Research Involving Animals: OLAW

>> Paula Knapp: Hello and thank you for joining me to talk about research involving animals. My name is Paula Knapp. I serve as an animal welfare policy scientist in the Office of Laboratory Animal Welfare. This presentation is about policy requirements for research involving animals. I'll begin with acknowledging that perhaps the grant application process may have you feeling a little bit like this guy spinning around in circles, accomplishing little. In this presentation I hope to provide you with an understanding of how to navigate this process when your research involves the use of live, vertebrate animals. After today's session, you should be able to define a live vertebrate animals for PHS award purposes, describe the requirements of the Vertebrate Animal Section, the VAS, recognize the significance of verifying Institutional Animal Care and Use Committee, IACUC, approval, identify the three types of animal welfare Assurances and describe noncompliance and understand some of its implications. In order to accomplish our objectives for this presentation, I'm going to have to begin with some regulatory framework, and I will try to keep this brief. Federally funded research involving the use of live vertebrate animals must follow the Public Health Service Policy on humane care and use of laboratory animals. The Health Research Extension Act of 1985 is a public law that provides the legislative mandate for the PHS Policy. The policy requires that assured institutions base their animal care program on the "Guide for the Care and Use of Laboratory Animals" known as the "Guide," and although the "Guide" may differ from USDA regulations in some areas, please know that the PHS Policy requires compliance with the Animal Welfare Regulations for USDA if your institution maintains USDA-covered species. OLAW is the NIH office who is responsible for the administration and coordination of the PHS Policy. OLAW's mission is to ensure humane care and use of animals used in PHS-funded research. We sit within the Office of Extramural Research at NIH, and we support institutions receiving PHS funding for research involving animals. All of this is to contribute to the overall quality of PHS-supported activities. OLAW accomplishes its mission by negotiating Assurances with institutions that receive PHS funds for animal activities. So this means that an institution writes a document describing their animal care program, and then OLAW works with that institution to develop their program description so that it is compliant with PHS Policy. OLAW also maintains a list of assured institutions on its website, and we oversee the implementation of the PHS Policy by providing interpretation and guidance, and we also do this by supporting educational activities through workshops, resources, training and webinars. OLAW does have the authority to review, approve or disapprove waivers to the PHS Policy. We monitor compliance mainly through institutional self-reporting as well as third-party allegations, and OLAW routinely conducts site visits to Assured institutions. Again, this is to contribute to the overall quality of PHS supported activities. The NIH Grants Policy Statement spells out the terms and conditions of NIH grants which align with PHS Policy. So there are three requirements of NIH Grants Policy that are specific to vertebrate-animal use. The first is that there must be a completed VAS. Secondly, the IACUC review and approval must occur prior to any contact of PHS-supported animal activity, and third, there must be a valid Animal Welfare Assurance. We're going to talk about all three of these throughout the rest of the presentation, but before we move on, I'd like to take a moment and ask you to look over this list and think about which federal agency or agencies do you think require research institutions to comply with PHS Policy, NIH, the Department of Veterans Affairs, NSF, National Science Foundation, NASA or HHS BARDA, and that's Biomedical Advanced Research and Development Authority or all of the above. I hope you think that all of these federal agencies are required to comply with PHS Policy. As I've been saying, OLAW assures and oversees PHS-funded animal activities. There are four federal agencies that account for the majority of extramural funding for research involving animals, and those are NIH, CDC, FDA and HHS BARDA, but OLAW is also authorized to oversee animal activity and negotiate Assurances on behalf of several other funding components that have MOUs with OLAW, and right now that's VA, NSF and NASA. I have a note on this slide to point out that OLAW does not oversee animal activities funded by DOD, USDA, nonprofit or for-profit organizations. Now that we've reviewed the regulatory framework for the use of animals in research, let's talk about the definition of an animal. So this is not your Urban or Webster definition. This is the Public Health Service Policy definition which states that any live vertebrate animal used or intended for use in research, research training, experimentation or biological testing or for related purposes. Based on this definition, I'd like to take a moment and look over these pictures that are representing studies and think about which of these studies do you think should be considered vertebrate-animal use. So a study involving zebrafish or tadpoles or a mosquito malaria study using a rabbit host, an octopus study or how about a cow spleen from a slaughterhouse, a pre-hatched embryo, goat antibody studies or chimp behavior study? So let's go over each of these. So the zebrafish and the tadpoles are vertebrates. So they would be considered vertebrate-animal use. A mosquito using a rabbit host would be considered animal use because of the rabbit. An octopus is not a vertebrate. It's a cephalopod. So it would not be considered verbrate-animal use, but institutions should use best practices when research involves invertebrates with highly complex nervous systems such as the octopus. A cow spleen from a slaughterhouse is not animal use if the cow is used for another purpose and not for the sole purpose of the spleen collection. An embryonated egg would be animal use if the study involves the mother or if extends all the way to hatching. However, here's another place to note that best practices should be considered because the current AVMA guidance on euthanasia states that embryonated eggs at 80 percent incubation have a neural tube, therefore they perceive pain. The goat antibodies study could go either way. So if ... It's not animal use if the antibodies are commercially available or off the shelf. If the antibodies are custom-made such that they are generated specifically for the purpose of the study, then that would be animal use, and the last one, a chimp behavior study can also be either. So if it alters or modifies the behavior of the animal it is considered animal use, but if it's purely observational, it does not modify or affect the behavior of the animal such as in a zoological setting, then it would not be considered animal use. Now that we've defined a live vertebrate animal, let's talk about the VAS. A complete VAS is required in a grant application. There are three criteria that must be fully completed in the VAS, and really it should serve eventually as a stand-alone document. So if the required information is described elsewhere in the grant application such as in the specific aims, it still needs to be included in the VAS. The first criteria is description of animal procedures. So here's where you need to provide a concise description of all proposed procedures. You also need to identify the species, strains, ages, sex and total number of animals by species, and if a cat or a dog are used, then you need to provide the source of that animal. The second criteria that must be completed is the justifications, and that is two justifications there. There's justification for animal use and justification for the species. So for animal use, you need to describe why you're not using alternative models such as computational models, human subjects, invertebrates or in vitro studies, and for the species justification, you need to explain why this species is appropriate for the research. And last but certainly not least, the third criteria is the minimization of pain and distress, and here's where you need to describe interventions for pain and distress such as analgesia, anesthesia, sedation and palliative care if appropriate, and also here you need to provide a description of your human end points. OLAW recently developed and released a VAS online training module to help out with investigators completing this VAS. The training module is fantastic. This is a screenshot from our website of how you can get to it. I also have a URL here, and it'll be referenced later in our resources slide. This training module is an interactive overview of the requirements. It provides a list for ... a checklist for applicants and reviewers, provides a detailed instructions. It takes 20 to 30 minutes. I've got through it. It's put together really well. The graphics are amazing, and I strongly recommend that you check it out so that you can submit a complete, acceptable VAS the first time to avoid having your VAS returned as unacceptable, and then you have to revise it and then resubmit it. So check this out. Now, let's talk about our third objective which is the IACUC approval. It's important for you to know that cost for activities with animals may not be charged to an NIH grant if there is not a valid IACUC approval. So NIH will delay an award for research involving animals until the awardee organization provides verification of IACUC approval. Also all Assurances need to be put in place, and we're going to talk about that next. The IACUC approval must be granted within 3 years of the budget period start date to be valid, but it may also be submitted with Just-in-Time procedures, and it is an institutional responsibility to ensure that the IACUC protocols are congruent with the research described in the application. Now, we'll focus on the Animal Welfare Assurance, and this hamster thinks that's a great idea. Going back and visiting the PHS Policy again in section IV.A, it states that no activity involving animals may be conducted or supported by PHS until the institution conducting the activity has provided a written Assurance that is acceptable to the PHS setting forth compliance with the policy. So as you've been hearing, OLAW is charged with overseeing PHS-funded animal activities, and so OLAW is the entity that will negotiate the required Assurance. OLAW sees the Assurance as an agreement that commits an organization to humane care of animals used in the research program. If using animals in PHS-funded research, each awardee organization and its performance sites must have an Assurance in place. The negotiation process begins with a request to OLAW from the funding component or your IC at NIH, and the takeaway here is that if you do not have an Animal Welfare Assurance, you may not conduct animal activities using PHS funds. Before I move on to the specific types of Assurances, I'd like to take a moment to point out that there are several resources together that make up the standards for animal care that are spelled out in the Assurance document. "The US Government Principles", the "Guide for the Care and Use of Laboratory Animals" known as the "Guide," the "USDA Animal Welfare Regulations" and the "AVMA Guidelines for the Euthanasia of Animals" and that is currently the 2020 edition. Now, I will provide a brief overview of the three types of Assurances. The Domestic Assurance is negotiated when a US organization controls its own animal facility, they have a complete animal care and use program with an IO and IACUC and a veterinarian and they conduct PHS-supported animal activities on site. That's a Domestic Assurance, and the Foreign Assurance is negotiated when an awardee is a foreign organization or it could also be that a domestic awardee is conducting animal activity at a foreign site, and in that case, the domestic awardee's IACUC is who approves the animal activity that is being performed at the foreign site. A Foreign Assurance also includes a statement that the organization will comply with all law, regulations and policies regarding humane care and use of animals in the region that the research is to be conducted. It must follow the "International Guiding Principles for Biomedical Research Involving Animals." The third type of Assurance is an Interinstitutional Assurance or IA for short. This is when a grantee organization does not have an animal care program or animal facilities or an IACUC, and the animal work is going to be conducted at a performance site that does have an Animal Welfare Assurance. The purpose of the IA is to tie the unassured organization who is receiving the award to the assured performance site, and it's the performance site that provides the IACUC approval. So IAs can be a little bit confusing. So I wanted to provide an example to help you understand. So in this example, Bob's Biotech receives a grant that involves animals. Bob's Biotech does not have an animal care and use program of their own. So the animal activity is going to be performed at Hopkins which is an assured institution. The IC or the Grants management is going to have to request an IA between Bob's Biotech, Johns Hopkins and OLAW, and then this is like a two-page document. It's signed by the IOs of both institutions, and then the IACUC Chair of the performance site, in this case Hopkins, is who needs to verify IACUC approval. We cannot talk about Animal Welfare Assurances without addressing consortium agreements or subawards. PHS Policy applies to all parties in a collaboration. That's primary and subs where animal research is conducted, but if all of these institutions have their own Assurance, it becomes the prime awardee who is accountable to confirm that they have an Assurance, and that they have valid IACUC approval so it's the prime awardee. So that wraps up the three types of Assurances. If you'd like a little more information, I have a URL here on this slide, and this URL will be listed later in the resource slide as well. Based on what we've gone over so far, I'd like to pause a moment again and ask you to take a look at this list and think about what the PHS Policy and NIH grants policy requirements are when making an award involving animals. Do you think there needs to be a completed VAS in the application? What about verification that IACUC has reviewed and approved those sections of the application that involve the use of vertebrate animals? Should there be an Assurance for the applicant organization and all performance sites or perhaps an Assurance for only the applicant organization? So it's the first three that are required when making an award. There must be an Assurance for the applicant organization and all performance sites. Now that you know the PHS and NIH grants' policy requirements when using animals in research, I'd like to be a little more practical here and take a look at the grant application itself. So there are three places that need to be completed when using vertebrate animals. There's the SF 424 project performance site locations and on the PHS 398, there's two places, the research plan section and the cover page supplement. On the SF 424, each performance site where live vertebrate animals will be used needs to be listed, and also on the 424, you need to complete sections two and 2A. So two asks if vertebrate animals are used and if they are, you would check yes. If you check yes, you must complete 2A which is asking if IACUC review is pending, meaning not approved yet. If it is pending, you would check yes, and you would have to leave the IACUC approval date blank because there's no IACUC approval yet. If the IACUC has approved the animal activity so it's not pending, you would check no and provide the IACUC approval date in the next blank. Then it asks for the Animal Welfare Assurance number which is always going to be the applicant institution's Assurance number. If the applicant organization does not have an Assurance, the response there would be none, and then OLAW would be contacted to negotiate the Assurance so that the award can be made. Now let's look at the 398. In the research plan section, you would upload your completed VAS as a PDF document. Remember that you need to complete all three criteria of the VAS. If you visit that online training module, I think you'll increase your chances of having an acceptable VAS submitted the first time, and then also in the 398, the cover page supplement asks if vertebrate animals will be euthanized. If yes, you need to state whether the method of euthanasia is consistent with the recommendations of the AVMA guidelines for euthanasia. Right now, that's the 2020 edition. If the method of euthanasia is not consistent with AVMA, then you need to provide a description of that method in that text box there and also provide scientific justification for that method, and then it comes to OLAW for review prior to the award. Now I'm going to close with some information about reporting noncompliance. Prompt reporting is required for any serious or continuing noncompliance with PHS Policy, any serious deviation from the "Guide" and any suspension of an activity by the IACUC. PHS Policy requires institutions to self-report noncompliance. Some of the implications for noncompliance may include special terms and conditions of the award. There could be a cost disallowance, suspension or termination of your award. There may be restriction or withdrawal of your institution's Animal Welfare Assurance. You could be put on enhanced reporting requirements and in an especially egregious noncompliance, there could potentially be criminal prosecution. We've now completed our five learning objectives. We defined a live vertebrate animal. We talked about the VAS, IACUC approval and the three types of Animal Welfare Assurances as well as some information about noncompliance. Here are some links from our website for educational opportunities. We have something called the ICARE Dialogues, and ICARE is Interagency Collaborative Animal Research Education Project, and that uses interactive learning. We have frequently asked questions on our website as well as a place where you can see our upcoming workshops and conferences. We do at least quarterly webinars, and those are on our website as well as recordings of past webinars. This is the resource slide where I have put together the URLs that have been referenced throughout the presentation, and the last slide is that there are some ways you can contact OLAW. We have our main number there. We have three divisions, Policy and Education, Division of Assurances and Compliance Oversight. We also have a Listserv that you can sign up for on our website. That way you would receive announcements, notices and policy interpretations. Thank you for your time and your interest in policy requirements for research involving animals. I hope you have a fantastic day.