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Note: Text has been edited for clarity.

Best Practices for Conducting a Search for Alternatives and Finding Animal Model/Model Organism Information

Speakers:

- Jessie Kull, MS, Animal Welfare Information Center (AWIC), National Agricultural Library
- Joelle Mornini, MLS, National Institutes of Health Library

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Slide 1: Best Practices for Conducting a Search for Alternatives and Finding Animal Model/Model Organism Information

>> Cate Pritchard: Hello, everyone. Welcome to the OLAW webinar titled "Best Practices for Conducting a Search for Alternatives and Finding Animal Model and Model Organism Information." Today is Thursday, December 9th, 2021. My name is Cate Pritchard, and I'm part of the Division of Policy and Education at OLAW. Today it is my pleasure to welcome our speakers, Jessie Kull and Joelle Mornini.

A few housekeeping details to begin -- today's webinar is being recorded. The chat is closed, but you can put any questions that you have for the speakers into the Q and A box, and we'll get through as many questions as we can at the end of the presentation. If we're not able to get to all of the questions, we'll ask the speakers to answer the questions after the webinar, and then append those questions and answers to the end of the transcript, which will be posted on our Webinars and Podcast webpage within the next week or so.

And now I'd like to introduce our speakers. Jessie Kull, MS, is the Animal Welfare Information Center, otherwise known as AWIC, coordinator at the USDA National Agricultural Library. Jessie attended Virginia Tech, and pursued her Bachelor of Science degree in Animal Sciences. She then earned her Master's in Animal Behavior and Welfare at the University of Tennessee. She started her career in Iowa as an on-farm Animal Welfare Auditor for the Swine Industry. In 2018, she joined the Department of Defense as their IACUC Compliance Coordinator overseeing their animal research labs, before returning to AWIC in March of 2020 in her current role as the AWIC Coordinator.

Joelle Mornini, MLS, is an informationist at the NIH Library supporting the data services program. She holds a Master's in Library Science from the University of Maryland, and has previously worked at a variety of biomedical libraries, including the Scientific Library, at the National Cancer Institute at Frederick, the Gorgas Memorial Library at Walter Reed Army Institute of Research, and the National Library of Medicine.

Welcome to you both. And with that, I'll hand the presentation over to Jessie.

Slide 2: Literature Searching for Animal Use Alternatives

>> Jessie: Thanks, Cate. And good afternoon, everyone. My name is Jessie Kull, like Cate said, and I'm the USDA's Animal Welfare Information Center's coordinator, which is located at the National Agricultural Library. And I'm really excited to be here and talk to you guys about AWIC, and how to conduct a literature search for animal use alternatives.

Slide 3: Objectives

For my portion of the presentation, I'm going to very briefly go over the Animal Welfare Act, just in terms of when and why AWIC was created. I'll quickly review the 3R's, and then I'll talk about how to conduct a search for alternatives, and end by going over some of AWIC's products and services that are available to you.

Slide 4: Animal Welfare Act

So some of you might be familiar with some of the history behind the Animal Welfare Act, and maybe even AWIC. But just to lay the foundation for the rest of this presentation, and why AWIC was created in the first place, I wanted to briefly cover the beginning of the Animal Welfare Act. So, the Animal Welfare Act, which at the time was known as the Laboratory Animal Welfare Act, was signed by President Johnson in 1966. And the real intent of this initial Act was to prevent pet theft. However, it's been amended numerous times since then, but we're mainly going to focus on the 1985 amendment, which is really where the welfare of research animals came into the picture.

Slide 5: Food Security Act of 1985

And specifically, Senator Dole, who actually just passed away this past weekend at the age of 98, helped amend this Act to state that the main thrust of the bill was to minimize pain and distress suffered by animals used for experiments and tests. And in doing so, biomedical research will gain in accuracy and humanity. So really, the intent of these amendments were, again, minimization of pain and distress in research animals.

Slide 6: AWA Defines service at NAL

And now that there are going to be so many more information requirements that were going to be asked from the IACUCs [Institutional Animal Care and Use Committees] and the PIs [Principle Investigators], such as having to consider and search for alternatives to painful and distressful procedures, Congress put a provision for an Animal Welfare Information Service at NAL that shall, in cooperation with the National Library of Medicine, provide information pertinent to employee training which could prevent unintended duplication of animal experimentation as determined by the needs of the research facility, and on improved methods of animal experimentation which could reduce or replace animal use and minimize pain and distress to animals. And this information service later became known as the Animal Welfare Information Center in 1986.

Slide 7: 3Rs Alternatives

Now that we've gone over some of the history, we're actually going to transition over to the 3Rs, and we'll talk about how they came to be, how they were defined, and I'll give you some examples and why we should care about them.

Slide 8: History of the 3Rs

The 3R's concept started with Dr. Russell and Dr. Burch, who lived in the U.K. at the time, when they were hired by the University's Federation for Animal Welfare to look at the concerns around using animals in research. They published their thoughts and ideas in 1959, in a book called The Principles of Humane Experimental Technique. They weren't necessarily against using animals in research, but instead proposed three areas where they felt that the research community could advance in humane techniques when using animals. Of course, those three areas are replacement, reduction, and refinement.

Slide 9: Replacement: Substituting sentient animals with insentient materials

Now let's get into actually defining the 3R's and giving you some examples. So Replacement is replacing or substituting living, sentient animals with insentient material, which means anything that is incapable of feeling or understanding things like, let's say, algae or a sponge, for example. And the photo on the slide actually shows an example of a replacement model that is called an organ-on-a-chip, which is a micro-physiological system that's used a lot in drug testing and development.

Slide 10: Traditional Method: Sentinel Animals

But the main example that I wanted to get in with you all is to talk about sentinel animals. This is a newer example of replacement, and it has to do with replacing sentinel animals. And what sentinel animals are, are animals used as a monitoring tool to see if an infectious disease or harmful agent is present in the animal colony of interest. So it is typically done in the animal colony's bedding of interest is collected, and is placed in the sentinel animal's cage to see if, then the animal becomes infected with some sort of bacteria, virus, or parasite, which allows the researcher to know what disease or agents that the animal colony of interest might have.

Slide 11: Replacement Method: Environmental Health Monitoring

But recently, new methods, such as exhaust air dust testing and PCR testing of filter media or swabs has been found to replace sentinel animals to detect their specific pathogens in the animal colony, and thus completely replace this whole group of animals that were previously required.

And to go a little bit more in detail what these methods are, exhaust air dust testing uses either sticky swabs or some type of specialized filtered material or media that is placed in a specific location, such as maybe at the end of a cage unit to collect as much dust as possible, and then those swabs or media are tested. And the PCR method is very similar, but they use large swabs or pieces of filter paper to test the colonies' soiled bedding. And some of the benefits, other than replacing animal use, is that it increases result sensitivity and accuracy, and also reduces labor and cost in the majority of cases.

Slide 12: Reduction: Reduction in the number of animals required per experiment/study while still achieving robust results

And the second of the 3R's is Reduction. And reduction is defined as reducing the number of animals required per experiment, but still achieving robust results or statistically significant data.

Slide 13: Animals Serving as Their Own Control

One example of reduction that can be applied really in any area of research is eliminating the use of a controlled group of animals, by allowing the main group of animals, or the ones that you're going to test or treat, to serve as their own control. This not only reduces the number of animals used, but also reduces variation of the data, since you are using that same animal across all groups and treatments. So for this example, if the study involved tracking the number of steps a cow has in a day, you could track this Cow A's steps during a baseline period, which would then serve as the control group, and then you could track that same cow's step during the treatment period, which in this case is a 24-hour lying-deprivation period. And that way, it would reduce animal use by eliminating, again, this whole additional group of cows.

Slide 14: Refinement: Methods that minimize animal suffering and improve animal welfare

And then lastly, our last “R” is refinement. And refinement refers to methods that minimize animal pain and suffering, and therefore improving animal welfare.

Slide 15: Handling & Training

And again, one example of refinement that can apply to any areas with using animals is handling and training. And again, this is important in any research or education setting, because trained animals are less stressed when asked to complete a specific task, and are more comfortable when they have to be handled by humans. And there is a lot of different options for training and handling opportunities, depending on the species that you're working with. But for example, in mice, we use mouse tunneling rather than picking a mouse up by its tail, which we know is painful and stressful to the animal. And in rats, something that's become relatively of a hot topic, is rat tickling, and that's frequently used where technicians are mimicking the natural rat play behavior. Actually, I have this short video of rat tickling I'm just going to briefly show you, but keep in mind that the volume is very low on this video, so I apologize for that. But it is a really good video that demonstrates rat tickling, so let's pull it up now.

[VIDEO]

>> Jessie: And I'm just going to stop it there. Again, I apologize for the low sound quality, but hopefully the important part is that you could see how the tickling occurs, and how the rats really do enjoy it. So let me switch back to the PowerPoint. Okay.

Slide 16: So What's The Problem?
But, so what? I'm giving you all this information about the 3R's, and the requirement and the Animal Welfare Act to consider alternatives if you're conducting animal research. But what's the problem? It all sounds pretty straight-forward, right? Just go to the literature and search for alternatives, and you've met this requirement.

Slide 17: Decreased Discoverability of the 3Rs Citations
Well, one of the challenges with looking for alternatives in the literature is, they're extremely hard to find. And one reason this is because typically, unless the research is focused on the 3R's or its main objective or topic of the study, scientists won't mention or write explicitly about the 3R's, making these papers and information extremely hard to identify in the literature, because the papers aren't being tagged or indexed on the back end, as such. Additionally, some scientists may not even realize that the method or procedure that they're using would be considered a 3R's method, and again, do not explicitly state anything about the 3R's, or animal use alternatives in their paper, such as maybe using an animal as its own control. They may not realize that, and then again, write that in terms of 3R's in their paper.

For example, if you look on the side of the first citation, it's about dairy calves. And it says, "This is the first study to demonstrate that pair housing improves the affective aspect of calf welfare," which suggests that pair housing is a refinement method, right, since it improves their welfare. However, you'll notice that there isn't any mention about refinement specifically in this paper. And further, if we go on to the third example, which talks about sentinel animals, it says that these media and pulled soil bedding samples is more effective than traditional sentinel methods for colony house surveillance. So, this goes back to that replacement example I just went over. But by considering the context clues and interpreting the sentence as humans, we know that it's an example of a replacement method. But nowhere is replacement mentioned in this paper. And again, the reason that this is a problem is because if it's not described in these papers as the 3R's method, then the automated indexing technology that we're using on the back end to tag or really categorize these citations, we can't just have it rely on the 3R's terms to identify these papers, thus making it hard for individuals to find information, because a lot of people searching in databases will likely use those 3R's terms; replacement, reduction, refinement, alternatives, in their actual search string to find this information. But if it's not in the paper, it's not going to come up in your results.

Slide 18: Conducting a Literature Search: Search Demonstration
So now that I've identified the problem, I'm actually going to take you through a real alternative search example so you can see how I construct it.

Slide 19: Search Example: Housing of Mice
So this example states that a research lab is planning multiple studies using a strain of common laboratory white mice. They're planning to house the mice in stacked wire cages with feeders and waterers. Mice are individually housed in steel cages with no bedding or other

enrichments. So our question is, what 3R's modifications could be made to this housing model to improve animal well-being and reduce stress?

Slide 20: Example: Identify Key Concepts/Keywords

So the first thing we want to do is identify the different topic areas within the question to then form those different parenthetic statements or concept groups that will then create our full search string. So, for example, for this search and for the question that we want to address, we want to make sure we have a concept on housing terms, animal keywords, like "mice," and then 3R's alternatives terms that are related to their housing or environment, such as maybe environmental enrichment. We don't necessarily just want to use the term "refinement" or the "3R's." Again, the reason I picked these three topic areas is because I'm looking for ways to improve the animal's environment, so I need to include words relating to housing, I need to include terms related to mouse, and then, of course, housing alternatives. I also can't just use these one terms for each concept, because there's going to be a ton of different ways to refer to housing or, let's say, the animal mice, such as mouse, or also murine. And if I don't include all other synonymous terms, I'm likely going to miss a lot of valuable information, because not all scientists write using the same terms to refer to the same thing. So I hope that makes sense. We'll go through some more synonymous terms in a second.

Slide 20: Terminology for Refinement Alternatives

So the next few slides I'm showing you are just some 3R's terms that we came up with that are examples of each R that you can include in your search string and likely lead to more productive results than using replacement, reduction, or refinement. So, for example, this slide is showing you refinement examples or related terms, and specifically the ones I've highlighted in yellow could actually even be used as keywords in this search example that I'm going over on environment enrichment.

Slide 21: Terminology for Reduction Alternatives

And I'm not going to, again, go through all these, they're mainly here for your reference. But this is the example of keywords on Reduction that you could use.

Slide 22: Terminology for Replacement Alternatives

And then lastly, here are some Replacement keywords. And again, my main point in showing you this that using these terms in your search string is going to lead to more productive search results than just adding in the terms 3R's or Replacement, Reduction, Refinement into your search string, because like I mentioned before, a lot of scientists won't include those terms in their papers. And if they do, it likely isn't in the context of the 3R's, which is why you might not be finding any relevant results.

Slide 24: Combining The Search Strings

But back to the search example. Here again are the three concepts that I just talked about, but written out on the slide with various synonymous terms. Then the Boolean operator "or" in between each term. So for Housing, I included other key terms like "cage" or "enclosure." For Animal, I included "mice," "mouse," the scientific and Latin terms, "murine" and "*Mus*," and

then lastly, for my 3R's terms, I included "social housing" to see if mice could be housed in groups. I also included specific enrichments like "toys" or "bedding" or "nesting material." So again, any terms, really, to housing opportunities that can improve their welfare. And I'm making sure to include multiple terms that refer to the same thing; again, so I can capture all relevant information. For example, if I only included the term "environmental enrichment," I'm not going to get any papers that talk solely about "social housing" or specifically about "nesting material" for mice. It would only bring back papers that specifically talk about environmental enrichment. And the same applies for housing. If I'm only using the term "housing," I'm going to miss papers that refer to housing maybe solely as "cage" or "enclosure." So, I hope that makes more sense now.

One other thing I wanted to mention before moving on is that you'll notice I didn't put quotation marks around the term "bedding," and that's because if it's a single word and not a phrase, like "animal welfare" or "social housing," you don't need quotation marks. However, they don't hurt to add if you do want to add them -- I just wanted to mention that. Some of you may have also noticed the asterisk on the term "nesting material." What I'm doing there is truncating the word "material," so that it captures all word endings of that term, such as "nesting material" or "nesting materials." Another term we typically like to truncate is the term "behavior." So instead, you would put an asterisk after the V in "behavior, so you would get terms like "behave," "behaves," the European spelling of "behaviour," "behaved," et cetera. Then lastly, you would take your three search strings and join or connect them with the Boolean operator "and" which tells the database that you want to search for papers that have at least one word for each search string in the papers.

Slide 25: PubMed

Now I'm going to go ahead and show you a very quick live demo in PubMed, so let me transfer over.

[ONLINE DEMONSTRATION]

This is the Advanced Search screen of Pub Med, and the first thing I want to draw your attention to is that this All Fields box -- the first thing I always do is change it to Title and Abstract, because I think all fields is just a bit too general and broad, and it's going to usually bring back way too many results.

So, I'm going to change it to Abstract, I'm going to put in my first search string on housing keywords. I'm going to say Add. It's going to add it to the query box, and you can see it's just searching each term by Title and Abstract. I'm then going to do my search string on mice. Now it's switched it to And -- remember I talked about the Boolean operator And, so added that down here, and you can see it's separated by the Boolean operator And. And then I'm going to add my last search string on 3R's alternatives -- same thing. Here's the whole search string. I'm going to press Search, and here are all my results.

You'll notice that it does search over 600 results, which is likely too many for anyone to go through. But this is where modifying your search string comes into place so you can get a more manageable amount of citations, and a set that is hopefully more targeted as well. And one thing you can do to modify it is add an additional search string at the end, so fourth search strings separate by the Boolean operator And, which would result in less citations, since you're putting more parameters on that search, or making it more specific. And just for example, that fourth search string could be on keywords related to your area of research, such as if you're in the area of toxicology, or immunology or nutrition, or whatever your area is. And this is going to reduce the amount of citations you get.

Another easy way to reduce the number of citations is the search by only the Title field instead of the Title and Abstract field, which is going to lead to a lot more relevant results because those keywords are now required in just the Title field, so let's try that. Again, this is a trial-and-error process. If this came up with zero results, we would know that title is too specific, and we'd have to figure out another way to modify it. You might have to go back to the All Fields.

Okay, so now I have all my search strings, I have environment, housing -- okay. Now I'm going to go ahead and search that. You'll notice this brings down the results to only 34, so it's significantly reduced, and a lot more manageable for you to go through. And I don't have time to go through them now, but I did want to show you how I quickly refined it. I'm going to go back to the PowerPoint.

Slide 26: Evaluate and Refine the Search Based on Results

Okay, so once you get your set of citations to review, you'll want to skim your results to see how relevant they are. If most of them are relevant, then there's no need to refine it any further. However, more than likely, if it's your first attempt at searching, you will need to refine your search string. Another way to refine your search results might be to limit by publication years, so limiting your results to only things published in the last five years, or maybe ten years. Or, like I mentioned before, limiting it to Title or Title Abstract. Keep in mind that what I'm showing you is a very basic search, so there was a lot of room for improvement. Also note that it really, again, is a trial-and-error process. It's highly unlikely that you're going to get the perfect set of results using the first search string you created.

Slide 27: Document Your Search

Then once you have refined your results to where you want them, the last step is to save them in a citation manager like Endnote, Refworks, or Zotero. What these are are essentially a citation database that helps you save, organize, and share your research citations.

Slide 28: Citation that Incorporates 3Rs Alternatives

And I did just want to highlight one of those citations that were in the set of 34 results I just showed you, just so you know that this whole search string and process I'm taking you through actually worked. This paper specifically talks about how using nesting material and shelters

improve their welfare without interfering with the experimental outcomes, so again, a study that directly answers a question we sought out to address.

Slide 29: Search Evaluation – Red Flags

Then lastly, before we close out this section, these are some items that I put together that would maybe be considered red flags when conducting a literature search. For example, if you're only searching one database, you're going to miss a lot of information because one database never covers a topic 100 percent comprehensively. Another thing, if you're doing the search last-minute, and you're realistically less likely to incorporate alternatives into your research, which again is why the consideration of alternatives, should come before your protocol's written, such as during the grant writing phase, because if you already have the funding, it's highly unlikely that you're going to make any 3Rs modifications at that point.

If you only put in terms related to painful procedures, it's not going to be very helpful in finding alternative methods, because you're mainly going to get results with that procedure which you're trying to replace, unless you know it's a painful procedure that, like oral gavage, where alternative research has been done. Also, if you use a term "alternatives" in your search string, you're likely not going to find anything useful unless you're working on a teaching or a toxicology protocol, which does use that term in the context of the 3R's more frequently than other animal research areas. Then, lastly, restricting your search by years can, again, be helpful to refine your results, but keep in mind it's also going to greatly limit the citations you're going to get back, so you may miss something.

Slide 31: Best Databases for Animal Welfare and Alternatives

Then just briefly, this is a list of databases that we typically use and recommend when you're looking for animal science or animal welfare information. And more specifically, Agricola, PubMed, Web of Science, and Scopus are great if you're looking for animal use alternative information. And one thing to keep in mind when using Agricola is that, yes, you can search it freely through the platform on NAL's website, but we recommend that you search your curricula through your own institution in a multi-database system, like EBSCO or AvID, if you have access to it, because using the NAL's platform of Agricola is sometimes a little hard or clunky to use on its own.

Slide 32: AWIC: Products & Services

Now we're going to discuss some of the resources that NAL and AWIC make publicly available to you.

Slide 33: National Agricultural Library Resources

The first I want to go over is the AWIC website, which some of you may or may not already be aware of. But you can find us by going directly to the link on the slide, or from the NAL home page. You can find all kinds of peer-reviewed information on animal welfare, as well as other topics like what's in the news, updates on laws and regulations to animal welfare, bibliographies on hot topics in animal research, and all of our upcoming training opportunities.

Slide 34: AWIC Workshops
Speaking of training opportunities, AWIC offers a free day and a half in-person workshop at NAL on meeting their requirements on the Animal Welfare Act. However, the past year or two we have had to modify the workshops to a virtual setting, but we're hoping that sometime in 2022, hopefully, October, we'll be back to in-person. But you'll notice that our next workshop is virtual, on March 9th. So, make sure to register if you're interested. And within this workshop, we do dive deeper into the Animal Welfare Act and animal welfare in the legislation. We discuss the 3R's in more detail. We also talk about various databases and other resources and organizations that are helpful for finding information on the 3R's. And then lastly, one of our main takeaways from our workshop is an improved understanding on how to conduct a literature search. So yes, we focus on alternatives, but the concepts that we teach can also be applied to any type of literature searching.

Then other than our in-person workshop and live webinars, we also host our workshop online in a pre-recorded, self-paced, and free format. And while it doesn't have the in-person activities and interaction that our other workshops and webinars do, if you can't make one of those trainings and you still want access to the information, this is one way to get it.

Slide 35: Customizable trainings: Freely provided upon request
Then kind of like we're doing for this presentation, we do offer free shortened or condensed webinars on request. The difference between these and our workshops is that we can really tailor the topics of the presentation to your institution's wants and needs, meaning we can really hone in on a specific topic and the length of training can vary, depending on what you're interested in.

Slide 36: Reference & Literature Search Assistance
Then AWIC does offer reference and alternative literature searching assistance upon request, so if you're having trouble finding alternatives or a specific animal-related procedure or method or model, feel free to reach out to AWIC for help. We just developed and posted a Literature Search Request form on our website that makes requesting a literature search from us a lot easier. Then also, just in general, if you have any animal-related questions, not just related to scientific literature or alternatives, feel free to reach out to us, and if we can't find that exact information or answer, we can at least point you in the direction of someone who does.

Slide 37: AWIC Newsletter
Then lastly, if you're interested, or not already signed up, AWIC does send out a monthly newsletter which covers topics such as information on the 3R's, highlights related to AWIC, the Animal Welfare Act, tips and tricks on literature searching, and any upcoming 3R's-related conferences and trainings, among other information. You can just click on the link on the slide and subscribe. Again, we only send this out once a month via email, so don't worry about being bombarded with tons of emails. It's just a good way to stay up to date on 3R's information.

This is our contact information if you ever need to reach us. And with that, I will go ahead and hand it over to Joelle.

[Restart Slide Numbering]

Slide 1: Best Practices for Finding Animal Model/Model Organism Information
>> Joelle: Great, thank you, Jessie. Hi, everyone. My name is Joelle Mornini, and I'm an informationist at the NIH Library. Today, I'll be providing an overview of Best Practices for Finding Animal Model and Model Organism Information. We'll take a look at how to locate biomedical research articles, patents, and NIH-funded research projects and genetic information related to animal models and model organisms.

Slide 2: Objectives
After completing this training, you'll be able to describe the difference between animal models, research organisms, and model organisms, and how these concepts are related. You'll be able to identify requirements and resources for the NIH Model Organism Sharing Policy. We'll take a look at how to locate biomedical articles related to animal models through PubMed, and how to locate patents related to animal models on Espacenet. You'll be able to locate NIH-funded research projects that utilize specific research organisms through NIH RePORTER, and also identify publications, patents, and clinical trials related to these research projects. We'll look at how to identify genetic information and biomedical literature about specific research organisms through the Taxonomy Browser from the National Center for Biotechnology Information. And finally, we'll also look at where to find model organism databases, which provide genetic and biological data about specific model organisms.

Slide 3: Animal Models and Model Organisms
First let's look at the definition of Animal Models, Model Organisms, and Research Organisms.

Slide 4: Definitions
According to the National Cancer Institute's Dictionary of Cancer Terms, an Animal Model is an animal with a disease either the same as or similar to a disease in humans. And the animal may be used to study the development and progression of diseases and to test new treatments before they are given to humans. Animals with transplanted human tissue such as cancer are called xenograft models. Many animal models may be genetically modified based on the requirements of the study. The article "A Brief History of Animal Modeling," published in 2013 in "Missouri Medicine" by Ericsson et al, describes how the first transgenic mouse, where the mouse carries the additional genetic materials from an unrelated organism was developed in 1976. Well, the first knockout mouse where genetic materials are inactivated was developed in 1987. Animal models are often used in pre-clinical research before testing new treatments on humans during clinical research. The National Institute of General Medical Sciences broadly defines a research organism as any creature that scientists use to study life, which can range from single-cell bacteria to more complex organisms like mice.

A Research Organism is identified as a model organism when it is used to examine elements of human disease. Reasons an organism may be used as a model organism include biology that is similar to humans, or a lot of information may already be available about the organism's genetic makeup. Some examples of model organisms include fruit flies, mice, rats, and

zebrafish. The term "animal models" and "model organisms" can often be used interchangeably. In this training, we'll take a look at terms related to animal models within controlled vocabulary and classification systems to more effectively locate journal articles and patents related to animal models. We will also take a quick look at resources and research strategies to locate NIH-funded projects and genetic information related to research organisms and model organisms.

Slide 5: Relationship of Model Organisms and Animal Models
Just to summarize, model organisms like mice, rats, fruit flies, and zebrafish are often used as animal models in the study of human disease. Model organisms and animal models may be genetically modified, based on the needs of the study. The terms "animal models" and "model organisms" can often be used interchangeably.

Slide 6: NIH Model Organism Sharing Policy
Now we're going to take a quick look at resources for learning more about the NIH Model Organism Sharing Policy.

Slide 7: NIH Model Organism Sharing Policy Description
The NIH Policy on Sharing of Model Organisms for Biomedical Research is an extension of the NIH policy on sharing research resource, and it went into effect on October 1st, 2004, for applications or contract proposals to NIH. This policy applies to extramural investigators funded by NIH grants, cooperative agreements, and contracts. A description of the policy is in a brochure available at grants.nih.gov, and states that “All NIH applications and proposals that will produce new, genetically modified variants of model organisms and related resources are expected to include a sharing plan or to state why such sharing is restricted or not possible.”

Slide 8: NIH Model Organism Sharing Policy Resources
You can check the NIH Model Organism Information page to find links to the original NIH Guide Notice [NOT-OD-04-042] related to the policy, an FAQ on sharing of model organisms and related resources that includes a searchable list of commonly asked questions, links to examples of plans for sharing of model organisms and related resources, including a simple plan, complex plan, and plan for sharing mice, and a brochure about the policy in PDF format.

Slide 9: Finding Biomedical Articles on Animal Models
Next, we'll take a look at how to find biomedical research related to animal models using PubMed.

Slide 10: Finding Biomedical Articles: PubMed & MeSH
PubMed is a free biomedical literature database from the National Library of Medicine, and it covers over 33 million citations for biomedical literature from Medline, life science journals, and online books.

Medline is the main bibliographic database from the National Library of Medicine, and it contains over 28 million references to journal articles in the life sciences and biomedical fields. Journal articles included in Medline have Medical Subject Headings, which are also called MeSH terms added to the article records to make them easier to find with a consistent and controlled vocabulary.

In PubMed, you can try searching for articles with "Models, Animal" added as a MeSH term. All narrower MeSH terms under a broader term are also automatically included in the search, so a search for articles with MeSH terms "Models, Animal" will also automatically search for articles with MeSH terms like "Disease Models, Animal." You can visit the MeSH Browser at ncbi.nlm.nih.gov/mesh to look at MeSH terms, and then add them to PubMed.

[ONLINE MESH DEMONSTRATION]

So, let's visit the MeSH Browser. And in this search, I've searched "Animal Models." And we come up with just one related MeSH term, “Models, Animal”. You can see there's a description of the MeSH term, followed by subheadings that can be added to further narrow the search. There's a number of entry terms which are various synonyms related to the term, in this case, "Animal, Model." If we scroll down, you can see all of the narrower terms under "Animal, Model," which includes "Disease, Models, Animal," and then a number of narrower terms related to various diseases. And if we want to search this term in PubMed, you can just choose Add to Search Builder, and then Search PubMed. You can see there's around 611,000 publications that have been tagged with the MeSH term "Models, Animal" or one of the narrower terms.

Slide 11: Finding Biomedical Articles: PubMed

This screen shot shows the search in PubMed for articles labeled with the MeSH terms "Models, Animal," and an additional search term can narrow the search to only articles related to melanoma. Note that the second search term doesn't include any search field tags that would limit the search for the term only to a specific field, like Title, Abstract, or MeSH Terms. If no search field tags is added to a PubMed search term, then PubMed automatically applies a feature called "Automatic Term Mapping" to the search term. Automatic term mapping could locate various synonyms, MeSH terms, and singular or plural versions of the search term in order to expand the search. You can go under the Advanced Search builder on PubMed to view the history and search details table and choose to expand the details column to view how your search term was expanded using Automatic Term Mapping.

[ONLINE DEMONSTRATION]

So if we go back to our search, we can type in "AND melanoma" in order to narrow our search further, just related to a specific disease. And if we go under the Advanced Search, we can scroll down and see how our search actually maps using the Details column. You can see that since we specifically added the MeSH field tag, we search just across MeSH terms for "Models, Animal," but for "melanoma," since there wasn't any field tags added, it searched across a

MeSH term that was automatically linked to melanoma, and it also searched across a variety of plurals of melanoma, melanomas, melanomas across all fields. So, the Automatic Term Mapping is a great tool for expanding your search, but I always recommend double-checking under the Detail section just to make sure that it's actually mapped to correct MeSH terms and related synonyms.

Slide 12: Finding Patents on Animal Models
Now we're going to take a look at how to locate patent documents related to animal models through the free patent database Espacenet.

Slide 13: Finding Patents on Espacenet: CPC
Espacenet is a free patent search tool from the European Patent Office that searches across more than 130 million patent documents. You can try using the Cooperative Patent Classification, or CPC Browser, to find classifications related to animal models and model organisms. For example, if you search by the term "animal model" within the CPC Browser, you can find relevant classifications like A01K2267/03, animal model, e.g., for test or diseases. You can then choose the checkbox beside a relevant classification, which will automatically select all subclasses, and then choose Find Patents in order to search for all patents labeled with this classification or related subclasses in Espacenet.

[ONLINE DEMONSTRATION]

So I'm going to go ahead and go to Espacenet. And you can see we can choose to search within the classification search, and I'm going to search for "Animal, Model." Then you may need to expand various terms in order to view more relevant subclasses. In this case, we come across animal, model, e.g., for test or diseases. And you can tell -- and there are narrower terms beneath it by the number of dots beside -- more dots equals a narrower subclass. And if you see /LLow, that just means it's going to search across all the subclasses as well. So, click on Find Patents, and that brings up about 6,900 patents related to that classification.

Slide 14: Finding Patents on Espacenet: Advanced Search
You can also try using the Advanced Search on Espacenet to search for keywords in the Title, Abstract, and claims of the patent documents, like organism name or disease, and combine with CPC code searchers. You can combine searching by classification and keyword to find patents related to animal models for specific organisms and diseases. For example, this screenshot shows a search using the animal models, e.g., for test or disease, CPC code in combination with a search for keywords "mouse" or "Mice" and "hepatitis" in the Title and Abstract of the documents, in order to locate patent documents related to hepatitis and mouse models.

[ONLINE DEMONSTRATION]

Just going back to our search -- I'm going to turn on the Advanced Search, and then we can add additional fields to narrow the search further. So, I'm going to just choose to search within a

text field, Title, or Abstract. I'm going to choose "any" so that it will include a Boolean operator "OR" between each of the different search terms, and then I'm going to enter "mouse" or "mice." I'm going to add one more field, and I'm going to enter "hepatitis." And I'll run the search, and that gets us down to about 25 search results.

If we want to view one of the actual results, you can click on the result, and that will open it in a separate window. You can view the IPC codes, the international patent classification, which is actually an older classification system which the CPC is built upon. You can scroll down and view the Title and Abstract. You can use Patent Translate if it's a non-English language patent, in order to translate it using machine learning into whatever language, usually English, so this is one tool that's helpful for translating non-English patent documents, if you need to just get a quick idea of what they're about. You can view the different sections of the patent. And if you click on original document, you can actually download the full patent document just by going under Download, and then Original Document. You can also view the patent family, which is filings of the patent around the world. If you click on IMPADOC family, that's usually the broader patent family that will include many filings of related technologies related to that patent. And if you want to download the entire list of patent documents, you can click on any of the checkboxes, and then click Download and list either into Excel, or you can even download the front pages of the documents.

So just now, I'm going to launch a quick poll. It looks -- let's see -- all right, so what database tools can be used to find more targeted results related to animal models? Just select all that apply. And the options are MeSH terms in PubMed for biomedical articles, Automatic Term Mapping in PubMed for biomedical articles, Basic search in PubMed for biomedical articles, CPC in Espacenet.

>> Jessie: I think I had to relaunch it. So it should be open now.

>> Joelle: Okay, thank you. I'll let it run for about 30 seconds. All right, give it about 10 more seconds, and we'll go ahead and see what the answers are.

Great. So I'm going to go ahead and show the responses. So the correct responses are Medical Subject Headings and the Cooperative Patent Classification -- those are two ways to narrow your search. If you want to expand your search, especially in PubMed, you can use Automatic Term Mapping -- that can be a helpful tool for expanding your search.

So moving on, now we're going to take a look at how to locate NIH-funded research projects related to specific research organisms using NIH RePORTER. You can use NIH RePORTER to find NIH-funded research projects, investigators, publications, and patents related to specific research organisms. Here are some tips for locating projects that utilize specific research organisms. Under the Advanced Projects Search, choose Advanced Text Search, and then enter all versions of the organism name, both the common and scientific, as well as plural, using the Boolean operator "OR" between each organism name search term. And you can also use quotes around phrases and parentheses to group all versions of the organism name. Then also use the

Boolean operator "AND" to add additional search concepts. So just as an example, to locate projects related to cancer and fruit flies, you could use "fruit fly" or "fruit flies" or Drosophila melanogaster or "D. melanogaster" and "cancer" within your search. For a shorter list of relevant projects, try limiting text search to Project Title, Protect Terms and Project Abstracts.

Let's go ahead and go under NIH RePORTER. And we'll click on Look for Additional Fields, and this will expand the full search, the full menu. And I'm going to just copy the search strategy that was listed in the slide. I'm going to paste it in the Search box, and go under Advanced. I've made sure that Project Title, Project Terms, and Project Abstracts are selected. And then I'm going to just choose the fiscal years that I'd like to search, I'll just search for within the last few years, and I'll run the search. And we get our search results. So just looking at the search result box, under the search results, you can view NIH-funded projects where any version of the organism name is listed in the Project Title, Project Abstract or terms, and also choose to view lists of publications, patents, and clinical trials related to those projects. You can find links to the publications on PubMed, links to the patents at the US Patent and Trademark Office database, and links to the Clinical Trial at ClinicalTrials.gov.

So just going back to our results, if you click on one of the project results, you can view a description of the projects with highlights of the search terms, so related to your research organism and other research terms you've added, and then you can find related publications, patents, clinical trials and more. If you click on the specific tabs, you can also view lists of publications, patents and clinical studies related to these particular projects. You can see that the publications will usually link to PubMed or Google Scholar, patents will link to the USPTO database, and clinical studies will link to ClinicalTrials.gov.

Now we'll take a look at how to find genetic information for a specific research organism through the Taxonomy Browser from the National Center for Biotechnology Information. We'll also look at model organism databases, where you can locate genetic information related to specific model organisms. The Taxonomy Browser is a tool from the National Center for Biotechnology Information, or NCBI, which is part of the National Library of Medicine. You can use the Taxonomy Browser to find links to genetic information and biomedical literature related to specific research organisms. Users can search the Taxonomy Browser by the common name for the organism, like zebrafish, or by the scientific name, like *Danio rerio*. So, if we go to the Taxonomy Browser page -- maybe just go directly, since it seems like it's freezing up a little bit -- one thing I recommend is click on Browser, and this will allow you to also just view a premade list of research organisms. You can also always just try searching by research organism; you can search by either the Latin, scientific or the common name. It seems like there might be some issues with the website, but let's do a search for zebrafish. And you can see that it'll bring up the Latin name, but you'll also see some information related to the common name [INAUDIBLE]. And when viewing it, you'll view a list of -- it says the Entrez Records; this is just a table where you can find links to various NCBI databases with premium searches related to that specific organism. And you can also scroll down to find links to external resources related to

that specific research organism, including model organism databases, like the Zebrafish Model Organism Database, which we'll discuss in just a second.

So pages for your specific organisms on the Taxonomy Browser include direct links to search results related to that organism, and the genetic makeup within other NCBI databases, such as the Nucleotide database, which includes genome, gene and transcript sequence data, the Protein database, which includes protein sequences, the Genome database, which hosts information on various entire organism genomes, including sequences, maps, chromosomes, assemblies and annotations, and PubMed Central, which includes full-text biomedical articles.

Pages for specific organisms of the Taxonomy Browser also list links to External Information Resources related to the organisms, such as model organism databases. Model organism databases, also known as MODs, provide in-depth biological data for commonly used modal organisms. These databases are often funded by grants from various government institutions, including NIH, and may be maintained by government, academic, or other nonprofit institutions. Examples of MODs include FlyBase, which covers fly genes and genomes, Mouse Genome Informatics, Rat Genome Database, and the Zebrafish Information Network [ZFIN]. Each model organism database may have varying layouts, tools, and data available, depending on the user needs and the resources available to the database developers. A toolkit created with NIH funding is available at GMOD.org, called the Generic Model Organism Database project, which offers guidance on open-source software tools for managing, visualizing, storing, and disseminating genetic and genomic data.

To locate model organism databases for specific research organisms, you can try checking the External Information Resources section for organism pages on the Taxonomy Browser. Just for example, the zebrafish page on the Taxonomy Browser links to ZFIN under the External Information Resources section. You can also try the Online Bioinformatics Resources Collection, or OBRC, by the Health Sciences Library System at the University of Pittsburgh. Some links may be outdated on the site, but it's still a useful portal for trying to locate MODs for specific organisms. You can browse databases for vertebrate and non-vertebrate organisms.

So just as a quick summary of what we covered today: Model organisms are often used as animal models in the study of human diseases, and the term "animal model" and "model organism" can often be used interchangeably. You should be aware of the NIH Model Organism Sharing Policy, and the policy applies to extramural investigators whose research will be generating new, genetically modified model organisms. You can find information on animal models and model organisms through PubMed for biomedical articles, Espacenet for patent information, NIH RePORTER for NIN-funded research projects, Taxonomy Browser, which can link to genetic information, as well as biomedical literature through PubMed Central, and model organism databases where you can find a variety of genetic information.

And here's my contact information. I believe I'll pass it back over to Cate.

>> Cate: Yes, thank you so much, that was great! Thank you, Jessie and Joelle. We do have time for one or two questions. And I see that we do have a lot of questions that are very specific to certain situations, and so I'd encourage the participants to contact the NIH Library or AWIC to get answers to those questions.

I'm going to ask one very general question. Do you have any tips for IACUCs that evaluate alternative searches associated with animal use protocols? And Joelle or Jessie, you're both welcome to answer this.

>> Jessie: I can take a stab at it first. Yes. I meant to actually include a slide on that. But some tips that I think the IACUCs should keep in mind is when you're reviewing a literature search, look at their keywords. One of the biggest mistakes we see is that there are only one keyword usually added, and be, like, heart or cardiac, and canine and cancer, or something like that model, where you're not adding all these additional terms, which are really going to strengthen your search. Then if they can say they come up with zero results, usually a red flag -- I mean, there might be in some searches zero results with a perfect search string, but it's kind of unlikely. And then keep in mind limited publication units. We typically like to go back at least the last 10 years, but sometimes 5 is sufficient in an alternatives search. Always having a librarian on staff of your IACUC committee is really helpful, because not everyone can be experts on literature searching. But the librarian serves as that expert, and can better evaluate the search.

>> Cate: Thank you. Joelle?

>> Joelle: Great, thank you, Jessie. I definitely agree with Jessie. It's always a good idea to have a librarian either working with the IACUC or to send any requests to them if they need assistance with literature searches, especially when doing it through PubMed. And oftentimes you may not be aware of some of the other databases that may be accessible through your institution's libraries, such as M-Base, or some other databases where you may be able to expand your literature search and find additional resources.

>> Jessie: Yeah, and then also again, red flags if they're just using the terms, like, "alternatives," and they say there's zero results -- you really have got to think outside the box. There's three -- I showed with examples of the 3R's, those are going to be so much more helpful, like using the terms "in vitro" or "mannequin" or "imaging," or real examples that's going to really strike your research.

>> Cate: Great, thank you. Do you want to flip to the next slide, Joelle? So, we have run out of time, but thank you both again for that in-depth discussion. We really appreciate your time, effort, and experience. Our next webinar is going to be next spring, and the topic is yet to be determined, but we'll make sure to advertise that in advance. So, until then, stay safe and healthy. And thank you, and goodbye.

>> Jessie: Thanks. And yeah, reach out if anyone has any questions.

>> Joelle: Great, thank you so much!

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ADDITIONAL QUESTIONS

Question A: Is it reasonable for IACUC searches to limit results to last 5 or ten years?
>> *Joelle*: In past searches I've done, I've always limited searches to at least the past ten years. You may miss some highly relevant results if you limit to only past five years. It's best to always check how many results you'd get without any date limits first, to see if you'd lose too many relevant results by adding a date limit.

Question B: Is there a benefit to using MeSH terms for searching vs. keyword searching?
>> *Joelle*: MeSH terms can help narrow your search to highly relevant results and also provide controlled vocabulary, since search terminology in title and abstracts are not always consistent. For example, some articles may reference tumors and others may use the term cancer, but both articles would be located using a search for the MeSH term neoplasms (search: "Neoplasms"[Mesh]). Keyword searching can be used to expand your search in PubMed, since PubMed uses a feature called Automatic Term Mapping (ATM), which maps keywords that don't have quotes or field tags and automatically expands the search to include related MeSH terms, synonyms, and plurals. You should always check what your search has actually mapped to with ATM, since sometimes it can add unintended synonyms to your search. To view how ATM has translated your search terms, open the PubMed Advanced Search, and expand the Details column under the "History and Search Details" table.

Question C: Is a search for alternative required for mice and rats bred for research?
>> *Jessie*: Yes, you should search for and/or consider alternatives for mice and rats bred for research. The AWA states that you should consider alternatives for *all* animals used in research.

Question D: What alternative search terms would be appropriate for protocols that use anesthesia for terminal blood collection with exsanguination? (The blood is needed for analysis.)
>> *Jessie*: The main thing to keep in mind for this research question is to make sure the animal doesn't experience feeling or pain as they are bled. So, make sure you keep them under an anesthetic that is deep enough so they don't experience pain. Some terms you could use in your search string are: refinement OR painless OR "reduce pain" OR "stress free".

Question E: Do you just search only Title/Abstract Fields? Should MESH be searched too?
>> *Jessie*: Yes, you should still do a literature search for alternatives. Animals may not always be able to be replaced, but there could be alternatives like using mannequins, simulations and virtual reality that could replace the live animal (at least during certain stages). We have a whole webpage on education and training-based alternatives

>> *Joelle*: In PubMed, the Title/Abstract [tiab] search field can be a useful field to use in combination with relevant MeSH terms. If you can't find a related MeSH term using the MeSH browser, try searching for the term using Title/Abstract field or the Text Word [tw] field. You could also include the search term without a field tag in PubMed, and the term would then be expanded automatically using Automatic Term Mapping (ATM).