how procedures with the animals are carried out compared to what is found in the application. Grant applications will usually give a more general description of the aims of the project or projects.

Slide 26 (Not Congruent)
What if the grant and the IACUC protocol are not congruent? If a procedure is in the grant, but not in the protocol, ask the PI for clarification. He or she may choose to modify the protocol to be consistent with the grant. If the PI does not plan to perform the procedure described in the grant, a note should be filed with the institution's record of the grant review. NIH should be informed of the change as part of the Just-In-Time pre-award notification.

What if a procedure is in the IACUC protocol and is not in the grant? Again, ask the PI for clarification. If the PI intends to conduct the procedure, then he or she should determine if the differences meet the definition of a "change in scope". Please note that this would apply when there is a 1:1 grant to protocol ratio. If multiple grants are associated with a single IACUC protocol, the institution must ensure that PHS funds are expended as described in the PHS grant or grants.

Slide 27 (NIH Change in Scope)
The NIH Grants Policy allows the PI to make changes in the methodology, approach, or certain other aspects of a project. However, he or she must obtain prior approval from the NIH awarding component for what NIH terms a change in scope. A change in scope is a change in the direction, aims, objectives, purposes, or type of research or training identified in the approved project. The grantee must make the initial determination of the significance of a change and should consult with the Grants Management Officer at NIH if unsure.

Slide 28 (Indicators of Change in Scope)
Potential indicators of a change in scope are found in the Grants Policy Statement. [NIH GPS Part II: Subpart A: 8.1.2.5] A few examples are listed here. These include a change from the specific aims approved at the time of award, substituting one animal model for another, a change from the approved use of animals, or a shift of the research emphasis

from one disease area to another. The examples are not intended to imply that any change in animal model, or in the approved use of animals, always represents a change in scope. As I said before, it's always better to have the PI consult with the Grants Management Officer to determine whether the NIH Institute or Center funding the grant considers it a change in scope.

Slide 29 (Change in Scope?)
So if the PI determines that there is a change in scope, he or she, through the AOR, is responsible for requesting approval of that change in scope. The request for a change in scope must be made in writing to the Grants Management Officer and an email is okay. The request must be made no less than 30 days before the proposed change and must be signed by both the PI and the AOR. If the PI determines there is not a change in scope, he or she should provide an explanation that the institution includes in the congruency review documentation.

Slide 30 (Issues that May Require Clarification)
What are the issues that you find most commonly need clarification, Sam?

>>*Varghese:* In our institution, we sometimes need clarifications for mostly procedures; procedures in grants are not always approved by the IACUC. We have also seen differences in animal numbers between grants and protocols that need clarification. We rarely see change in scope such as change in species or change in performance sites and so on.

>>*Brown:* Thanks, Sam.

Slide 31 (Does the IACUC Protocol Match the Grant?)
With the congruence review, NIH is asking the institution how it knows if the IACUC protocol matches the grant when it verifies IACUC approval. If the aims, animal numbers, and information in the Vertebrate Animals Section match with the approved protocol, then the grant can be certified as congruent. Institutions should maintain their congruence review records for their own purposes and so that they can provide them for review by NIH, if NIH requests them. We recognize that there are numerous ways to achieve and verify congruence. Institutions may develop and implement their own policies and procedures, as long as those policies and procedures satisfy the requirements of the PHS Policy and the terms and conditions of NIH Grants Policy.

Slide 32 (Congruence Review Strategy Summary)
In summary, when conducting the congruence review, start with the Vertebrate Animals Section. In looking at the Research Strategy Section, the Approach part of this section may contain information on animal use. It is recommended to look for the same key words that describe the procedures in both the IACUC protocol and the grant. If inconsistencies are found, have the PI clarify and provide an explanation. Make the changes necessary to the protocol or grant and notify NIH if the grant is impacted by IACUC review or a change in

scope.

Slide 33 (Webinar Objective 4)
Our next focus is on best practices for congruence review and how they may be applied to your institution.

Slide 34 (Some Best Practices for Congruence Review)
Sam is now going to share with you how he conducts congruence. He will explain best practices that he finds effective. Sam?

>>*Varghese:* First of all, I wish to thank Dr. Pat Brown, Susan Silk, and other OLAW staff for giving me this opportunity to participate in this webinar.

My part of the presentation is going to be based entirely on my experience with developing and implementing the congruence review process in our institution. A few years ago, when we brought up grant congruence review with our University's faculty, we met with a lot of resistance. Our researchers were not used to IACUC approvals for all animal studies in their grant proposals before receiving funding. We had to put in a lot of effort into convincing our Department Chairs and faculty that we are not allowed to accept funding from Federal agencies unless the IACUC has approved all the proposed animal studies.

After discussions with our Dean and Department Chairs of the Medical School, the Dean has appointed a subcommittee to review regulations and develop an institutional process for doing congruence reviews. In the next few slides, I will go over the process we have developed.

Slide 35 (U Mass Med Policy Statement)
The subcommittee charged with developing policies and processes for congruence review came up with a mission statement which is shown in this slide. A congruency review is required for all PHS funding that uses live vertebrate animals to ensure that the work described in the proposal is in agreement with an active, approved protocol. The IACUC office, not the IACUC committee, was given the responsibility to oversee the congruence review process in our institution. These reviews are done by those with background in biomedical research and experience in reviewing IACUC protocols.

Our institution does not have strict guidelines for linking grant proposals to protocols. We use one-to-many or many-to-one system, which means a funded proposal can be linked to one or many protocols. At the same time, one protocol can be linked to one or many proposals. I would like to point out that it is easier to do congruence reviews if there is a 1:1 ratio between grants and protocols.

Slide 36 (Congruence Process)
Our congruence review process is outlined in this slide. We ask the PIs to contact the

congruence reviewer when they receive a fundable priority score. We leave it up to the PIs to determine if they have a fundable priority score and would like to submit their grant for congruence review.

We have a dedicated website, mail box, and a reviewer for congruence reviews. When our Research Funding Office receives the notification that the study section review has been completed for a grant, the Funding Office will send the PI a reminder to contact the congruence reviewer if there is a possibility of getting funded, based on the priority score. The congruence reviewer will then perform a side-by-side or direct comparison of the IACUC-approved protocol with the official or final version of the grant application.

The congruence reviewer will make the determination if the grant and the protocol are congruent based on a set of criteria. I will go over the criteria we use for congruence review in a later slide. If the grant and protocol are found to be congruent, the reviewer will notify the PI and the Funding Office about verification of congruence. The Funding Office will then process the necessary paperwork for accepting funds on behalf of the institution.

If the grant and the protocol are not congruent, the congruence reviewer will contact the PI and ask for modifying the IACUC protocol to make it consistent with the grant. In most cases of non-congruence, the PIs modify the IACUC protocols according to the recommendations from the congruence reviewer. After modifying the protocol to become congruent and approved by the IACUC, the congruence reviewer will notify the Funding Office and the PI about verification of congruence.

In rare cases, we had changes in scope and contacted the Grants Management Officers at NIH regarding these changes. Examples of changes in scope for us include change in species and change in performance sites.

Slide 37 (Typical Timeline)
The timeline of a typical congruence review, in the context of a grant cycle, is shown in this slide. In this example, an NIH grant is submitted in the beginning of February and the funding start date is in October. The peer review by the study section will likely occur in June or early July, and the priority score will be available to the PI in July. As mentioned earlier, our Funding Office will contact the PI after receiving the priority score and ask the PI to initiate the congruence review process at this time if he or she has a fundable score.

This is the ideal time for congruence review if the PI needs to make significant changes to the protocol. In our institution, it may take 4 weeks or more to receive the IACUC approval for new protocols and about 2 weeks or more to receive approval for significant changes that require Designated Member Review [DMR] or Full Committee Review [FCR]. We want to make sure that the PIs have sufficient time to submit modifications to the IACUC protocols, get the reviews completed, and protocols approved. If the PIs wait until the Just-In-Time notification from NIH, which is usually 2-3 weeks before the funding start

date, there is not enough time to complete the IACUC review process.

We like the approach of doing congruence review immediately after the priority score notification for multiple reasons. First, the investigators do not have to waste time to modify the IACUC protocols if they have very little chance of getting funded. Secondly, it is less stressful for the congruence reviewer as he or she does not have to rush to review and fast track the IACUC approval for any protocol changes. Thirdly, this approach will also save time and resources for the institution because we don't have to allocate time to review all grants and compare them with corresponding IACUC protocols.

Slide 38 (Review Focus)
We prefer to do a side-by-side or direct comparison of the grant application with the IACUC-approved protocol for congruence review. Our reviewer will focus on the Vertebrate Animals Section and Research Strategy Section of the grant application. Congruence review done by side-by-side comparison could be a time-consuming process; however, we feel that there is no viable alternative to a side-by-side comparison to ensure congruence.

During congruence review, we focus on 6 areas shown on this slide. First, we focus on the general scope of the work. The overall objectives stated in the grant proposal should be similar to the study objectives indicated in the IACUC-approved protocol. Second, we make sure that the different types of experimental procedures and endpoints described in the grant are approved by the IACUC. We will not focus on the minor details of the methodologies used. The review of the experimental procedures will be time-consuming since most of the pieces of information are scattered throughout the grant proposal, not just in the Vertebrate Animals Section. Third, we will also look at the experimental and therapeutic agents used in live animals. Our goal is to verify that the various agents listed in the grant are also approved by the IACUC. We will confirm that the species indicated in the grant are approved by the IACUC. We will also verify IACUC approval for strains critical for the study, if the conduct of the proposed study or the disease model is dependent on the choice of strains. We look at the number of animals in the grant. We will verify that the investigator has approval for sufficient number of animals in the IACUC-approved protocol for the studies proposed in the grant. Occasionally, we found that there was insufficient number of animals in the IACUC-approved protocol when compared with the grant application.

Lastly, we look at euthanasia method in the grant. We do not require the euthanasia method in the grant and the protocol to be in full agreement as long as the methods are consistent with the AVMA guidelines. We will, however, ask the PI to follow the euthanasia method approved in the IACUC protocol. If the euthanasia method proposed in the grant is not consistent with the AVMA guidelines, we will make sure that there is IACUC-approval for using the method specified in the grant.

As Pat said earlier, beginning 2016, the Vertebrate Animals Section in the grant does not require a description of the euthanasia method unless the PI is planning to use a method

that is not consistent with the AVMA guidelines. Based on this, we will continue to verify IACUC-approval if the PI has proposed the use of a method for euthanasia that is not consistent with the AVMA guidelines.

Slide 39 (Congruence)
Our definition of congruence is outlined in this slide. A reasonable matching description of the 6 areas listed in the previous slide in the grant and the IACUC-approved protocol will be regarded as congruent. I just want to point out that there may not be 100% identity between the grant and the protocol. In our view, a congruent grant proposal should not warrant significant changes to an IACUC protocol. If significant changes to the IACUC protocol are necessary, the grant proposal will be considered non-congruent. If minor changes to the protocol are necessary, we will consider the grant to be congruent.

Slide 40 (If Not Congruent)
If the grant is found to be non-congruent, there are 3 options available to the investigators. The reviewer will first of all contact the PI for clarification for the differences between the grant and the IACUC-approved protocol. If the PI does not plan to perform a procedure described in the grant, the PI can clarify that by providing a justification. This information will be kept as part of the congruence review record and notified to NIH at the time of Just-In-Time. In our experience, we have only seen very few numbers of such clarifications that did not require protocol modification. For example, one of our investigators proposed ovariectomy in the grant, but it was not in the protocol. He later clarified that he decided after the grant submission to buy ovariectomized animals for his studies from a vendor.

In majority of the cases, if there are differences between grants and protocols, the PIs will amend the IACUC protocols. As mentioned earlier, significant modifications to an IACUC protocol may take a few weeks to process in our institution. We also had situations where the PIs did not have IACUC-approved protocols and had to submit new animal study protocols for IACUC approvals. This may take several weeks so we encourage PIs to start congruence review after receiving priority score. On rare occasions, our Funding Office had to contact NIH to inform change in scope. Usually, the changes in scope were related to changes in species or changes in collaborations.

Slide 41 (Now, for Some Real World Scenarios…)
>>Brown: We will now share some real world scenarios to help illustrate some of the issues encountered during congruence review.

Slide 42 (Scenario 1)
Sam, what do you do when you find that even though the PI has an IACUC-approved protocol that is congruent with the grant application, the protocol is expiring before or within a few weeks of the start date of the grant?

Slide 43 (Scenario 1)

>>*Varghese:* My solution is to advise the investigator to submit a new protocol or a 3-year renewal of the IACUC protocol as soon as possible.

>>*Brown:* You may wonder why this is important to do. It is important because the verification of IACUC approval given to NIH must be based on a protocol that is active at the time of award.

Slide 44 (Scenario 2)
Sam, a grant application is funded for 5 years but the IACUC protocol covers studies in the grant for 3 years. How do you verify IACUC approval and congruence for the animal studies planned for the 4th and 5th year?

Slide 45 (Scenario 2)
>>*Varghese:* We ask the PI to provide a brief description without experimental details and procedures for the studies planned for the 4th and 5th year in the IACUC protocol for review and approval. The 4th and 5th year studies must be addressed in more detail at the time of protocol renewal. We believe this is a commonly used approach by several institutions in such situations. We don't usually require a Full Committee Review or DMR process to approve such brief description of experiments and procedures without details.

>>*Brown:* That's a good way to handle it. There has to be congruency between what's in the grant and what's in the IACUC protocol, recognizing that the details for the 4th and 5th years of what's in the grant may not be the same level of detail that the IACUC is approving for the first 3 years. The information can be there with the explanation that this is the out years and will be refined or amended at a later time or at the time of the 3-year renewal.

Slide 46 (Scenario 3)
Sam, what do you do when you find an investigator's IACUC-approved protocol does not include the alternative experimental approaches described in the grant application? Does the IACUC need to approve alternative approaches since the investigator is not likely to use most of the alternative approaches?

Slide 47 (Scenario 3)
>>*Varghese:* We will advise the PI to include a brief description of the alternative approaches in the protocol, without experimental details and procedures, for review and approval by the IACUC. The PI must amend the protocol to include the alternatives if he or she uses them. This approach is similar to the approach described in the previous scenario.

>>*Brown:* That's a good approach Sam. You are meeting the requirement for congruence by asking the PI to add a brief description of the alternative approaches to the approved protocol. And, it is important to remind the PI that if he or she does decide to use those alternative approaches that the protocol will need to be amended to include the details of

those procedures.

Slide 48 (Scenario 4)
Our next scenario asks, “If vertebrate animal studies are to be performed off-site by collaborators, how do you verify congruence of the off-site animal studies?”

Slide 49 (Scenario 4)
>>*Varghese:* This is perhaps one of the most common situations we run into. We have two different options. We ask the PI to submit a U Mass off-site protocol form that contains a brief description of the studies, supporting documentation such as IACUC approval letter from the other institution, proof of collaboration, and if necessary, a copy of the IACUC-approved protocol and sometimes a memorandum of understanding asserting congruence review.

Alternatively, we ask the administrators at the collaborating institution to perform a congruence review and provide documentation to our institution verifying congruence. So, these are the two mechanisms we use.

Slide 50 (Scenario 5)
>>*Brown:* The PI of the IACUC-approved protocol is not the PI of the grant. Sam, what do you do in this circumstance?

Slide 51 (Scenario 5)
>>*Varghese:* If the IACUC protocol PI is mentioned in the grant as an investigator or collaborator, we will use that protocol for congruency review. If the IACUC protocol PI is not even mentioned as a collaborator in the grant, we will advise the PI of the grant application to submit a new IACUC protocol. In several occasions, we have seen the grant PIs trying to use IACUC-protocols of those who are not listed in the grant as collaborators.

Slide 52 (Scenario 6)
>>*Brown:* Sam, you find that some of the reagents (for example, custom antibodies) in a grant application are to be produced by a vendor registered with USDA and accredited by AAALAC, but without an OLAW Animal Welfare Assurance. Is it OK to use the vendor’s IACUC-approved protocol for congruency review or are there other steps you take first?

Slide 53 (Scenario 6)
>>*Varghese:* No, it is not OK, because NIH requires the vendor used by the grantee to be Assured. Therefore, we will address this immediately so that the PI’s research is not delayed. We could require the vendor to contact the NIH grants manager to request that OLAW negotiate an Assurance. Or, require the investigator to switch to a PHS-Assured vendor before verifying congruency. In our experience, the PIs who were receiving reagents from vendors without PHS-Assurance preferred switching to vendors who had PHS-Assurance at this point rather than waiting for the vendor to receive Assurance.

Slide 54 (Scenario 7)
>>*Brown:* Here's another scenario involving multiple performance sites. We have an investigator who has proposed to collaborate with a researcher in a foreign institution that does not have a PHS Foreign Assurance. Can we use the foreign collaborator's protocol for congruency review or are there other steps you take first?

Slide 55 (Scenario 7)
>>*Varghese:* Yeah, so it's no. First, we would require the foreign institution to contact the NIH grants manager to request that OLAW negotiate a Foreign Assurance with them. Even after they obtain a Foreign Assurance, the domestic institution remains responsible for animal activities conducted at a foreign site and must provide verification of IACUC approval. The domestic IACUC may accept the approval of a foreign Assured institution's IACUC review; however, the domestic IACUC is responsible for the review as if it was their own.

In fact, I remember dealing with 2 such cases resulting in different outcomes. In one case, the foreign institution received a Foreign Assurance from the NIH, formed an IACUC, and approved an animal study protocol which our IACUC also reviewed. In the second case, the foreign institution's protocols were approved by a governmental agency, not by an IACUC-like oversight committee. They did not want to change their process and did not apply for a Foreign Assurance from NIH. Our investigator was unable to collaborate with them.

>>*Brown:* That's a good approach, Sam. When the awardee is a domestic institution but some of the animal activities occur at a foreign performance site, the awardee remains responsible for the animal activities conducted at the foreign site and must provide verification of IACUC approval. That approval certifies that the activity, as conducted at the foreign performance site, is acceptable to the awardee's IACUC.

Slide 56 (Scenario 8)
>>*Varghese:* Pat, I have a question for you. Training grants from NIH support training only and provide no funds for animal care and use. Is a congruence review necessary for training grants?

Slide 57 (Scenario 8)
>>*Brown:* Well, this one has an answer that I am sure you are happy to hear. No. Training grants, where no independent research with animals is supported, do not require a congruence review.

Slide 58 (Additional Resources)
This slide provides a list of additional resources about NIH grants policy and congruence review.

- *NIH Grants Policy Statement* *http://grants.nih.gov/grants/policy/nihgps/index.htm*
- *OLAW Frequently Asked Question D10* *http://grants.nih.gov/grants/olaw/faqs.htm#623*
- *Garnett, N.L. & DeHaven, W.R. A word from OPRR and USDA [protocols and grant applications]. Lab Animal 28, 21 (1999).*
- *Klemfuss, H. Matching protocols to grant proposals. Lab Animal 31, 36-39 (2002).*
- *Wolff, A., Garnett, N., Potkay, S., Wigglesworth, C., Doyle, D., Thornton, V. Frequently Asked Questions About the Public Health Service Policy on Humane Care and Use of Laboratory Animals. Lab Animal 32, 33-36 (2003).*

Slide 59 (Question 1)
>>*Mohan:* This is Swapna Mohan. We now have some questions from the community. Our first question is: Is it correct that the IACUC should not feel pressured to review a related amendment, for example, within 48 hours to support a Just-In-Time (JIT) award?

>>*Brown:* NIH grants managers understand that obtaining IACUC approval may take more than 48 hours. Verification of IACUC approval should be provided at the earliest date available and based on reasonable expectations for IACUC review. IACUCs should not be pressured by PIs to review and approve a new protocol or amend an existing one just because of a Just-In-Time request.

>>*Varghese:* In our institution, we won't be able to complete the IACUC review and approval within 48 hours. It may take our IACUC several weeks to process an IACUC review and approval, and this is the reason why we ask the PIs to initiate congruence review right after they receive a fundable score. If a situation like this happens in our institution, we will ask our Funding Office to contact Grants Management Officer to inform that we can only provide the IACUC approval at a later date and request if a restricted award can be made.

Slide 60 (Question 2)
>>*Mohan:* Thank you. The second question is: If a grant funds multiple IACUC protocols, which IACUC approval date should be provided? The most recent one?

>>*Brown:* This is up to the discretion of the institution, but it's my understanding that most institutions choose to put in the most recent IACUC protocol approval date.

>>*Varghese:* It depends. We will go with the most recent approval date unless the majority of the studies in the grant are approved under a protocol that was approved at an earlier date. If there is collaborator involved who has a later approval date, we will go with the PI's earlier approval date rather than the collaborator's later approval date.

>>*Brown:* Yes, that is a good approach, Sam.

Slide 61 (Question 3)

>>*Mohan:* If two institutions are involved in a project, which one is responsible to ensure congruence? The institution that receives NIH funds or the institution that has an IACUC and provides animal care?

>>*Brown:* The institution that accepts the funds verifies by providing the IACUC protocol approval date that there is congruence between what is in the grant application and what has been approved at the institution where the activity is going to be conducted. The NIH Grants Policy Statement requires that the prime grantee have a formal written agreement with collaborating institutions that addresses the administrative, financial, and reporting requirements of the grant.

>>*Varghese:* If we are the prime grantee institution receiving the funding from NIH, we will make sure that the congruence review is done either by us or by the collaborating institution. If most of the animal studies are done in the collaborating PHS-Assured domestic institution, we will have a memorandum of understanding [MOU] with that institution which will include verification of congruence by them as one of the conditions of the MOU. In case the other institution does not agree to verify congruence, we will ask for a copy of their IACUC-approved protocol and verify congruence ourselves.

Slide 62 (Question 4)
>>*Mohan:* What constitutes a change that needs to be conveyed to the NIH? A hypothetical situation, for example: During a congruency review, it is determined that anesthetics being used for procedures specified in the grant are different than those specified in the protocol. The PI indicates that he will use the anesthetics described in the protocol, and not the agents that are specified in the grant. Should this change be conveyed to the NIH?

>>*Brown:* NIH is looking more for significant modifications made by the IACUC that would alter how the PI is going to be conducting the research with the animals. Refinements, such as modification to an anesthetic or an analgesic, are well within the IACUC's role and not something that NIH would need to be informed of. It is important to remember that what's written in the IACUC protocol is what must be done. So if there is a discrepancy, make sure that the IACUC protocol is defining which drugs are going to be used.

>>*Varghese:* We will consider change in an anesthetic or analgesic agent to be a significant change which is consistent with the 2014 NIH Guide Notice, Guidance on Significant Changes to Animal Activities (NOT-OD-14-126) and we will require the PI to amend the protocol before certifying that the grant and protocol are congruent. If the PI proposed to use an agent (for example, Avertin) that the IACUC does not approve, but approves an alternative agent, our institution may report that modification to NIH. However, we will not consider refinements, such as change in dosage or route of administration, important enough to be reported to NIH.

Slide 63 (Question 5)
>>*Mohan:* What are the responsibilities for congruency review after the first year of a multi-year award? For example, if a congruency review (for all animal use) is conducted prior to Year 1 of an NIH award and found to be congruent, are additional reviews required for the Year 2, etc.?

>>*Brown:* NIH grants policy requires congruence review prior to award. NIH also expects ongoing IACUC review and approval of the animal activities as required by the PHS Policy. Once the award is made, IACUC review and approval must continue but additional congruence review is not required.

>>*Varghese:* We only perform congruence review before the award is made. We will also perform congruence review when a new investigator joins our institution and brings in a grant with him or her from a previous institution.

>>*Brown:* We would say that is an appropriate time to do a congruence review, when you have a new investigator who is bringing a grant and you want to be sure that what your IACUC is approving is in line with what the grant is funding.

Slide 64 (Question 6)
>>*Mohan:* A PI has an IACUC approval for Aim 1 and 3 of the application. Aim 2 is not in the IACUC protocol because it will not be performed until a much later date. How do we indicate this in the congruency approval?

>>*Brown:* The least burdensome approach to meet the requirement for congruence is to ask the PI to add a brief description of Aim 2 to the approved protocol and acknowledge that the protocol will be amended to include the details of Aim 2 prior to its start. The grant and protocol are now congruent.

>>*Varghese:* We will ask the PI to modify the protocol to include all the animal studies in Aim 2 if it is to be conducted in the next 3 years. If the studies in Aim 2 are going to be carried out in the years 4 and 5, the PI could include a brief description without details in the protocol.

>>*Brown:* And that's a good approach, Sam.

Slide 65 (Question 7)
>>*Mohan:* Now our last question: Is it better to have one protocol for each grant or to have several grants associated with one protocol?

>>*Varghese:* In my view, it is better to have one protocol for each grant because it is easier to perform a congruence review. However, most experienced PIs in our institution prefer one protocol for many grants as they find it easier to keep all animal studies in one protocol. If there is one protocol for several grants, our congruence

reviewer has to sort out the procedures and animal studies for different grants. So, it is a lot more work for us to perform a congruence review, however, we are happy to serve our community of faculty and we are okay with having one protocol for many grants.

Slide 70 (Upcoming OLAW Online Seminars)
>>*Brown:* Thank you Sam for your excellent contribution to this webinar and thank you to all of the participants for joining us today.

>>*Varghese:* Once again, I would like to thank you for allowing me to participate in this webinar. We are very grateful to OLAW for bringing these educational programs and all of us find the webinars most useful and informative.

>>*Silk:* My thanks to all of you – Sam, Pat, Swapna, and especially our participants. We look forward to meeting with you again at our next OLAW Online Seminar in June 2016, when Allyson Bennett will talk about Risk-Benefit Analysis: Science, Ethics, and Public Interests. Happy spring and good bye for now!

Additional Submitted Questions Not Addressed During the Webinar

[Pending]

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