Cate Pritchard: Thank you for joining this webinar, research involving animals. My name is Cate Pritchard, and I'm an animal welfare program specialist in the NIH office of laboratory animal welfare, also known as OLAW. And I'm your moderator for this 45 minute session. Now I'd like to introduce our presenter for today, Dr. Neera Gopee. Neera Gopee, DVM PHD is the director of the division of policy and education at OLAW. Dr. Gopee earned her veterinary degree at the University of the West Indies, and holds a doctoral degree in toxicology from the University of Georgia. Prior to her appointment at OLAW, she served as a veterinary medical officer at the National Center for toxicological Research, at the US Food and Drug Administration in Jefferson, Arkansas. She is board certified in toxicology and laboratory animal medicine. So welcome, Dr. Gopee. The format for this session is a short presentation followed by Q and A with Dr. Gopee. During the presentation we will have Q and A staff to answer questions in the Q and A box, and others that'll ask Dr. Gopee at the end of her presentation, so let's get started.

Neera Gopee: Thank you, Cate, and hello everyone. As Cate mentioned, my name is Neera Gopee, and I'm the director of policy and education in the office of laboratory animal welfare at the National Institute of Health, and today I will be discussing the policy requirement when research involves the use of [Indistinct] animals. So I've included this slide to acknowledge that the grants application process can seem quite complicated and frustrating, but I do hope to shed some light today on the application process at least when your research involves the use of live animals, so you can better navigate the process, and you won't feel like this poor guy spinning around in circles, accomplishing very little. Although I do admit, he does seem to be having some fun. So today I plan to review the five objectives. I hope to by the end of this discussion you should be able to define animal, you should be able to describe the requirements of the Vertebrate Animals Section, also known as the VAS. You should be able to recognize the significance of verifying Institutional Animal Care and use Committee, or IACUC approval. Identify the three types of animal welfare assurances, and finally I'll briefly describe noncompliance, as well as so that you can have a better understanding of its implications. So in order to accomplish my objectives for today's presentation I'd like to begin with a regulatory framework. Federally funded research for sub-federal agencies involving the use of live vertebrate animals must comply with the public health service policy on the humane care and use for laboratory animals, also known as the PHS policy. The Health Research Extension Act of 1985 provides a legislative mandate for the PHS policy, and PHS policy requires institutions to base their animal program on the guide for the care and use of laboratory animals, also known as the guide. Institutions are also required to comply with all other federal statues and regulations, including the Animal Welfare Act for USDA covered species where [Indistinct]. So my office, the Office of Laboratory Animal Welfare, or OLAW, administers and coordinates the PHS policy. So I'd like to start off with a quick poll, and Sarah, if you can launch that poll. And I'd like to hear your thoughts on whether you think a statement is true or false. OLAW's mission is to ensure the humane care of animals used in research. Is this true or is this false? Ah, so we have 98 percent of the folks say it's true, and that's correct. Our mission is to ensure the humane care of animals used in research. So let's see if I can get this .. So OLAW's mission is to ensure the humane care of animals used in research, and we do so by providing guidance and interpretation of the PHS policy. We support educational programs, and we monitor compliance with the policy, all in an effort to contribute to quality of research by assured institutions. And not surprisingly, our responsibility related to our mission, in that we are responsible for negotiating the animal welfare assurances, and we've made these assurances publicly, the list of assured institutions publicly available on our website. We also oversee implementation of the PHS policy, and we do have the authority to approve waivers to the PHS policy. We also support educational programs through webinars, resources, training sessions, and workshops. And we monitor compliance with the policy by assured institutions to ensure humane care and use of laboratory animals, mainly through institutional self-reporting. And last but not least, we do conduct announced site visits, whether they be for course or random to selected assured institutions. The grants policy statement, which aligns with the PHS policy, spells out terms and conditions when your research involves the use of animals, and there are three main requirements. When your proposed research involves animals you must have a completed Vertebrate Animals Section, or VAS. You must provide verification that the IACUC has reviewed and approved those sections of the application that involve the use of vertebrate animals, and you must have an animal welfare assurance for the applicant organization as well as all performance sites where research involving animals will be conducted. So I do have a second poll question for you, and this might be a little tricky, but I'd like to hear your thoughts on this. Which federal agency or agencies do you think require research institutions to comply with the PHS policy? Is it A, NIH, B, Department of Veteran's Affairs, or VA. C, the National Science Foundation, NSF, D, the National Aeronautics and Space Administration, NASA. E, the Biomedical Advanced Research and Development Authority, or BARDA, or is it F, all of the above? Please choose one of these five answers. And we do have a consensus, of 92 percent of you are correct. We do oversee funding by these agencies. Good job. So OLAW oversees ... Assures PHS funded activity, animal activities, and there are four PHS funded agencies that account for the majority of all of extramural funding for research involving animals, and these agencies include NIH, our one and only NIH, the CDC, Center for Disease and Control, FDA, Food and Drug Administration, and BARDA. Now through memorandum of understanding, OLAW also oversees animal activities conducted by the VA, NSF and NASA. And please note that OLAW does not oversee animal activities conducted by the Department of Defense, or DOD, the USDA, United States Department of Agriculture, and nonprofit or for profit organizations. So not that we have reviewed the regulatory framework, I'd like to now go into the definition of an animal. And the PHS policy defines an animal as any live vertebrate animal used or intended for use in research, research training, experimentation or biological testing or for related purposes. I'd like you to keep in mind some key words in this definition. Live vertebrate animals, and use or intended for use in research. It is important to note that the generation of custom antibodies and surgical manipulations that are conducted in response to a specific request by a PI, an investigator, solely for the purpose of an NIH grant is considered activities involving live vertebrate animals, and covered by the PHS policy. So what I'd like to do is I'd like to do a really fun polling here, and it involves eight different animal species that's on the screen, and I'd like you to please tell me which studies do you think involved the use of live vertebrate animals. Is it A, a zebrafish, B, tadpole, C, a mosquito malaria study using a rabbit host, D, octopus, E, a cow's spleen from the slaughterhouse, F, pre-hatched embryos, G, goat antibodies, and H, a chimp behavior study. Now choose all that you think apply, and keep in mind the definition of PHS policy of an animal. Live vertebrate used or intended for use in research. I'll give you about a minute to think about this and see what you come up with. All right, let's see. Okay, interesting. So 60 percent of you said zebrafish, 35 percent, tadpole. So zebrafish and tadpole are both vertebrate animal species, and therefore they would be considered live vertebrate animals, and they would be covered by the PHS policy. Good job for those two, the 60 and 35 percent who got that correct. A mosquito malaria study using rabbit hosts, this would also be considered live vertebrate animal because of the use of the rabbit host, which is a vertebrate animal. So that's also considered ... That's also yes. For octopus, 23 percent of you said that the octopus would be considered live vertebrate animal use. An octopus is actually an invertebrate, and therefore would not be covered by the PHS policy. However, we do expect best practices when your research involves such highly cognitive species with a highly complex nervous system, and they do have the ability to feel pain. A cow's spleen from slaughterhouse will not be considered live vertebrate animal use, and the reason being is that these animals were intended for use for food and they were killed for that purpose, not for the purpose of a grant. And therefore, harvesting tissues from these animals would not be considered live vertebrate animal use. And pre-hatch embryos would also not be considered vertebrate animal use until they hatch. So pre-hatching embryos will not be covered by the PHS policy. If the mother was involved in this study it would also be considered a vertebrate animal study. Goat antibodies, as I mentioned earlier, this depends. It depends if your goat antibodies were generated and it's commercially available, it's off the shelf, it will not be considered live vertebrate animal use. If, however, your antibodies are being generated in response to a specific request by the investigator for the sole purpose of the grant, it would be considered live vertebrate animal use, and covered by the PHS policy. And finally, a chimp behavior study, again, it depends. If it's not invasive, purely observational and does not modify the behavior of the animal it will not be considered a live vertebrate study. So there's a lot of nuances here, but please keep in mind the definition of the PHS policy of an animal and you can figure out hopefully whether or not your proposed study involves the use of live vertebrate animals. So let's move on. So now that I have defined animal, I would like to go into the three requirements of the policy. The PHS policy and the grants policy statement. The first requirement is a completed vertebrate animal section, and there are three criteria that must be addressed in the VAS. The first criteria is you must ... Requires a concise description of all proposed procedures involving animals, and the description must able be able ... You must identify the species, strains, ages, sex and total number of animals by species. If cats or dogs are used, you must also provide the source in your VAS. The second criteria that must be addressed is a justification that the species are appropriate for the research that's being proposed, and you must also provide rationale as to why an alternative model cannot be used to accomplish the research objectives. Such models include computational, human, invertebrate or in vitro. And finally, a description of the interventions including analgesic, anesthesia, sedation and palliative or supportive care, as well as humane end points must be included in your VAS to minimize pain, distress, discomfort and injury. Based on what I've just explained to you with regards to a VAS, if a PI was to submit a VAS ... Darron, can you turn ... Can you minimize that. Let me see if I can move. Oh, yeah. If a PI submitted a VAS as noted on this slide, would you think it's acceptable as written? For the first criteria in the VAS, the description, the PI stated that pharmacokinetic studies will be performed on mice. For the justification, PI stated that mice are inexpensive, and are one of the least sentient laboratory animals, and for minimization of discomfort, distress, pain and injury, PI stated that moribound mice will be examined by the veterinarian. In your opinion and based on what I've said so far, do you think this VAS is acceptable as written? We can bring that poll up now, Darron. Thank you. So let's see. Thank you, 95 percent of my participants. You're correct, it is unacceptable as written. Just please keep in mind your VAS and your grant application has to be a standalone document, and must provide a concise description of your procedures including identification of your species, strain, sex, age and total number of animals. You must also provide justification as to why the research goals cannot be accomplished using alternative model, as well as a justification for the species used, and you must include interventions to minimize pain and distress. So it would be considered unacceptable as written. And what I'd like to say right now is that in 2020, OLAW actually developed and launched a VAS online training module. It's an interactive 20 to 30 minute module, and it really helps for those who are first time applicants, I strongly recommend that you check it out and avoid having your VAS deemed unacceptable, and it can be found on the URL shown on the slide. So now I've completed the VAS. The second requirement is verification of IACUC approval, and I will say that NIH will delay an award for research involving animals, live vertebrate animals, until the recipient organization and all performance sites where animal work will be conducted have provided verification of IACUC approval. IACUC approval must have been granted within 3 years of the budget start date, and it can be submitted in accordance with just-in-time procedures. So those of you who have submitted, have a grant that may be in a fundable range, you may wish to proceed with IACUC review for those applications that have not yet received IACUC approval, because it can be submitted in accordance with just-in-time procedures. And it is an institutional responsibility to ensure that the research that's outlined in the application is congruent with what's in the protocol that IACUC will verify and approve. And absolutely no [Indistinct] activities with live vertebrate animals may be charged to the grant until NIH has received a valid IACUC approval. And our third and final requirement, policy requirement when research involves the use of animals is an animal welfare assurance. PHS policy states that no activity involving animals may be conducted or supported by the PHS until the institution conducting the activity has provided a written assurance that's acceptable to the PHS and complies with the policy. So what is an animal welfare assurance? Well, in essence it's like a contract between the federal government and the recipient organization, as well as the performance site where animal work will be conducted that commits the organization [Indistinct] to the proper care and use of treatment of animal, and it describes the organization's animal care and use program. OLAW is the entity that will negotiate the appropriate animal welfare assurance when requested by the funding IC. So please, we do not negotiate assurances when requested by the investigator, it has to be initiated by the funding IC. Whether it's a program official or the grants management specialist. If an organization has a pending award but no assurance, the funding IC will work with OLAW to initiate the negotiation process, and OLAW will work with the organization to make sure they obtain the appropriate assurance so they can get their award. Before I move onto the three different types of assurances, I'd like to mention that for the PHS policy standards for animal care and use as shown on this slide, there are four documents that you must be familiar with. The first document on the left, the US Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training. Consists of a framework of nine ethical principles governing the humane care and use of animals in research. The second document, the Guide for the Care and Use of Laboratory Animals. It's also known as the guide. It must be used by institutions to base their animal care and use program, and it also is intended to assist investigators in fulfilling their obligation to plan and conduct animal studies in accordance with the highest level of scientific, humane and ethical principles. All institutions are required to comply as applicable with Animal Welfare Act and any other federal statutes and regulations related to animals. And finally, the PHS policy also requires that the methods of euthanasia be consistent with American Veterinary Medical Association, or AVMA guidelines for the euthanasia of animals. If such methods are inconsistent with the euthanasia guidelines, investigator must provide scientific justification for deviating from these guidelines. So I'll provide a brief overview of the three animal welfare assurances that can be negotiated. Domestic, foreign and interinstitutional. A domestic assurance is negotiated and required for US institutions that receive funding from the agencies that we oversee. Either through a grant, a cooperative agreement or a contract, and these institutions have their own animal care and use program, with an institutional official, an IACUC, a veterinarian, and animal work will be conducted on site at this organization. Okay, so and domestic assurances are approved for up to 4 years, and will be renewed only if there is continued funding from the agencies, either directly or indirectly. A foreign assurance is negotiated when the awardee or the recipient is a foreign organization, or the domestic awardee is conducting animal work at a foreign site, in which case the domestic awardee's IACUC is responsible for reviewing and approving the animal work that is conducted at the foreign site. The foreign organization commits to compliance with all laws, regulations and policies regarding the humane care and use of animals and the region that the research is being conducted, and it must be guided by the International Guiding Principles for Biomedical Research Involving Animals, also known as the CIOMS principles. And finally, the interinstitutional assurance is negotiated when a grantee organization does not have an animal care and use program or animal facilities, and it does not conduct animal work on site. Instead, the animal work will be conducted at a performance site that does have an animal welfare assurance. If that alternative performance site does not have assurance, OLAW will negotiate the appropriate assurance upon request by the funding IC. And interinstitutional assurances are approved for the life of the grant, for up to 5 years. So I have another poll question for you. Based on what we've discussed in terms of definition of an animal, the requirements of a completed VAS, as well as assurances and verification of IACUC approval, what do you think is needed to make an award? Quartz Biotech is submitting an NIH grant application for research involving animals. So the VAS has been submitted. The animal activity will be conducted however at Flintstone Technology, which has an assurance on file with OLAW. The PI, Dr. Barney, says Quartz Biotech has a memorandum of understanding, or MOU with Flintstone in place, therefore he's ready to conduct the research when he receives the award. Is Dr. Barney correct? A, Dr. Barney is correct because he has an MOU. B, Dr. Barney will need IACUC approval with the MOU. C, Dr. Barney will need an interinstitutional assurance through OLAW. Or D, Dr. Barney will need an interinstitutional assurance through OLAW and IACUC approval. Which one do you think it is? You should choose the most appropriate answer for the scenario. And we have an overwhelming agreement that the correct answer's D. And you are correct, very good. So remember, in this case, Quartz Biotech, Dr. Barney's from Quartz Biotech and he submitted a grant application, so he completed a VAS. We're assuming he completed a VAS in his grant application, however, the animal work is not conducted at Quartz Biotech, but rather Flintstone Technology. Flintstone Technology has an assurance, but we'd still need an assurance for the awardee institution, which is Quartz Biotech. So therefore an interinstitutional assurance needs to be negotiated, and of course he needs to have verification of IACUC approval as well before receiving this award. I'd like to also mention that the policy requirements also applies to all parties, primary and subs in collaborations, whether it be cooperative agreements or contracts where animal work will be conducted, and this means that they must have a completed VAS during the time of application. There must be verification of IACUC approval within 3 years of the budget start date. I will mention that there may not need your IACUC approval for the same activity that may be being performed at two different sites, and they must have an appropriate animal welfare assurance for the awardee institution as well as all of the other performance sites where animal work will be conducted. So you may be asking where in the grant application will I need to look for if I my work includes vertebrate life, vertebrate animals. So I'll give you a brief overview of the sections of the grant application where it's applicable, and it would be the project performance site locations and research and related, SF424. As well as PHS398, research plan and cover page supplement. So let's go through each one of these. In SF424, performance site, please be sure to list all of the performance sites where proposed animal work will be conducted. It's important that you list these performance sites so that OLAW can negotiate the appropriate assurances if needed once requested by the funding IC. Okay, in section two of the research and related of the SF424, the question is asked are vertebrate animals used. Based on the PHS policy definition of an animal, you should have a good idea of whether or not it involves live vertebrate animals, and if you do check yes then you need to then check whether or not IACUC review is pending. Remember, verification of IACUC review can be submitted in accordance with just-in-time procedures. And so if it is pending there's no need to include the IACUC approval date at this point. However if it's not pending, please ensure and include that IACUC approval date, which must be within 3 years of the budget start date. And animal welfare assurance number, if you, as the applicant, if your institution has an animal welfare assurance number, please be sure to include that there. If your institution does not have an assurance number, just state none. Do not put the assurance number for the alternate performance site, only for the applicant organization. Section five of the PHS research plan, this is where you'll upload a PDF of your completed vertebrate animal section, which included an addresses all three criteria of your VAS. Please be sure that you provide a concise description, a justification, as well as minimization of pain and distress, and you upload your PDF of this completed VAS. And last but not least, in the PHS398 cover page supplement, the question is asked whether your vertebrate animals will be euthanized at the end of the study. If your answer is yes, please check that yes box, and then you must check whether or not your method of euthanasia is consistent with the American Veterinary Medical Association or AVMA guidelines. Okay, if it's not, then you must include in the text box on this form, describe your method for euthanasia, and you must provide scientific justification as to why the method is inconsistent with the AVMA euthanasia guidelines. So I do have one final poll question for you, and my question is based on everything that's been discussed so far, what do you think are the PHS policy and NIH grants policy requirements when making an award involving animals? Is it A, a completed VAS in the application? B, verification that IACUC has reviewed and approved those sections of the application that involve the use of live vertebrate animals? C, animal welfare assurance for the applicant organization and all performance sites. Or D, an assurance for only the applicant organization even though there are other performance sites. And please check all that apply, so it can be a multi answer. It's a multi answer question. Okay, very good. So the majority of you got this correct. The correct answers are A, B and C. A completed VAS, verification that the IACUC has reviewed and approved those sections of the grant that involve live vertebrate animals, and C, an animal welfare assurance for the applicant organization, as well all performance sites where animal work will be conducted. Good job. So before I end and wrap up, I'd like to just briefly mention a little bit about noncompliance. The PHS policy is based on a philosophy of self-regulation, self-monitoring and self-reporting. And therefore any identified noncompliance with includes a serious noncompliance from the PHS policy, a deviation from the guide, or suspension by the IACUC must be promptly reported to OLAW, and included in your report, your final report to OLAW, you must also include the corrective measures that were implemented by the IACUC in order to prevent recurrence of such noncompliance. What I'd like to mention is there are implications of noncompliance, and such implications may include imposing special terms and conditions of your award. The funding agency may determine that absolutely no costs may be charged to the grant during the period of noncompliance. The funding agency may suspend or terminate your award, and OLAW may even restrict or withdrawal your assurance. Sometimes OLAW may put the institution on enhanced reporting requirements until they're satisfied that such noncompliance has been resolved completely, and may even escalate to sanction as much as criminal prosecution. So it's important to know that compliance with the PHS policy when your research involves animals is important. It's required, and the use of animals is a privilege, not a right, and it's your ethical responsibility to ensure that animal welfare is always your top priority, and to ensure the credibility of your data. So I've completed all five objectives, hopefully you do have a better understanding of what is defined as an animal, as well as the three requirements, policy requirements when your research involves the use of animals, as well as the implications of noncompliance with the PHS policy. Please remember that if you have any questions or concerns, that you can reach out to us, we can be reached via e-mail, phone, our website has a wealth of information, and you can follow us on Twitter or you can subscribe to our LISTSERV for any updates or announcements. And with that, I'll take any questions that you may have. Thank you.

Cate Pritchard: Hi, Neera. Thank you. That was great.

Neera Gopee: Hi, Cate. Thank you.

Cate Pritchard: Okay, we have a lot of good questions. I'm just going to warn you. So I'm going to try and cruise through these. Okay, so the first question is does the NIH require the gaining institution to perform a congruence review prior to the awarding of a type seven transfer application. So that is where this is a change of institution request. So they're asking if they have to perform a congruence review in that case.

Neera Gopee: Can you repeat that question, Cate so I understand what's going on there?

Cate Pritchard: Yeah, so basically if a grant is going to be transferred to another institution, and the institution that it's being transferred to, do they need to perform a congruence review.

Neera Gopee: So I don't know the answer to that one, and I will definitely find that out, and you can find some way of getting back to that individual about that answer to be honest.

Cate Pritchard: Great. The next one, can our institutional animal care and use committee be in the process of reviewing our protocol, but not yet have approved it when we apply for a grant?

Neera Gopee: Yes. And that's the beauty of this, it's an attempt to reduce burden, because a lot of applications, NIH receives 80,000 plus applications a year. I'm not sure how much of that actually involves animal use, but not all of those will be funded. So instead of wasting the IACUC's time in reviewing every single proposal that may be going through the application process, what we try to do is streamline this where during the submission process they may not need verification of IACUC approval, but if you do have a fundable score, you will be notified and that's when you need to submit that IACUC approval. So there may not be IACUC approval at submission, but it needs to be submitted in accordance with just-in-time procedures. Yes.

Cate Pritchard: Thank you. All right, could you just talk a little bit about chimp studies? So we got a comment that says the NIH does not support chimp studies anymore, but there are a few caveats there. Would you like to talk about that?

Neera Gopee: Yeah, we do not ... We do not support anymore invasive chimp studies, but there are some studies that we do still allow, and those are noninvasive studies, and they have to be a lot of them tend to be observational. And if chimp studies are being proposed, whether it's collection of feces or something like that, as I said it's noninvasive, it goes through a special review process as well, to make sure that it's not invasive and it's meeting the requirements of what NIH had submitted that no longer will support chimp studies, invasive chimp studies.

Cate Pritchard: Okay. We have about 2 minutes left before we need to close up. Quickly, who reviews the VAS?

Neera Gopee: So the pair reviewers do that through the study review section, they review it. If there are any issues that arise, like animal welfare concerns, it's given a special code, and in the summary statement it does say whether or not there are animal welfare concerns, and when there are animal welfare concerns it then comes to OLAW, and OLAW is the only entity that can actually resolve those concerns. And it's a back and forth process, it goes through the program official back to the investigator for the investigator to address whatever concerns OLAW may have with the VAs or with the procedures that's described in the VAS until it's resolved, and then that code is removed. It's like a bar to funding, and when that code is removed then it can proceed naturally through the process. So in essence it's a pair reviewers, if there are no concerns it's just a pair of reviewers. If there are concerns it gets escalated to OLAW.

Cate Pritchard: There's one that I think a few people may have, it seems to be about congruence review. So adding a new protocol in the study, would you have to perform congruence review, and I put some of our resources in the chat, but I wonder if you could talk about if there are significant changes, and what you would need to do.

Neera Gopee: So it depends on what ... Okay, so once you have ... Congruence review is only required prior to award, at the first time, when you verify IACUC approval, that by itself says that your institution has conducted congruence review. Verification of IACUC [Indistinct] in a sense is telling us that you've conducted a congruence review. It's only required one time prior to award, okay? If you do have significant ...

Cate Pritchard: Yep, I'm just going to put in there that significant changes you can find that information on our website, and you also need to be aware of change in scope, but we have less than a minute left and I just have a few closing things that I have to say. I'm sorry.

Neera Gopee: Okay. No, it's okay, it's okay.

Cate Pritchard: And we have participant information that we can get back to. So I want to thank you all for participating in this session. You can send us an e-mail to OLAW@NIH.gov. Mail.nih.gov? Yes. OLAW@mail.nih.gov if you have more questions.We always get back to you. And your feedback is important, so please take a moment and let us know what you think. There's a session feedback button located in the description and presenters in the auditorium list. So thank you again and we hope you have a great day.