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Contents: **Transcript**

Balancing Public Interests, Benefits, and Risks in Animal Research

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Slides 1-2 (Balancing Public Interests, Benefits, and Risks in Animal Research)
>>*Silk:* Hello, today is June 9, 2016. I am Susan Silk, Director of the Division of Policy and Education at OLAW. It is my pleasure to welcome Dr. Allyson J. Bennett to OLAW Online Seminars to present **Balancing Public Interests, Benefits, and Risks in Animal Research.**

Allyson J. Bennett, PhD, is Associate Professor of Psychology and Faculty Director of the University of Wisconsin-Madison Animal Program. She is a developmental psychobiologist whose research has advanced scientific insight into how social and physical environments "get under the skin" to affect behavior and health across the lifespan. Professor Bennett teaches courses in research methods and animal cognition. She has a long-standing commitment to public education about science, animal welfare, and research ethics. Dr. Bennett is a former Chair and current member of the American Psychological Association's Committee on Animal Research Ethics and serves on the executive committee of the international advocacy group, Speaking of Research. Welcome to OLAW, Dr. Bennett.

Slide 3 (Balancing Public Interests, Benefits, and Risks in Animal Research)
>>*Bennett:* Thank you [Ms.] Silk, and thank you to [Ms.] Hampton and OLAW and [Dr.] Brown for inviting me to share in this webinar and to discuss the topic of ethical consideration that protects the public interest in scientific advances resulting from animal research.

What I will talk about today are approaches and factors that play a role in the process of weighing and balancing scientific goals, specific research objectives, and animal welfare. Sometimes this is called benefit:risk analysis. Sometimes it's called harm:benefit analysis. However, it really is not – as that label sometimes is thought to imply – some

form of mathematical analysis. Nor is it the kind of equation that can be “solved” objectively. And so I won’t offer a template for doing that.

Rather, what we’re talking about is a thoughtful process that is undertaken in order to inform decisions in a way that incorporates a range of expert knowledge, public expectations, and estimation of likely outcomes from different choices. It is a process that occurs at many levels, by individuals, and by different groups. It is a process that informs decisions about what research should be conducted, about how to minimize potential for negative impact on animal welfare, and how to balance the two.

This is in no way a new concept, nor is it a new process. It is one with a very long history and it is a fundamental consideration that underlies decisions and actions by scientists, science and health agencies, and by the public. In many ways, the process is so integral to decisions that it may not always be explicitly described in formal terms, or in terms of strategies for analysis, and, specifically, in terms of weighing scientific objectives and animal welfare.

Perhaps as a result, it can sometimes be the case that the fact that evaluation of benefit, of risk, and balance occurs regularly as a part of review is not always widely appreciated or understood. Reviewing how that process occurs, where is occurs, and what factors are involved is the subject of this webinar.

The IACUC is one of the groups that plays an important role in this process. Their role is largely focused on evaluation of procedures and potential impact on research animals. How that evaluation occurs and whether there is need for a different type of accounting of the process has been a recent topic of increased interest. For example, we’ve seen proposals for worksheets and “scores”, color-coded graphic representations of relative benefit and risk, and even mathematical algorithms. In each case, the general idea is that by assigning categories and scores, tallying them up, a metric can somehow be established that will give us answers to complex moral questions.

What I will talk about today is why a meaningful weighing of scientific objectives and animal welfare is a process – one that occurs at multiple levels. It is a process that must be informed by understanding how science works, by an appreciation of the timescales between discovery and translation, by consideration of the value of basic knowledge and of null findings, and, finally, by the risks and likely outcomes of doing nothing at all – what’s called the harm of inaction. Each of these is fundamentally important to decisions about research and to decisions that protect the public’s interest in scientific progress that benefits humans, other animals, society, and the environment. As is appropriate for an OLAW webinar, I will focus on the US and on publicly-funded research with animals – in particular, on basic science – and on understanding the core principles in our system for evaluation and review.

Where I will start today is at the beginning, with first questions.

Slide 4 (Ethics, morals, rules, laws, decisions, and actions. Considerations of nonhuman animal research)
The best place to start in identifying a good process is often to first ask why: Why is analysis of potential benefit versus potential risk required? Assuming that the requirement is meaningful – not simply a box-checking exercise – the question of why it is expected, or sometimes even required, is related to its goal. So the second question is simply – what is the goal? What is it that the analysis should accomplish? And what would success in accomplishing that goal look like?

Slide 5 (In the US, the use of nonhuman animals depends on a social contract with the American public.)
Understanding one of a number reasons that we consider the balance between scientific objectives and animal welfare begins with the fact that in the US research with nonhuman animals depends on a social contract with the American public. Research occurs because the public finds benefit in it and, via the democratic process, allows for it by law.

Slide 6 (In the US, formal ethical justification is required for almost all nonhuman animal research.)
In the US, as in other countries, humans interact with nonhuman animals in many different ways. These include using animals for food, clothing, labor, entertainment, and companionship. However, in the US, as in many other countries, it is only the use of animals in research that requires – by law – formal ethical justification.

That is not to say that other activities are exempt from law, standards, and ethical consideration – that wouldn't be true. But it is research with nonhuman animals that requires, by law, ethical justification. That requirement can be summarized with a set of core principles.

Slide 7 (The public, via law and regulatory agencies, requires...)
At its core, the framework for ethical consideration of animal research in the US is that it only be conducted under the following conditions:

First, when there are no feasible alternatives to achieve the same objective or purpose.

Second, when the work has potential benefit and the scientific objectives are balanced with consideration of animal welfare. The public stake in research includes benefiting from the results of scientific study – that may be benefit to human health, to other animals, to society, or to the environment.

Acknowledgement of – and desire for – that benefit is reflected in public funding for science. That includes public funding of the National Institutes of Health [NIH] and funding for animal studies that are critically important to the NIH's mission to improve

scientific understanding and public health. Thus, research is in the public's interest and, ultimately, for public benefit.

At the same time, the public – along with the research community – have an interest in balancing scientific objectives and the benefits of research, with their concern for animal welfare. Thus, another condition of research is that animal welfare standards are upheld in order to ensure responsible humane treatment and every effort to reduce unnecessary harm.

Slide 8 (Public Interests:)
We can distill public interests in animal research into these 2 statements. Foremost, those animals are in research for a reason, and it is one that is morally justifiable. And second, when animals are in laboratories they receive excellent, humane care. In other words, because the sole ethical justification for having animals in research facilities at all is the science, the scientific objectives must be balanced in decisions about the animals' care and treatment.

These two principles are what guide our decisions about research and about care for animals – that is true at the level of individuals, institutions, organizations, and federal agencies. The remaining question is: How does the public know that these conditions are met?

Slide 9 (Responsibility to the public is to conduct analysis and to communicate:)
It is for this other reason – how the public knows – that our responsibility is not only to consider the ethical justification for research, but also to communicate about the process to the broader public. That is not a check-box kind of activity. Rather, it is a broad set of principles that are shared in order to accurately convey what it is we are doing, what we know, and what we don't know.

That can include the considerations we use in decisions – the scientific objectives and how they are balanced with consideration of animal welfare, evaluation of procedures, and humane animal care. We can also share our knowledge and experiences with the factors that play a role in assessing benefit and risk. We can share information about why and when alternatives are – or are not – feasible, as well as why that is specifically. But what we must also share is a full and inclusive acknowledgement of the different levels of review and analysis – from the scientist to study sections at NIH to local IACUCs. What we should be sharing is not only the goals of different evaluations, but also the inherent limitations of any decision-making process. In other words, our obligation includes being clear about the nature of science, the scientific process, and what cannot be done, or known, with certainty ahead of making decisions.

So going back to the first questions about process – understanding why we consider benefits and risks. What our goal is. What a successful process might look like. Our goal is not only to fulfill our own moral obligation to balancing scientific objectives with animal

welfare, but also to convey how we fulfill this commitment to the public. Thus, evaluating success in reaching that goal is going to depend partly on how well we convey the factors involved in the analysis – including the full range of a complicated process that cannot be reduced to a simple computing scheme that can be applied on a case-by-case basis to compute a score and an automated decision.

Given that complexity, what can we say about ethical consideration of animal research?

Slide 10 (The Goal:)
First, we can say that the overarching goal – or core principle – guiding decisions about research is to ensure that scientific goals – new knowledge and discoveries – are met. In other words, the scientific community performs research that the public supports and from which it benefits as is shown in the graphic here. At the same time, those scientific objectives are balanced with compassion and commitment to our moral obligation for humane care and treatment of research animals.

Slide 11 (How do we judge the merits and the balance?)
The next question is how we judge the merits of research projects and the balance of scientific objectives and animal welfare. There could be many ways to judge – opinion polls, popularity, surveys – what the public expects, and what occurs in the US system for evaluation of federally-funded research is that the judgements are based largely in facts and in expert knowledge. One of the reasons for that, as I will discuss here, is that knowledge is essential to best identifying the most likely outcomes of a set of actions or decisions. And for animal research, there is a range of knowledge and different types of expertise that play a role in evaluation and decisions.

Slide 12 (Levels of benefit and risk analysis for animal research)
This process for evaluating potential benefits, risks, and the balance of scientific objectives and animal welfare occurs at many levels in the US system. It involves a range of individuals and groups as shown in this slide.

The first among these are researcher's selection of questions, methods, and experimental design. In simplest terms, of all of the research studies and questions that scientists could pursue, those they choose are not random. Rather, they are selected on the basis of the importance of the question, the strength of the hypothesis, and the likelihood of success. Furthermore, the methods and experimental design are selected to be the most likely to succeed in testing a hypothesis and providing meaningful data.

It is not only the researcher who evaluates whether the question is important, whether the hypothesis and rationale are sound, whether the methods and design are likely to produce meaningful data. Funding agencies such as the NIH also critically evaluate proposals for research. They do this through expert scientific review panels and also through selection of priorities for NIH's mission – to improve public health. In addition to funding agencies, scientific review occurs prior to publication of study findings. Scientific

organizations, journals, and funding agencies also have ethical codes that include expectations for weighing scientific objectives and standards for animal welfare and care.

In addition to scientists, funding agencies, scientific organizations and journals, there are also external agencies charged with formulating standards and providing oversight for animal research. These include both the USDA and NIH's OLAW, for example.

Finally, institutions may choose to seek voluntary accreditation from private organizations such as AAALAC.

Slide 13 (Factors in Play in Benefit:Risk Analysis)
When we look at the system of review of animal research in the US, we can see that there are clearly different groups and levels of review. There are also common principles and core considerations. For example, there are a number of key factors and concepts that play a role in thinking about the balance of scientific objectives and animal welfare. Those include such things as potential benefit, including the benefit and the importance of null results. It includes potential risks and actual harms, as well as the harm of inaction. It includes timescales between discovery and realized benefit, and the range of impact of findings and discoveries. I will address each of these in turn.

Slide 14 (Interest Holders)
First, evaluating both potential benefit and potential harm begins with identifying the interest holders – that is, who and what are potentially affected by the decision to conduct research. As shown here, that can be individuals, species, society, the environment, or some combination. For example, the interest holders may be the potential beneficiaries of the research – which could be humans and society, but it is also those in the research – which could be research animals.

It's important to keep in mind though, that this includes those affected by both the action or the choice of inaction. What do I mean? For example, in research aimed at developing a vaccine for Zika virus, those affected would include those at risk for Zika virus. A choice to do the research would potentially benefit those individuals. Conversely, a choice not to do the research, or not to address the health threat, would likely result in harm from inaction. No research increases likelihood of no vaccine or no progress in better understanding the health threat.

Slide 15 (Interest Holders: who and what …?)
After identifying potential interest holders, shown here as columns, the next consideration is of how those interest holders are affected, shown as rows; the potential benefit and the potential risk.

Slide 16 (Broad and inclusive ethical consideration)
In this slide we are bring the information together in one place. Identifying the range of interest holders and the potential outcomes allows for a broad and inclusive ethical

consideration – as is shown in this model. And the purpose of bringing all this together is to represent the factors that inform responsible decisions about research. So if we look at this model, we see what informs ethical consideration – what can drive decisions by IACUCs and others. I hope this diagram will be useful to you and if you would like more information I've included the reference at the bottom of the slide here. [Bennett, A.J. (2015) *Developmental Psychobiology*, 57(3), 279-288.]

Slide 17 (What is morally justifiable?)
At the heart of the process we are engaged in when thinking about these issues is really the question of what is morally justifiable. In part, what we are evaluating is whether the scientific objectives are balanced with consideration of animal welfare. Or whether the potential benefits outweigh the potential harms. What makes this difficult, however, is that the "weighing" must occur in advance of conducting the work. The evaluation occurs prior to an action and is of potential, rather than actual consequences.

The actual consequences can only be evaluated after the action. That is because in science, we do not know the answer to the question ahead of doing the research. If we did, we would not do the study. The study is aimed at producing new knowledge, determining the answer to a question where the outcome is as of yet unknown.

Thus, our evaluation is based in predicting likely outcomes of action. We make that judgment not out of random opinion – but based in known facts, solid rationale, expert analysis – nonetheless, it is a prediction and not a guarantee.

Slide 18 (Possible outcomes, potential consequences…)
Given that the evaluation and decisions must occur ahead of taking action and without a guaranteed outcome, what are the factors that are considered? Some of those possible outcomes, potential consequences, what we don't know, and what we consider are listed here.

First is the likelihood that the study will succeed. What is critical to remember on this point is what is considered a success. In science, success does not only mean a statistically significant, positive result. In fact, null results and "failures" are a critical positive feature of science. Ruling out hypotheses is important to critical evaluation of theories, to establishing facts, and to making progress in understanding. In other words, it is an inherent feature – not a bug – of the scientific method.

For that reason, likelihood that a study will be successful revolves around a well-developed hypothesis, approach, and method. In turn, the evaluation considers the likelihood that the study will produce useful knowledge.

What we also consider is the benefit that the study may have – what it might accomplish and what kind of benefit it might yield. To whom might those benefits accrue?

Alongside evaluation of the scientific objectives is the evaluation of potential harm, the risks of the research. In the case of animal research, risks and harms are typically considered in terms of effects on animal welfare. Here the goal is to balance the scientific objectives with animals' welfare, taking care to minimize potential for unnecessary suffering, pain, or distress.

The other thing to consider on the potential harms side is the risk of doing nothing at all, and the consideration of who bears that harm. For example, if we choose not to do research to better understand brain development, epigenetics, immune function, Parkinson's disease, Zika virus, neonatal lung development, and so on – whose lives will be affected? And in what ways?

Together, these are some of the considerations that underlie evaluation and decisions about whether or not to conduct a research project. That is true whether the process is formally articulated in this manner, or not, because these are the core questions and factors at the heart of our review systems. And they are also the questions that scientists wrestle with in choosing research topics, specific studies, and study designs.

In each case however, it remains a fact that the evaluation necessarily takes place before the study is conducted. Decisions have to be made in absence of knowing the outcome. But that doesn't mean that we have no source of information that can guide our decisions and the process by which we evaluate research. In fact, we can gain very useful knowledge by turning to what we do know.

Slide 19 (Moral dilemmas and societal challenges:)
As is the case for other moral dilemmas and societal challenges, we can learn from history. In the case of research, we can learn from post hoc analysis. Here I don't mean some kind of very short-term, say 5-year retrospective, analysis meant to count up the number of animals in a study and assess whether or not a single study resulted in a cure for a disease.

What I do mean is that post hoc analysis is aimed at broad questions, aimed at better understanding the nature of science and what it means in terms of reasonable expectations. For example: the concept of timescales – or what the time between discoveries and realized benefit may be for interest holders.

I will turn now to 2 specific examples that illustrate the use of post hoc analysis. There are many more, I've chosen these as familiar topics that illustrate each of the concepts quite well.

Slide 20 (Examples for consideration…)
The first example is the discovery of insulin as a treatment for diabetes.

Slide 21 (Diabetes: benefit clear?)
The outcome of that discovery is quite clear. What you see here is an early patient before and 4 months after treatment with insulin. In fact, although many may forget now, prior to the discovery and availability of insulin, the prognosis for children with diabetes was suffering and a fair certainty of early death.

Slide 22 (Diabetes)
If we view the process – not a single study – but the entire process by which the role of insulin in diabetes, the basic understanding, and the development of insulin as a treatment was developed, we can rapidly gain appreciation for the timescales in research and the breadth of studies and testing – with a range of animals – that was needed to get to that point.

In brief, in 1879 we had the critical, foundational discovery that the pancreas produces insulin. How did that happen? By removing the pancreas from a healthy dog, that then developed the symptoms of diabetes. Not a correlational approach, but the definitive experimental approach to establish causation.

Nearly 30 years later, insulin from healthy dogs was injected into diabetic dogs. The diabetic dogs were restored to their normal state. The next step was to refine the extraction of insulin from the pancreas of cattle, then to test the dose, purity, and safety of insulin with rabbits serving as test subjects prior to the use of insulin for humans with diabetes. By 1922, the first human patient received insulin.

We can now widely appreciate the benefit that insulin provided. What the post hoc analysis tells us is that the benefit was realized only after a timescale of roughly 40 years – that is 4 decades – involving studies and testing with dogs, cattle, and rabbits. If a 5-year retrospective analysis had been done following the 1879 initial discovery, what would the conclusion have been? Probably the study would have been judged as a complete failure if the metric for success had been the number of lives saved, or whether it had produced a cure for diabetes.

The case of insulin and diabetes is informative, but the example I will turn to next provides perhaps a better illustration of how basic research works, of unanticipated outcomes, and the inherent difficulty in predicting the range of benefits from a particular set of scientific studies.

Slide 23 (The Discovery of Serotonin)
The example I will use is a very brief history of the discovery of the brain chemical serotonin. Many people know about serotonin because it is involved in a wide range of behaviors and health outcomes, among them depression, anxiety, sleep, eating, impulsivity, alcoholism. What may be less widely appreciated is how it is that we came to know about serotonin and how we learned about what it does in the brain.

That story begins with the discovery of enteramine by a scientist named Erspamer. What was Erspamer doing? Looking for the substance in blood that caused smooth muscle contraction. A little over 10 years later, another group of scientists who were working on understanding vasoconstrictors identified serotonin (also enteramine). What happened next was rapidly moving from determining the structure of serotonin and creating synthetic serotonin to facilitate research aimed at better understanding the substance.

But it was not until 1954 – nearly 20 years after the initial discovery – that a scientist named Betty Twarog discovered serotonin was in the mammalian brain. And it was that critical discovery – building on all of the previous studies – that provided the foundation for a new theory that had a critical and lasting impact. Nearly 10 years after Twarog's discovery, a scientist named DW Woolley built upon the new knowledge of brain function to hypothesize that psychoses – or some forms of mental illness – had a biochemical basis. He hypothesized that serotonin was key to diseases like depression.

That basic research occurred over a 35 year timespan and with a range of animals that included cattle, clams, frogs, rabbits, and primates. It provided the foundation for the development of targeted pharmacotherapies for depression. By 1970, the first selective serotonin reuptake inhibitors (antidepressants) were developed. And although it is true that we continue to learn and develop new treatments for depression and that the current treatments do not work for everyone, there can be no doubt that as a result of these studies and the development of antidepressants, suffering was alleviated – and continues to be – in a great many people.

Slide 24 (The Discovery of Serotonin)
These brief examples – 2 out of many – illustrate some of the fundamental principles that must play a role in considering the potential outcomes of scientific research. They provide a powerful demonstration that the time between discoveries and realized benefits is often in the timescale of decades, not a year, not 5 years, 30, 40, or more. Furthermore, when we step back and consider timescales, we see that the realized benefits of the discovery of serotonin did not end with the development of antidepressants in the 1970s. Rather, they extend into the future and to future beneficiaries. In other words, while the number of animals used in those initial discoveries will remain constant as a historical fact, the number of individuals who continue to benefit will continue to increase.

Slide 25 (Timescale for realized benefit extends into the future.)
Another important thing to consider is this: not only does the timescale for realized benefit extend into the future, but the range of interest holders, or beneficiaries, may also increase. For example, we can look to the use of insulin for the treatment of diabetes. The basic research depended on dogs, drug development and testing on cattle and rabbits, and the initial beneficiaries were humans with diabetes. At this point that range has extended to include other animals.

Slide 26 (Evaluating potential consequences:)
What post hoc analysis also tells us about evaluating the breadth of potential benefits and risks is that we would be foolish to think that we could accurately predict the full range of impact of a study or a particular finding, or discovery. Post hoc analysis – particularly of basic research – provides ample evidence of why analysis of potential benefits and harms of any single study will fall far short of the goal. That is, far short of the goal of guiding decisions about research in a manner that best protects public interests in scientific and medical advances.

Slide 27 (The Discovery of Serotonin)
Post hoc analysis also illustrates the nature of science and how discoveries depend on previous knowledge and foundations. By doing so, it provides a robust illustration of why it is difficult – likely impossible – to determine the range of impact of a particular discovery. We can identify gaps in knowledge. And with expert knowledge of a field or specific area of understanding, we can determine that a missing piece of knowledge is critical in order to move forward and advance our understanding – to make further progress in meeting challenges to human, animal, societal, or environmental health. We can even hypothesize how filling a gap in knowledge, or testing a hypothesis, may advance our knowledge.

While we know with certainty that science works and that the scientific process is among our very best ways to advance knowledge, understanding, and make progress, we cannot say with certainty what range of impact of a single study, or a specific finding, will have, and on how many different fields. For example in the case of serotonin, those initial studies and discoveries have has a range of impact that is remarkably broad. It includes all subsequent discoveries and applications that depend on knowledge of the neurochemical, its function, and identification of its roles. The impact extends into the future.

Overall, the discovery of serotonin demonstrates the value of basic research, as well as the likelihood of unanticipated outcomes. Scientists working on an understanding of smooth muscle contraction and vasoconstriction would not have identified basic knowledge about brain chemistry and its contribution to mental health as the objective or rationale for their studies. Together then, consideration of the serotonin story should provide a cautionary note. It is a caution against simple approaches to tallying potential harm and benefit of a single research project.

Slide 28 (Post hoc analysis underscores importance of timescales…)
Given that cautionary note and the complicated picture that emerges from post hoc analysis, what can we say about the topic of this webinar? How should we evaluate and convey our processes for evaluation of the balance of scientific objectives and consideration of animal welfare?

First, that it is important not only to appreciate timescales and range of impact – in the manner illustrated in the graphic here – when considering research, but also to keep these facts in mind in conveying to the public the nature of science, animal research, and the ethical considerations that inform those decisions.

Slide 29 (Performing a reasonable analysis to estimate potential benefit…)
The second conclusion should be that it is exactly this complicated picture that underscores why multiple types of expertise and multiple levels of review are so central to performing a meaningful and reasonable analysis. In particular, post hoc analysis highlights why specific content area expertise is necessary to best inform the evaluation of the potential impact of a study, the potential value of testing a particular hypothesis, the value of studies that aim to fill a particular gap in knowledge, the value and potential importance of conducting work to know – or to better understand – something as yet unknown. And, in turn, to assess how that new knowledge might open pathways for understanding and for progress that can benefit the public.

In terms of review, those are exactly the types of questions that are addressed in researchers' selection of questions, in funding agencies' decisions, in expert scientific review of research proposals, and the publication of study findings. It is in this manner, together with the IACUC and all the other levels of review of proposals for animal research, that both the scientific objectives and animal welfare are critically evaluated for balance.

Slide 30 (One size does not fit all)
I have focused largely on basic and translational research of the type that NIH funds. I will turn now very briefly to a broader consideration and acknowledgement that one size doesn't fit all. The use of animals in research and testing is actually quite broad.

Slide 31 (Purpose and necessity:)
But the foundational questions that guide decisions about animal research are common; they are about weighing and balancing scientific objectives with animal welfare, or potential benefits with potential risks. And these are the same regardless of whether a project is basic, translational, preclinical research, or testing.

A second foundational question – instantiated in policies for IACUC proposals – is whether there are alternatives that are feasible to address the same question. For example, could a cell culture, computer simulation, or other approach be used? It is for this question, that it can often be important to remember key differences in types of animal use.

Slide 32 (Animal Testing ≠ Animal Research)
In particular, it is important to realize that animal testing and animal research are not the same thing. This difference is relevant to ethical consideration and decisions. In particular, the estimation of benefits and risks differ in critical ways. This is especially

true with respect to availability of suitable alternatives, but also in terms of timescales and range of impact.

Slide 33 (Research – Basic Discovery Science)
What are some of the differences? Some critical differences are summarized and highlighted here, although we should be clear that there is some overlap. In terms of basic discovery science, animal research often has the goal of providing new knowledge to understand normal function and disease. It has long timescales. It delivers necessary building blocks for subsequent basic research, but also for translation and clinical application. In turn, without basic research, progress and new understanding halt.

Animal testing differs in some important aspects. In general, when we talk about animal testing we mean studies that evaluate the safety or efficacy of a treatment, drug, device, or product. Animal testing is often the focus of alternatives development – particularly in the case of toxicology studies – because some testing can be done without animals and some testing doesn't require novel discovery.

These key differences have obvious implications for evaluation of proposed studies, or uses of nonhuman animals. They are also differences that are sometimes not well understood or identified in public discussions of animal research. That is particularly true of the focus on alternatives, where there is often a lack of clarity about the fact that a growing number of alternatives for one application – toxicology, for example – does not generalize to mean there are non-animal alternatives for basic discovery science.

In turn, consider this within the context of one of the goals we started out with – conveying to the public that animal research is subject to careful evaluation of scientific objectives balanced with consideration of animal welfare. To do that accurately, it is important that we are careful to be clear about where alternatives are possible, feasible, and useful, and where they simply do not exist and are unlikely to exist in the near future, if ever. To do otherwise, I think, is deeply misleading to the public and, ultimately, deeply harmful to public interests in both scientific discovery and in thoughtful partnership in the complex decisions we make about research.

Slide 34 (Key differences between animal research and animal testing)
Another way to think about this issue is in the context of something we often hear people say – even within our own community – and that is that we look forward to a day when no animals are involved in research. If we step back and think about the broad range of animal research – some of it represented here – we see the problem. Research is how we learn new things about the world, and do so in a world that does not remain static. That is, environments, individuals, societies, all change. As a result, new questions and new challenges arise.

Animal research includes studies of environmental impact, animal care and handling, clinical medicine for animals, basic and biomedical science, and studies of animal

cognition, emotion, and behavior. Ending research closes a major path to discovery and understanding. And as such, I'd argue it is not a positive goal. In other words, we need to be clear about the diversity of animal research and its value not only to humans, but also to other animals, society, and the environment.

Slide 35 (Basic Principles for Ethical Evaluation, Conduct, and Regulation…)
I'll turn now to the second set of questions that are examined in ethical consideration of animal research. These are the questions that are the primary focus of the IACUC, that are most often and thoroughly discussed. It is here that we see the shorthand –3Rs – replace, reduce, refine. After purpose and necessity are evaluated, we turn to the question of if the research is justified, then how is animal welfare balanced with scientific objectives? The kinds of questions that are addressed surround providing humane care and treatment for animals, minimizing discomfort and harm, using the fewest number of animals that are needed without compromising the scientific objectives that justify the animal use in the first place.

These are all topics that are the subject of extensive guidelines, regulation, rules, and discussion – for example, in the *Guide for the Care and Use of Laboratory Animals* [*Guide*] that serves as the rulebook for all PHS and other federally-funded research with rats, mice, birds, and other animals that are additionally subject to the specification of care, handling, and conduct of research that is articulated in the Animal Welfare Act.

Slide 36 (Risks and Harms: How Do We Evaluate These?)
When we turn to the question of risks, harms, and their evaluation, the factors that play a role typically involve consideration of diminished quality of life, pain, suffering, loss of potential, or death. In each case, two things are of concern to evaluate and guide decision-making. One is acknowledging that risks and harms are part of understanding potential benefit. That is, what harm might be reduced as a result of research findings and discoveries?

We also think about the risks in terms of the welfare of the animals in a study. We evaluate whether the procedures cause diminished quality of life, pain, or suffering and what we can do to reduce those risks to animal welfare. In order to evaluate the impact, a number of factors come into play that includes the type, extent, degree, and amount of time that the animal might experience any potential for decreased welfare. This kind of analysis is represented in IACUC policy and in the USDA categorization of research.

For example, procedures are categorized as those that involve short-term, limited pain (such as an injection) versus those that require anesthesia or pain relief in order to ensure that that animal does not experience pain or distress. For a very small number of studies, those in Category E, the analysis shows that scientific objectives cannot be met without the animal experiencing unrelieved pain. In those cases, the balance of scientific objectives against animal welfare requires special consideration and every effort to minimize unnecessary pain and minimize the amount, duration, and degree of pain.

Slide 37 (What do we need to know in order to evaluate harms?)
In the evaluation of animal welfare or potential harms, there is also consideration of differences between species and there should also be a recognition of what we know and what we do not know. For example, similarities and differences between physiological systems and subjective experiences that are relevant to quality of life, pain, and suffering. Whether these are the same for all species – which is often not the case – and how those differences matter, is a key consideration in our ethical framework for decisions about animal research and testing. It is also the basis for a key feature in our system. That is, the requirement to use "the lowest species" – using mice instead of monkeys, for example – the lowest species suitable to address the research question. It is also the basis for the requirement to justify the choice of species for a particular project.

What is also true in this realm, and in the realm of refinement of procedures, animal care and treatment, is that continuing advances in scientific understanding can result in changes in our views, procedures, and evaluation.

Slide 38 (Summary)
In summary, what can we say about the topic? Overall, what we know about the process of ethical consideration of animal research is that it is a complex analysis that involves unknowns and uncertainties, open questions and – ultimately – judgements that can impact the lives of many individuals, of society, of entire species, and the environment. There is no easy calculus or plug-and-play module that will deliver a meaningful number representing relative ratio of benefit to risk.

What we also know, however – as scientists, members of the research community, members of the communities involved in research regulation and oversight – is that thoughtful and serious consideration of potential benefit and risk – informed by expert knowledge – occurs at multiple levels and at each stage of research. All of this together fulfills the public's interest in making sure that the use of animals in research and testing is ethically justified and that there is a serious, thoughtful, and multilevel process for evaluation of that justification.

Another part of the obligation to the public, however, is communicating about the process, about how decisions are made, how the evaluation occurs, and its inherent limitations. Acknowledging those multiple levels of review and the interplay between them is critical to providing an accurate representation of the process of analysis that informs our decisions about research proposals. It is for that reason that I'll end by saying it is important to consider the IACUC's role in full and inclusive context and also to guard against the impression that we can do impossible things without risking harms to science and to society.

I'll thank you for your participation in this webinar and thank you again very much to OLAW for organizing and hosting.

Slide 39 (Questions?)
>>*Silk:* And thank you, Allyson. Now we will answer several questions that we received before the webinar. We also welcome live questions from the audience. Please type them into the questions pane on your control panel now. If you think of a question later, you can send it to OLAW at the email address shown on the slide. [olawdpe@mail.nih.gov]

Slide 40 (Question 1)
The first question: How do you conduct risk benefit analysis with animals at the University of Wisconsin?

>>*Bennett:* I think similarly to many other universities, at UW-Madison, much of our research is federally-funded by NIH and other agencies and, as I've discussed here, it undergoes rigorous review by expert scientific panels at the NIH.

In addition to that, our IACUC proposal requires that the following are addressed and each of these is part of the consideration and the factors I've talked about today. So for example: the rationale for the study; the potential benefits of the findings; justification for choice of species in the research; justification for the animal numbers; a very detailed description of procedures that allows for evaluation of potential for distress, pain, and a description of measures that are taken to minimize risk of unnecessary distress and pain.

Together with that information, the scientists, veterinarians, staff, and public members of the IACUC can use the information to evaluate whether the scientific objectives are balanced with animal welfare, and whether appropriate steps have been taken to minimize risk of unnecessary distress or pain.

Slide 41 (Question 2)
>>*Silk:* Question 2: Risk benefit analysis is a complicated process with a lot of unknowns. Have people tried to develop a way to conduct an analysis using a scoring method or mathematical approach?

>>*Bennett:* Yes. There have been efforts to devise a categorical approach, or a scoring approach. And I think here, the question isn't whether a worksheet system, or a categorization, or scoring system could be devised. It is whether that system would produce meaningful information. In other words, would it improve decision making? Would it adequately protect the public interest in scientific progress? Because the converse is, would it lead to bad decision making with long-term negative consequences, at worst, or, at best, simply increase paperwork and burden without a compensatory benefit for scientific objectives, public interests, or animal welfare? All of those harms, I think, should not be taken lightly and should be considered explicitly if one devises one

of these systems. And I think that this process is one that requires thoughtful, serious deliberation, with the appropriate range of expertise.

One could also argue that it is a disservice to the public and to the research community to behave as though something that is impossible is a realistic goal – for example, predicting with accuracy the likely range of impact and benefit of the outcome of any single study. That flies in the face of what we know about science.

Slide 42 (Question 3)
>>*Silk:* Do IACUC members at the University of Wisconsin-Madison engage in public outreach?

>>*Bennett:* Yeah, at UW-Madison we have a very broad and diverse set of public outreach education and engagement activities and those include efforts by a great many faculty, staff, and students and that would include IACUC members.

Slide 43 (Question 4)
>>*Silk:* Here is a question for OLAW. What is OLAW's expectation for risk benefit analysis by IACUCs?

So I'll answer that one. OLAW expects that during its deliberative process, the IACUC will ensure a thoughtful analysis of the risks to the animals balanced against the potential benefits of the research. Principle II of the US Government Principles guides IACUCs to ensure that procedures involving animals are designed and performed with consideration of their relevance to human or animal health, the advancement of knowledge, or the good of society.

The *Guide* states in the first chapter that the decision to use animals in research requires critical thought, judgment, and analysis and that using animals in research is a privilege granted by society to the research community with the expectation that such use will provide either significant new knowledge or lead to improvement in human or animal well-being. The *Guide* expects IACUCs to "weigh the objectives of the study against potential animal welfare concerns."

Slide 44 (Question 5)
And here is another question for OLAW. What is the position of the *Guide for the Care and Use of Laboratory Animals* on scientific merit review?

The *Guide* offers the following guidance for IACUCs on scientific merit review. While the responsibility for scientific merit review normally lies outside the IACUC, the committee members should evaluate scientific elements of the protocol as they relate to the welfare and use of the animals. For example, hypothesis testing, sample size, group numbers, and adequacy of controls can relate directly to the prevention of unnecessary animal use or duplication of experiments. For some IACUC questions, input from outside experts

may be advisable or necessary. In the absence of evidence of a formal scientific merit review, the IACUC may consider conducting or requesting such a review.

Slide 45 (Upcoming OLAW Online Seminars)
[Question 6] And now we have some questions that have come in from the audience: A search of AWA, AWAR, HREA, and the PHS Policy for ethics/ethical finds no requirements for ethical justification. A question as to whether OLAW is now going to stress ethical justification of animal research activities rather than scientific justification?

Okay. So the way this reads to me is this individual searched the databases for the word ethical or ethics and they determined there was no requirement. So OLAW's answer is we did address this just a moment ago in Question 4. The US Government Principle IV and the *Guide* provide the expectation that the IACUC considers the balance between the benefits and risks of a research protocol.

[Question 7] And now here is one that came in for you, Allyson. If the timescale is decades, how does an IACUC evaluate the benefits?

>>*Bennett:* The IACUC can identify the likely benefits by thinking about whether the research project – the research question – is well formulated, whether the methods and the approaches used are likely to succeed in answering and addressing that hypothesis. So they can evaluate the likelihood that the study will succeed. They can evaluate whether it is a good question to ask, whether the knowledge is likely to be useful. What they can't do is predict the range of benefit, the depth of benefit, or the potential application of the finding.

>>*Silk:* And we're bumping up against our timeline. [Question 8] We do have one more question for you, Allyson. This commenter says very nice presentation. AALAS and FELASA just published 2 articles on performing a harm benefit analysis. The rationale is a presumption that this term "harm" is in the *Guide*. The only term used in the *Guide* is risk benefit. Risk benefit has served the biomedical community well. Risk puts the definition of pain, distress, and welfare that is linked to the 3 R's. It is objective and well-defined.

In contrast harm is not well-defined for animal research. Harm is subjective. For human clinical trials, harm is defined as a risk. It includes mental health and economic earning potentials as well as pain and distress. Harm also includes a definition of wrongdoing and evil. Using the term harm will deter the public understanding of the benefits of animal research. Your presentation of informing the public on the benefits and ethics of animal research and how investigators mitigate the risks with ethics, compassion, the 3Rs that balance with scientific objectives. And this commenter encourages using the term risk rather than harm. Do you want to comment on that, Allyson?

>> *Bennett:* I think that's an excellent point and I agree. I appreciate the commenter's articulation of that. I think what's happened is we have a lot of these different terms floating around out there and the commenter's point is one that probably should encourage us to be a little bit more thoughtful about why we're using the terms we're using. And for the case of animal research, to use the term "risk" and not "harm". So point well taken.

>>*Silk:* Okay. We will all try to do that. We have come to the end of our webinar. My great thanks to Dr. Allyson J. Bennett for a fascinating, thought-provoking, interesting talk. And I thank all of you for participating in our webinar, with special thanks to those who sent in questions.

We look forward to continuing an exciting 2016 webinar series. The next OLAW Online Seminar will be on September 8 when we will discuss *Implementing Veterinary Verification and Consultation (VVC) Significant Change Guidance*. We also have another Online Seminar scheduled for December 15 on *Self Evaluation & Reporting: Always let the Guide be your Conscience.* Good-bye, everyone, and thank you for joining us today.

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