Preparing a Small Business Application Involving Vertebrate Animals Webinar – February 2023

Stephanie Fertig: All right. So, thank you all for joining us today as part of our series of webinars that we're having around preparing the SBIR and STTR application, we're pleased to talk today about Preparing a Small Business Application Involving Vertebrate Animals. A couple of quick housekeeping issues. We will be making this recording and the slides available after the webinars. So please do look for those on our events page, we will provide information around that. I know that's a question we always get. So, I want to let you know, don't worry, we will be providing the recording and slides after the fact. If you have any questions, I encourage you to put those in the chat. We will have some- we're hoping to have some time for Q&A after the fact. But please do-- I'm sorry, put them in the Q&A, not the chat, put them in the Q&A. We're going to be providing links within the chat. So that's going to be a wealth of information for you as we're going along, but the Q&A section for questions, and we'll either try to answer those via text within the Q&A or in-- we'll answer those in the Q&A section.

So, for those who don't know me, my name is Stephanie Fertig, I'm the HHS Small Business Program Lead. And I'm joined today by two of my colleagues: Jane Na, who's the Director of the Division of Assurances in the Office of Laboratory Animal Welfare, and Nicole Lukovsky-Akhsanov, who is the Senior Animal Welfare Program Specialist in the Division of Assurances in the Office of Laboratory Animal Welfare. And so, before I turn it over to them, I'm just going to provide a brief, very brief overview of the Small Business Programs and to kind of provide a backdrop to what we're talking about today.

So, when we're talking about the NIH mission, which can really be summarized as turning discoveries into help, the small business programs take those great innovations that are often developed in laboratories across the country and help get them into the hands of the patients, clinicians, caregivers, and researchers that need them.

These small business programs, also known as America's Seed Fund, are programs that have a set-aside specifically for small businesses. So, we have about $1.2 billion for small businesses in

NIH's research and development budget. Now, when we talk about the small business programs, we talk about both SBIR and STTR. And in the federal government, sometimes you'll just hear it as SBIR, we'll refer to one and we might not refer to the other but in this, today, we're going to be talking about both of these programs. What do you need if you've got animal subjects in either the SBIR or STTR program?

I'm not going to go into a lot of details around the particulars of the programs, but I really do encourage you to go to our small business website, seed.nih.gov. It's a wealth of information. It includes open funding opportunities, it's a little small on this slide, but there's a big blue button right top front and center that has information about open funding opportunities, so you can see where, how you can currently apply. But we do have a number of resources that are available. And again, we're going to talk specifically about animal subjects today, but there's a wealth of information online on how to prepare an application from application instructions, always important, to an annotated form set and sample applications.

We do have a number of programs for applicants. If you've not received an SBIR or STTR in the past, I encourage you to take a look at the NIH applicant Assistance Program, as well as the Health Disparities Pre-Application Program. And again, these are programs that really do help individuals through that application process.

The most important piece of advice though, and I'm sure you're going to take that this time, is the program officers, program staff, individuals, NIH, we're here to help. Please talk to us. I'm hoping we're going to dispel the myth that we are unapproachable. We try to be very approachable, and we try to be here to help you. Please talk to a program officer. We have lists of program officers at the seed website. If you're not sure who to talk to, you can see what institutes and centers have supported similar research in the past on the report.nih.gov, or you can email us directly: seedinfo@nih.gov. And the list of all those program managers, look for the big NIH and right underneath that is that list. So, with that, I'm going to turn it over to Jane, who's going to talk a lot about what to do if you've got an application that has small animals, vertebrate animals in it.

Jane Na: Thanks so much, Stephanie. And good afternoon. Thank you for joining us. And thank you to SEED for hosting this informational webinar. My name is Jane Na, and I'm the Director of the Division of Assurances in the Office of Laboratory Animal Welfare, which is a part of the NIH Office of Extramural Research. And with me today is Senior Animal Welfare Program Specialist, Nicole Lukovsky-Akhsanov, who will be presenting the second half of today's presentation. So, without further ado, I will get right into the content.

There are some objectives for today. And although it looks like a lengthy list, we'll be walking through it and having some interactive polling that we hope that you will be engaged in as well, to help learn about how to learn what you need to while applying for small business, small tech transfer applications, grants and contracts, and whatever other funding mechanisms.

So, we'll summarize oversight responsibilities of the office that we're from. And we'll talk about the origins and requirements of the Public Health Service policy on humane care and use of laboratory animal, which we'll refer to as PHS policy. We'll define live vertebrate animal, and we will hopefully help you understand the requirements of the Health and Human Services Acquisition Regulations for contracts and the NIH grants policy statement, which apply to grants.

We also hope you will identify PHS policy requirements for an institution receiving funding involving the use of live vertebrate animals, as well as identify three types of animal welfare assurances, and discuss the vertebrate animal section, which is the component in the grant or contract application that describes the animal use. And we'll discuss IACUC verification requirements and help you understand compliance oversight requirements, touch on 21st Century Cures Act information, as well as provide information regarding additional educational opportunities.

So, OLAW's mission really is to ensure that humane care and use of animals in PHS supported, so Public Health Service supported research and testing and training. And through this mission, we use the PHS policy to implement the Health Research Extension Act of 1985. And that provides the legislative authority for OLAW. And I'll go into our responsibilities. So, we oversee

the implementation of the PHS policy and provide an interpretation and guidance for this document, as well as the prime component that we use for oversight of institutions.

We negotiate animal welfare assurances, we either approve, negotiate one till it's satisfactory to our office, or, you know, in the event that the institution does not qualify for animal welfare assurance, we'll assist individuals with identifying an assured institution to work with. In addition, we evaluate compliance, and Dr. Lukovsky will discuss more about these topics. And we're also engaged in educational activities such as this webinar that we are in today.

Our office is composed of three different divisions. So, our director of the OLAW office is Dr. Pat Brown. And we're both from the Division of Assurances. And as indicated, there's a Division of Compliance Oversight, as well as a Division of Policy and Education. So those are the main areas of our office. And as I had indicated, we really implement the PHS policy, which outlines institutional responsibilities if you do receive Public Health Service funds for animal research. And some the major components of this is included in this list, the animal welfare assurance, again, the main mechanism of oversight, and that's the description of your animal care and use program, basically a document, sort of a contract with the US government.

The Public Health Service policy also talks about the functions of the Institutional Animal care and use committees and goes into review of PHS conducted or supported research projects, and the information required in applications and proposals that you're going to be submitting to PHS to hopefully get funds for your projects, as well as record-keeping requirements and reporting requirements.

So, I have indicated that Public Health Service funded institutions are the individuals that we oversee. So, some of the agencies that fall under the Public Health Service include NIH, but it also covers FDA, BARDA, which is the Biomedical Advanced Research and Development Authority, as well as CDC. So those are some of the more frequent agencies under PHS policy. But in addition to NIH and FDA, the PHS agencies, OLAW has MOUs or Memoranda of Understanding with other agencies, including the National Science Foundation, the Department of Veterans Affairs, as well as NASA. So those animal activities projects funded by those institutions or agencies are actually also overseen by OLAW.

I apologize, and I got a slow hand as far as advancing the slides. And again, you will receive the slides after the presentation, they will be made available. So, I apologize that I did miss those. So, moving on to PHS policy, PHS policy also relies and indicates that institutions that are performing the animal research are in compliance with other documents. So, these documents in the upper left are the USDA Animal Welfare Act and Regulations. So, if animals in that arena are also regulated by the USDA, you would also have to abide by the USDA regulation. The blue document in the middle, the US government principles for the utilization and care of vertebrate animals used in testing research and training, is also a document that generally outlines principles that are covered in PHS policy and good humane care and use of animals.

And then the book in the bottom left is the guide for the care and use of laboratory animals. And then the document in the kind of middle at the bottom is the AVMA guidelines for the euthanasia of animals. So, all of these documents are required for institutions to follow, be followed in order to be compliant with PHS policy in addition to being compliant with PHS policy itself. So, one part of PHS policy is the definition of an animal. So how the PHS policy defines animal is any live vertebrate animal that's used or intended for use in research, research training, experimentation, or biological testing or related purposes. And where this comes into play is because it determines if PHS policy applies to you.

So as a little exercise, if we get the poll started, there is a list available of potential studies that are going to be a multi-select, you can choose more than one, which of these studies would be considered vertebrate animal use? And we did include the PHS policy definition in the corner for your reference, but please do try to make your selections as to whether or not you think that per PHS policy, the study involving whatever animal is listed, would be considered vertebrate animal use. You would be choosing from whether embryonated eggs, tadpoles, zebrafish, cow spleen from a slaughterhouse, custom antibodies from a goat, chimp behavior study, octopus nerve study, and mosquito malaria study.

So, we've got the poll results up. And looking at the results here and we see some answers, it looks like at least one person answered yes to all of them. And it's not necessarily an incorrect answer for some of these because a lot of these situations depend. So, for example, embryonated egg, technically it is not considered animal use because OLAW defines an animal

to be counted for PHS policy purposes once that hatches, so an embryonated egg has not yet hatched, and would not be considered animal use.

The complication comes in when it's possible that an animal's mom, so whoever laid the egg, is on the study, and that is a vertebrate animal, theoretically. So, if that's the case, then yes, it would be considered animal use, but embryonated egg itself is not. A tadpole is a vertebrate. So, it has a backbone, and would be considered animal use. Same with zebrafish. And cow spleen from slaughterhouse also is a little bit of a wishy-washy situation. The cow spleen, if it is leftover tissue that was not specifically where the cow was slaughtered for purposes of the research, that wouldn't be considered vertebrate animal use, because it's considered extra tissue if it's already going to be slaughtered for normal purposes. So that's why it's not checked.

And then we have custom antibodies for goat. So, if the antibodies are custom made and generated specifically for the purpose of the study, we do consider that animal use because the animals are undergoing procedures in order to generate those antibodies. So that's why custom antibodies from a goat would be considered animal use. But it would not be considered animal use if the antibodies were commercially available just off the shelf because that is not specifically animal use for your project.

And if you're getting kind of a little bit of a picture here, it's very case-specific dependent on the situation, and OLAW is always here to assist you. At the end of the slides, and again, you will receive the slides from SEED after the webinar, our contact information is here. So, if you're ever in doubt, you can certainly contact our office and run by scenarios for whether or not this would be considered animal use.

And then to finish off the list, everybody-- well, no, 90%, a lot of the majority of people thought that chimpanzee behavior study would be considered animal use. And kind of on the surface, it would be considered animal use, as long as the animals were actually being manipulated or impacted in some way. So, it's a very fine line because purely observational studies that don't impact their behavior at all, wouldn't be considered vertebrate animal use. But we know it's very not straightforward and are willing to help you if you do have any question.

And then the last two, octopus nerve study and mosquito malaria study are not considered vertebrate animal use because the octopus is not considered an animal that has a backbone. So, it is an invertebrate, and therefore not included in the definition of an animal per PHS policy. And mosquitoes are insects, so that would also not be considered.

And with the animal use at the institution, there's committee that oversees the use of animals, and that's called the Institutional Animal Care and Use Committee. And they are responsible for overseeing the animal studies that go on at any institution. And again, it would be required for them if they received PHS, NSF, NASA, or VA funds to follow PHS policy and the guide for the care and use of laboratory animals. And they have very many federally mandated functions. So, part of the functions are the IACUC review of the animal research. So, there are specific components listed specifically in PHS policy that the IACUC would be responsible for reviewing.

So listed on the slide are the items that they would be required to ensure are part of the research projects described and reviewed and approved by that committee at each institution. And the additional information that is required in applications or proposals from institutions also cover some of the items from the previous slide, but also the identification of species, providing the number, rationale for use of the animals, the appropriateness of the species and the numbers, and the full description of the animal use procedures to ensure good humane use, so minimization of pain and discomfort, and description of any euthanasia method to be used. So that's a lot of information that would be required in your grant or contract proposal.

And the HHS acquisition regulations also has certain clauses that are included or any contracts that are funded. And they also similarly include vertebrate animals per PHS policy. And I previously mentioned if there are USDA regulated animals, that would also apply. So, grants and contracts are covered if funded by any of those agencies I previously included, but most importantly, NIH.

The PHS policy, as well as the HHSAR, the HHSAR require compliance with PHS policy and so do grants policy statement. So, NIH grants policy statement are essentially terms and conditions of the grants award. So, it's a little bit of a corollary to- you have to follow the HHSAR if you're

getting a contract, and you have to follow grants policy statement if you're being awarded a grant.

Also, as part of the application or contract proposal, there are requirements, previously mentioned, the animal welfare assurance, and the vertebrate animal section, and then the IACUC review and approval of the vertebrate animal procedures at the institution. So, we're going to go into each of these one by one. So, for the assurance, as I said before, it's kind of a description of the animal use and then it also has to include description or methods that describe the minimization of pain and distress and the minimization of animal numbers.

Okay. And there are three different types of animal welfare assurances, domestic, inter-institutional, and foreign. On the main OLAW webpage, which is screenshot on this slide, you can look up domestic and foreign assured institutions on our webpage, there's little buttons that are visible, that you can do searches. We do not list Interinstitutional Assurances on our website, because they are project specific. And there's quite a number of them. So, we do about 800 to 850 Interinstitutional Assurances with the majority of those being SBIR/STTR awards.

So we'll go into individual types of assurances, the Domestic Assurances for a domestic institution, there are some criteria that the institution in order to qualify for Domestic Assurance has to control their own facilities, conduct research on-site, and have an animal care and use program with an institutional official, the IACUC, a veterinarian, and you're only eligible when you receive PHS, NSF, NASA, technically VA funding. And the process is that the funding component request negotiation of this assurance from OLAW.

And once we receive the funding component request for an assurance, we ensure that all the appropriate documentation is submitted, and the vertebrate animal section is reviewed. And then we'll work with the institution in order to approve the assurance. The Domestic Assurance will remain in effect for up to four years, and it can be renewed if there's continued involvement with animal projects funded by PHS, NSF or NASA. And the assurance was signed by the institutional official who's committing the institution to follow in PHS policy, grants policy statement, a HHSAR if it's a contract, and all those previously mentioned document.

Next, I'm going to talk about Interinstitutional Assurances. So again, this is the majority of SBIR/STTR awards. So, this is when awardee institutions, so theoretically, you if you're at an institution planning to apply, these are when awardee institutions don't have an animal care and use program themselves but are going to have the animal work conducted at an assured institution. As I previously said, they are project-specific, and so they're valid for the life of the award, or up to five years, whichever arrives first. And again, they're not listed on our website. And they are only valid between the institutions signing the Interinstitutional Assurance. So, the awardee institution as well as their paired assured institution. And as with domestic and foreign, you only qualify for this once you're imminently going to receive the award, grant or contract. And the funding component requests this of OLAW before the process gets started.

And finally, the foreign assurance. It's similar criteria to Domestic Assurances, the foreign institution must control their own animal facilities, conduct the animal research on site, and they have an institutional signing official. The thing that varies or is different from the Domestic Assurance is that the foreign institution is guided by the international guiding principles for biomedical research involving animals. And they are also to follow their laws of their jurisdiction, so their own laws, regulations for that local area.

Like the previous assurances, again, we don't negotiate foreign assurances, until there's funding imminently to be awarded, and the funding component informs OLAW of this award and the need for the assurance, and then we'll negotiate the assurance. Currently, foreign assurance remain in effect for up to five years. And it can be renewed if there's continued involvement with animals funded by PHS, NSF or NASA. And like the Domestic Assurance, the assurance is signed by the institutional official.

So oftentimes, there are people that kind of cooperate, collaborate, or have consortium agreements and have sub awards. Essentially, the prime awardee is always accountable for all of the regulatory requirements regardless of all of the other collaborators they may involve. This also applies to small businesses that have their animal work conducted at another location, at an assured location. The prime awardee is who the award is going to, so they're accountable, and they have to ensure that all of the animal performance sites have an approved assurance and the IACUC approval dated within three years in order to be compliant with the terms and

conditions of their grant award. And all of the animal welfare requirements apply to all consortium participants, and sub-projects.

Next, we're going to talk about vertebrate animal section. So again, this is the section of the grantor contract proposal that describes the animal use. On our webpage, we actually have a fantastic resource that steps individuals through the components of what a vertebrate animal section is comprised of. There is, under fast facts, if you click on one of the menus, the VAS requirements of the vertebrate animal section requirements. And there's a cute little module tutorial that will step you through and it's an interactive learning mechanism that is highly encouraged for if you would like to know or learn what makes an appropriate vertebrate animals section.

So, there are criteria or items to be addressed in the vertebrate animal section, such as the description of the procedures themselves. So, in addition to what is actually going to occur to the animals, the identification of species, the strains, breed, ages, sex, and total number of animals by species is required. And if the animal work involves dogs and cats, the source of the animals is to be provided. Then justifications of the appropriateness for the species and why the research requires use of live vertebrate animals instead of why the research goals can't be accomplished by computers or doing human trials or use of invertebrates such as octopi, octopus, squid, or why in vitro studies are not sufficient.

Then there is a single criteria that, again, it's a description of the minimization of pain and distress. So, as the OLAW mission is to ensure for the humane care and use of animals, we want to make sure that institutions are also applying appropriate pain-relieving methods, anesthesia, in order to ensure that the animal use is as humane as possible for the research. And then finally, the method of euthanasia, if the animals will be euthanized, needs to be provided and the AVMA guidelines, or one of their methods, the method that is used for euthanasia must be approved, or the description of the method, if it's not AVMA approved, needs to be described and a scientific justification for the reason why the unapproved method must be used is to be provided.

So, that's the vertebrate animal section. And kind of the last requirement to be discussed is the verification that the IACUC has reviewed and approved the part of the application that involves the vertebrate animal use. So, the IACUC is going to review and approve the animal work, and in order for the award to be made, the awarding institution or sometimes it is the assured institution, will provide the verification of IACUC approval. So, sometimes that provided in a date that the IACUC approves the protocol, and it has to be within three years or 36 months of receiving that award.

And it is also part of in providing the verification of IACUC approval, by providing that date, the institution is kind of like stating or are confirming that they've ensured that within the grant or contract application or proposal, is in the IACUC approved protocol at the institution. And that's where the HHSAR and the NIH grants policy statement sections go into that requirement. And no cost for activities with live vertebrate animals are supposed to be charged if there is no approved assurance, and no valid IACUC approval for all animal performance site. And Nicole will talk a little bit about compliance consequences later on in her slides.

The OLAW website includes a very, very nuts and bolts description of what investigators need to know about the use of animals for NIH funded research and that's available at the link on the slide and it has just very good general information some of which was covered today. And I will now turn this over to Dr. Lukovsky. Thank you.

Nicole Lukovsky-Akhsanov: Thank you, Jane. I am Nicole Lukovsky-Akhsanov, a Senior Animal Welfare Program Specialist with OLAW, and today, I will take you through some additional topics for discussion. First, we'll briefly touch upon our office functions regarding compliance that is overseen by our division of compliance oversight.

So, our office opened up about 5,492 cases between 2016 and 2021, with about 966 cases opened in 2021. There was about a 11% increase in the number of cases reported for calendar year 2021 as compared to 2020. And that's likely due to institutions restarting or ramping up research. So how and from whom do these reports make their way to our office? So, there's a variety of way that cases come to us, the most common being institutional self-reporting. The PHS policy is based on the concept of enforced self-regulation. So once an institution has

prepared an animal welfare assurance, and the assurance has been proved by OLAW, the institution is in a position to regulate itself. The concept is described as enforced self-regulation because if the institution fails to self-regulate, the approval of the assurance may be restricted or withdrawn from the OLAW.

Other cases reported to us stem from allegations from employees, reports from other oversight entities and funding components, and non-compliance identified during annual reports and assurance reviews. Additionally, allegations from other third-party sources are also provided to our office.

As far as who's responsible for reportable issues provided to our office, as reported in fiscal year 2021, the investigator and the research team make up the large majority, around 66%, with the animal care staff coming in at a distance second, around 14%, the IACUC around 3%, VET staff around 3% as well, and other comprised of individuals that don't necessarily fall under any of these categories also at 3%. "None" is around 11%, and those are typically involve adverse events, natural disasters, things of that nature. And additionally, the institution was found to be responsible for about 1% of reportable issues.

So, this chart illustrates the type of reportable incidents OLAW received in 2021. Animal study issues accounted for about 27% of reportable incidents, with almost 90% of those study issues related to not following or not being familiar with the protocol. Also, here are those incidents that occur where cases overlap with another category, such as protocol non-compliance resulting from a training failure. Failure to follow institutional policies accounted for around 19%, followed by animal husbandry issues and clinical issues. Physical Plant represents issues with the facility itself, such as HVAC or water concerns. And the category Other Issues represents human error, natural disasters, and other similar events.

So, preventing avoidable and non-compliance. So, the reason I wanted to share this slide is that we've seen non-compliance issues stemming from organizations either not obtaining an assurance or sub-contractors or sub-awardees of the prime awardee that are performing live vertebrate animal work not obtaining an assurance. Obtaining proper assurances is key to following PHS policy, which is Federal law. In addition, ensuring there's a valid IACUC approval

for the work to be conducted is key. This is one area where OLAW works hand-in-hand with the funding components and the awarding institutions to provide education in an effort to help avoid preventable non-compliances such as the absence of a valid assurance, the absence of a valid IACUC approval. Today's training session is just one example of the many types of outreach we conduct to provide education and uphold OLAW's mission.

So ultimately, what does a non-compliance reported to our office mean? So, in most cases, the goal is to be ensuring that the organization has implemented appropriate effective corrective actions with a goal to prevent recurrence of the incident leading to program improvement. This involves evaluation of the processes implemented by the organization by our office, and sometimes we can have additional feedback until concurrence on the resolution is reached. In cases where charges had been made for unauthorized animal activities, appropriate adjustments may be required to be made to the grant to remove those charges.

NIH expects that recipients continue to maintain and care for animals during periods of when animal activities are conducted in the absence of a valid animal welfare assurance or IACUC approval. Additionally, in situations where there's more serious concerns, outcomes can include limitations being placed on the assurance or withdrawal of the assurance altogether. Special terms and conditions can be placed on the organization, suspension, or termination of the award altogether, and in rare instances, even going up to criminal prosecution for egregious events.

So importantly, reporting is a cooperative process with the goal of being improvements in the quality of animal care and use program. As discussed, the organization must provide evidence of implementation of corrective actions and our office takes an active role in evaluation and providing additional guidance when needed. It seems to be an issue with the slides. Bear with me. Okay.

So, reporting non-compliance, so OLAW's website about reporting non-compliance has more information about what specifically constitutes a non-compliance, and the details on how to submit a report. We aren't going to get into the finer details of reporting non-compliance here.

However, if your institution has any questions about reporting, there's a variety of ways to get in contact with our division of compliance oversight via telephone and email.

So now we'll move on to a lighter topic, I wanted to briefly touch upon some ways OLAW is working to reduce regulatory burden. So, one topic that has generated a lot of interest is OLAW's implementation of the new guidance based on the report for reducing administrative burden for researchers in response to 21st Century Cures Act. The 21st Century Cures Act directed the NIH in collaboration with the USDA and FDA to conduct a review of applicable regulations and policies for the care and use of laboratory animals and to make revisions as appropriate to reduce administrative burden on investigators while maintaining the integrity and the credibility of research findings and the protection of research animals.

So, our efforts are more directly focused on stakeholders, such as assured organizations, however, this topic has significant amount of information and far-reaching effects. More details can be found directly in our main website, which has a link to the landing page to a more detailed discussion of how OLAW in coordination with the USDA and FDA has been working to address this directive. Current topics of interest include grant and contract protocol congruence review details, prompt reporting guidance, and annual reporting to OLAW, among others.

Next up, we'll discuss some educational opportunities that may be of interest to you. So OLAW's Division of Policy and Education works to provide access to training opportunities, developed both externally and internally within our office for a variety of different audiences on a variety of different topics of interest. The photo is a screenshot from our website that can be reached by clicking on the Education tab. From here, there's a drop-down list containing webinars and podcasts created by OLAW that could be found here with information on upcoming webinars, in addition to access to previously recorded webinars that have been archived.

Links to workshop and conference information are also available and externally hosted training opportunities can be found on this website. I encourage you to take some time and explore the website as there may be information that will be helpful to your specific question or your specific situation.

So briefly, here's a list of some upcoming external educational opportunities, including the USDA hosted Animal Welfare Information Center, or AWIC workshop. It's both virtual and has free registration. Additionally, the Scientists Center for Animal Welfare or SCAW is hosting an IACUC training workshop in June of this year. And again, all this detail plus more can be found on our website under the Education tab.

So, we want to take some time to have an interactive trivia session based on what we just discussed. There'll be a series of questions and we'll use the prop-up polling feature in Zoom that we use previously to allow you to- for what- for the answer what you think best fits the question. So, without further ado, we'll proceed.

So, Scenario 1, part 1. So, Bob's Biotech will be the awardee for an award involving animal research. Bob's Biotech does not have their own animal facility but has made preliminary plans with Lark University to conduct the animal studies in Lark University's facility. What are the requirements for the contract to allow animal activities to proceed? So, is it a completed VAS for animal work to be conducted? List Lark University as a performance site? Both sites need an assurance- Lark University needing a Domestic Assurance, Bob's needing an IA with Lark University? IACUC approval from Lark University? Or all of the above?

I think we are all set. So, in this situation, all of the above would be required, something 95% of you, 94% of you got it, which is great. So, a vertebrate animal section is required for review, Lark University is the physical location where work will be conducted, so they are the performance site. Both organizations need the assurance; Lark University needs that full Domestic Assurance, and Bob's Biotech needs and Interinstitutional Assurance with Lark University. And of course, IACUC approval for the work conducted at Lark University is required.

All right. So, we're going to move on to Scenario 1, Part 2. So, in this situation, Lark University is no longer able to conduct the agreed upon studies. So, Bob's Biotech identifies BioCorps, a US contract research organization, as a new animal performance site. What is necessary? So, is it nothing, the funds were already dispersed, and changes happen all the time with science? Bob's Biotech must inform the funding component to obtain approval for a change in animal performance site? BioCorps must have an approved Domestic Assurance? Or Bob's Biotech

must have an approved Interinstitutional Assurance with BioCorps who provides verification of IACUC approval?

And this is a multiple choice multi-select. Great, thank you. So, it looks like it's pretty good. So, Bob's Biotech, that's correct, must inform the funding component. In addition, Bob's Biotech must have an approved Domestic Assurance, and Bob's Biotech must have an approved Interinstitutional Assurance of BioCorps who provides verification of IACUC approval. Additionally, not noted on this slide, but however, as before, a vertebrate animal section for review is required. Great work.

Okay. We'll move on to the next scenario. So, Scenario 2; a PI at Research Inc indicates that she will not be performing any animal activities, but in the application, she indicates she will be obtaining custom rabbit antibodies from Alpha Omega Enterprises. What are the requirements for the grant to allow the animal activities to proceed? Is it a complete VAS for research animal activity? Listing Alpha Omega as a performance site? Both sites needing an assurance- Domestic for Alpha Omega, and an Interinstitutional for Research Inc? IACUC approval from Alpha Omega? Or is it all of the above?

Here are their responses. Okay, all of the above. That is correct. So, let's go through that and let's break that down. So, in this situation, all the above would be required. Animal work consisting of generation of a custom rabbit antibody is considered live vertebrate animal work as Dr. Na alluded to previously. So given that detail, animal activities will be performed. Therefore, VAS or vertebrate animal section for review is required. Alpha Omega is a physical location where work will be conducted. So, they're the performance site for that custom antibody generation. Both organizations will need assurances; Alpha Omega needs a full Domestic Assurance and Research Inc needs an Interinstitutional Assurance with Alpha Omega, and of course IACUC approval for the work conducted at Alpha Omega is required.

All right. Scenario 3. So, Beaker Scientific Inc is submitting an application as completed a VAs for contracts for research involving animals. The animal activity will be conducted Expert Bio, a CRO. Expert Bio has an assurance on file with OLAW. The PI, Dr. Beaker, says Beaker Scientific has a Memorandum of Understanding or MOU with Expert Bio in place and he is ready to

conduct the research when he receives the award. What are the requirements for the grant to allow the animal activities to proceed?

So, is Dr. Beaker correct because there is an MOU? Will Dr. Beaker need an Interinstitutional Assurance with OLAW and IACUC approval? Will Dr. Beaker need IACUC approval with the MOU? And Will Dr. Beaker only need an Interinstitutional Assurance through OLAW? All right, looks like the responses are in. Okay, great. So that's correct. Dr. Beaker will need an Interinstitutional Assurance through OLAW and IACUC approval. So specifically, that's correct. In addition, specifically, NIH grants policy section 15.2.1, under the written agreement section, states that a formal written agreement such as an MOU with each consortium participant is required. So, Dr. Beaker is correct that an MOU is needed. However, the MOU is not reviewed by OLAW. OLAW-specific requirements include the Domestic Assurance, the Interinstitutional Assurance and verification of IACUC approval that are all in place.

So, we'll move on to Scenario 4. So, Dr. Rhinder is working on conducting an exciting new study looking at the effect of a chemotherapeutic agent in zebrafish. When submitting the contract application, he is unsure if he should check "yes" or "no" for live vertebrate animal use and calls you for help. How would you advise him?

Is it yes, all zebrafish would be considered live vertebrate animals? No, because they're not a warm-blooded species? Or is this a trick question? All right, 95% of you got it right. Yes, all zebrafish should be considered vertebrate animals. However, there is a small caveat here. PHS policy applies to zebrafish larvae immediately after hatching, which is typically three days post fertilization under optimal conditions. Great work, everyone.

All right. We'll have some more questions for you. So, the PHS policy, the NIH grants policy, and the HHSAR requirements, when making an award involving live vertebrate animals include which of the following? An animal welfare assurance for the applicant organization and all performance sites? Verification that IACUC has reviewed and approved those sections of the application that involve the use of live vertebrate animals? A complete Vertebrate Animals Section in the application? Or is it all the above? Okay, it looks like 95% of you got it right. It is all of the above. Great work.

All right. So now we're going to switch gears for a moment. The slides should look familiar to you as there are several points of information required and applications and proposals for awards submitted that have live vertebrate animals. To review details such as identification of species and approximate animal numbers, the rationale for the use of the species, a complete description of work proposed with the details on procedures designed to limit any pain or distress in animals, along with euthanasia methods need to be provided. Next up, we'll take a look at a VAS provided to our office to see if this fits the criteria as described.

So, the question here is, is this VAS acceptable? So, what do you think, is the VAS acceptable here? I'll give you a couple moments to read over it and decide. Okay, so 83% of you said unacceptable, and I would agree with that. So, let's review. So, our office would classify this as unacceptable as written. The PI alludes to pharmacokinetic studies and surgeries. However, a concise description of these activities are not provided. The PI does provide that 100 mice will be used in total, however, details such as strain and age are missing. The justification section does not provide the rationale as to why mice are the most appropriate species for the study, and there is no justification as to why that alternate models cannot be used.

The minimization of pain and distress section does not provide any details regarding potentially painful procedures and interventions proposed, such as anesthesia and analgesia, especially given that the PI proposes surgery. Other details such as post procedure monitoring and specifically defined human endpoints have not been provided. Overall, this VAS is missing a lot of very crucial details that are needed to be provided to facilitate a complete review. I'll make another plug here for the training module the Division of Policy and Education created that would have been helpful here to guide the PI to provide a complete VAS.

So, this concludes our presentation for today. And hopefully, we've met today's learning objectives, which include being able to summarize all those oversight responsibilities, describe the origin and requirements of PHS policy, defined live vertebrate animal, and understand the requirements of the HHSAR and NIH grants policy statement. In addition, identifying PHS policy requirements for an institution receiving funding involving the use of live vertebrate animals, and identify three different types of animal welfare assurances. We discussed the vertebrate animal section in addition to IACUC verification requirements and understanding some basic

compliance oversight requirements. We discussed the 21st Century Cures Act and provided some additional opportunities for education.

So, here's our contact information, including our general inbox along with phone numbers and email addresses of all the divisions at OLAW and our main websites provided at the bottom of the slide for you as well.

So, in conclusion, collaborative relationships exist between NIH and awardees. Importantly, each partner has responsibilities and obligations as stewards of public funds. At the end of the day, I believe that something we can all agree on is that good animal welfare is good science. So, this is our contact information. If you have any additional questions or if certain topics have piqued your interest, and you need some more resources, please do not hesitate to reach out. Thank you for generously taking time out of your day today to attend this presentation. And I believe with that, we have some time for questions.

Question and Answer Session

Stephanie Fertig: So, I think we're at the end, we ran right up against time. But the good news is we actually answered pretty much almost all of the questions already, we typed in the answer. I do want to talk briefly about one question that I saw, which was about when there are changes or switching to a different CRO or switching to a different sub-awardee for animal studies. And I think you all touched on that really well when you talked about the questions, and I love the Q&A. I love the multiple-choice option because I think you hit a lot of the questions.

I think summarizing it, in the federal government, it's always better to ask for permission than ask for forgiveness. A little bit different from what a lot of small businesses may be used to. But please ask. You've got some contact information here. Please just ask before making that change, reach out to your program officer, really, you know, ask those questions.

The second question that we did receive that you all didn't touch on was a question around doing work outside the United States. It's important to note that for SBIR and STTR projects, work must be conducted within the United States, and this is part of the statute. In rare and

unique circumstances, we can allow a small portion of the research work to be conducted outside the US when it is not possible to conduct it domestically. So, the bar there is you cannot do it in the US. And that's a pretty high bar. So, the examples we use are when there's really limited materials or supplies or in the case of human subjects, patient populations. So, if you want to do work outside the United States, that foreign involvement will be considered on a case-by-case basis, it does have to be thoroughly justified in the application. And that's something, again, that is really important to reach out and talk to your program officer well in advance.

So, with that, again, I really thank everyone for joining us today. We are going to make the slides and the information both on the Q&A as well as the recording available to you. Give us a couple of weeks, it may take a couple of weeks to get that all processed, but we will make that available. But again, I just want to thank both of you for coming, sharing all that information, and also doing some fun interactive components. Always great to see, and I was happy to see there was a lot of right answers towards the end there. So fantastic. Great job, everyone. Thank you again, and I hope everyone has a wonderful afternoon.

Jane Na: Thank you, everybody.

Nicole Lukovsky-Akhsanov: Thank you.