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Meeting Requirements for Alternatives Searches: Information for IACUCs and Investigators

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Slide 1 (Meeting Requirements for Alternatives Searches: Information for IACUCs and Investigators)
>> Babcock: Today it is my pleasure to welcome Kathleen Gregory to the OLAW seminar series. Ms. Gregory is the science and engineering reference librarian at the University of Denver (DU). She presented a talk on alternatives searching at the 2013 IACUC Administrators' Best Practices meeting. It was a terrific talk, very helpful, and we are pleased to have her here today to share her expertise with all of you. Kathleen serves as a consultant to the University of Denver's IACUC, assisting in evaluating literature searches in submitted protocols. In addition to alternatives searching, her active projects include investigating scientific information literacy and implementing research data management services. Kathleen earned her master's degree in library and information science from Drexel University and her MA in instruction and curriculum from the University of Colorado, Boulder. Kathleen?

>> Gregory: Hi, everyone, and thanks, George, for that introduction and for the invitation to speak today. In today's webinar, I'm going to speak a bit about the

role of literature searches in the consideration of alternatives, as well as some strategies and resources that can be helpful both when performing literature searches and when evaluating them.

Slide 2 (Why perform a literature search?)
Why is it important to conduct literature searches when doing research involving animals? Well, as I tell our researchers, comprehensively reviewing past research in any discipline can help to eliminate the unnecessary duplication of experiments and to inform experimental design, which leads to saving both time and money, and hopefully produces improved results as well. When working with animals, there are additional ethical considerations to think about. Reducing the duplication of experiments also has the benefit of reducing the overall number of animals used in experimentation. Literature searching can also be used to identify and incorporate modifications that can minimize animal pain and distress.

In order for a literature search to really effectively meet these goals, it's important that the search is truly comprehensive, and that all pertinent information is retrieved and considered. If potentially relevant studies are not included in the literature search results, important information may be missed that could have led to a more effective experimental design. That means – and this won't be the last time I say this today – that more than one resource needs to be consulted. In addition to these ethical considerations, there is, of course, the small matter of the law. Both the Public Health Service Policy [PHS Policy on Humane Care and Use of Laboratory Animals] and the Animal Welfare Act require the examination of alternative models and alternatives to potentially painful procedures. Although a literature search is not the only way to investigate alternatives, Policy Number 12 in the Animal Care Resource Guide recommends a literature search as the most effective method.

Slide 3 (The IACUC's Role)
What exactly does the Animal Welfare Act say about the literature search and specifically about the IACUC's role? The IACUC is responsible for determining that a PI has considered alternatives, and the document that they have at their disposal to make that determination is a written narrative detailing what sources the investigator used and, most importantly, how he or she used those sources. So let's speak a little bit more about this narrative that the IACUCs [receive].

Slide 4 (The Narrative)
The written narrative should include, at a minimum, the name of the databases that were used in the literature search, the date the search was performed, the time period of the literature that was covered, so if the literature was just looked at for the last five years or the last ten years, as well as the search strategy. [The search strategy] is perhaps the most important part. That's what the researcher actually

entered into the database, or the databases, to get the results that they used in their [alternatives] consideration. The most effective way for researchers to create this narrative is to document what they're doing as they're actually performing the literature search. If you're trying to remember search terms and resources that were used months after the fact, it's quite possible that the narrative may not actually be representative of what [was done].

There are, luckily, some tools that can be used to make this in-process documentation easier. For example, [Altweb](#) from Johns Hopkins has designed a worksheet that can be used to help document the search process as it's being conducted. There are often tools built into databases, and we'll take a look at some of those today, that will allow researchers to save their searches and to manage the results they find as they find them.

Additionally, some researchers may be able to use existing workflows, many researchers are familiar with using bibliographic or citation managers such as EndNote, Mendeley, or RefWorks. These [tools] can be also used to help organize the material in an alternatives search. You can usually add notes to the files in these programs also that can help to document what search terms were used and what strategies were used so that it's much easier to pull that narrative together for the IACUC.

I think it might also be important for IACUCs to think of ways to educate investigators about some of these strategies for creating the narrative as the literature search is being conducted, with the end goal, of course, improving the quality of the narrative so that it more accurately represents the literature search that was performed which, of course, also makes the review process easier.

Slide 5 (Timing of the Literature Search)
It's important to remember that the goal of the literature search is to actually inform the experimental design; and in order for that to happen, the search needs to take place before any work in the lab, and early enough to actually inform the planning process. If this doesn't happen, the literature search just becomes another hoop to jump through, rather than a helpful resource.

Slide 6 (A Scientific Approach)
It may also be helpful to remember that textual research or literature searching is similar to experimental research in that some forethought and planning can go a long way to improving the success of a project. Following a general plan while constantly reevaluating and tweaking it can really help to transform an incomplete search – and I'm sure none of you have ever seen a search like this before – into a more comprehensive search strategy. So let's talk about that overall strategy.

Slide 7 (The Overall Strategy)

This is a road map for what this overall strategy may look like. The first step in the cycle, which is up here at the top, which I'm calling The Question, involves thinking of different angles and components of a project, and then really brainstorming different ways to express those concepts. It's much more than just having an overall research question. It involves explicitly thinking about other possible animal or non-animal models, identifying any potentially painful procedures up front, and maybe making notes about any possible alternatives that a researcher may have heard of from either past research, from conversation or from the literature. The search terms involved in this question should really be a mix of terms related to the 3R's, as well as more project and research-specific words.

The second step here, which I'm calling The Strategy, involves thinking about how to combine all of those different concepts and keywords into a search strategy that will be entered into the database. This is not just as simple as typing in "frog alternative" into the search box, as we will see in a few minutes. Then finally, after we've done a lot of thinking and planning, finally we're ready to actually search. But this step also involves some planning. You need to think about which database is really going to be most helpful for a particular project.

This third step involves thinking about and choosing different resources that will be used. Different databases contain different information, and while there's often some overlap between the sources – the literature in different databases, there's usually enough unique information to merit searching more than one place. So while PubMed is a fabulous database that is very useful, in order to ensure that the search is truly comprehensive, as I mentioned before, more than one resource needs to be searched. We need to keep in mind also that each database has a unique way of operating and interpreting the search strategies. This means that the search that you use in PubMed most likely will not work the same if you copy and paste it into another database like the Web of Science. It's important to know how the database is working as you're searching within it.

While I show this cycle as a very clean and orderly process, there's a lot of adjustment that goes on, and it's actually pretty messy. As different search strategies are tried, the researcher needs to be constantly evaluating the results and going back up here to the earlier steps in the process to come up with new keywords, new concepts, new ways of combining those terms, and then possibly trying out different databases also before finally reaching the point, over on this side of the diagram, where he or she is confident that they've retrieved all of the relevant results and are ready to manage the literature and construct that narrative.

The best way to learn about how to conduct and how to evaluate a literature search is to actually see how this works in action. We're going to work through a few examples in PubMed to get our feet wet with this type of searching. But before we do, I think it's important to review a few general concepts and general search strategies.

If you're a researcher, some of these general strategies that we're talking about can be used in your literature searching, and you may be familiar with some of them. If you're an IACUC member, hopefully you're going to start to see some more comprehensive reports of searching. You might start to see some of these general search strategies being reported, in which case it's important to know exactly what you're seeing.

Slide 8 (General Strategies)
My first general search tip that I wanted to address is using Boolean logic to appropriately broaden or narrow the scope of the search, depending on your goal. Let's talk through this diagram here. This first part of the diagram represents the Boolean operator "And." For example, if I were searching in PubMed and I was going to write the words "cancer and neoplasms," I would only retrieve the small green section here where the circles overlap that represents the articles that mention both of those words in the searchable fields. That's a relatively narrow search.

In the beginning of a search, I usually like to have a very broad scope, so I might consider using the operator "Or" to expand my search. To stick with this same example, if I wrote "cancer OR neoplasms," I would retrieve articles that mention either cancer or neoplasms, as well as that overlapping bit that mentions both terms in the searchable fields. And then the last one that I'll address here is the unsung hero of Boolean logic, and I think it's my favorite Boolean operator. I'm a librarian. I can have a favorite Boolean operator. This is the "Not" operator, which can be used to exclude terms that you don't want to search. So in this example, if we wrote "cancer NOT chemotherapy," none of the results that I retrieved would mention this second term, chemotherapy.

My second general tip is to use what librarians call phrase searching to force the terms that you search to appear in a certain order. In this example, by enclosing the term "tissue culture" in quotation marks, I'm excluding results that mention "tissue," for example, in the beginning of an abstract, and then "culture" in an unrelated context. It forces those two terms to be searched together in that order.

The third general strategy you may see in the narratives or that you may use is truncation or wild card searching. And although the symbol here for the truncator may be different in different databases – I used an asterisk here, which is

commonly used – the end result is the same. This search, handl*, with an asterisk, would retrieve all variations of a word that have the same initial stem. So, for example, this search would retrieve handler, handling, handled, etcetera.

Finally, perhaps the most important general concept is to know the difference between keywords and subject headings. Keywords are akin to the natural language that we would use to describe concepts in everyday life. Subject headings are a defined way of expressing these concepts. They're also called a controlled vocabulary. When a new article is added to a database, a librarian or scientist reads it, decides what it's primarily about, and then he or she files it into the appropriate bucket of information, or the appropriate category, [and assigns] the appropriate subject heading. [Information within a particular] subject heading only contains information about that particular topic.

Once you know the correct subject heading for your project, you can really quickly narrow down your search to very on-topic information and eliminate some of the guesswork that's involved. For example in PubMed, in the example we were speaking about, I wouldn't need to brainstorm all the different keywords (such as cancer or neoplasm or tumors); I would just need to identify the appropriate subject heading – in this case it would be neoplasms – within PubMed and search within that area of the database.

Now that we have an understanding of some general strategies, I think we're ready to see how we can put these to work in a few examples. So we're going to transition over and do some live searching.

Slide 9 (*live literature search demonstration*)
If I were to ask researchers in the life sciences at my institution which database they use to perform literature searches, almost all of them would answer PubMed. That's where we're going to spend our time today, because I'm guessing that many of you would also have that same answer. So what exactly is PubMed? Well, as you can see here on the screen, PubMed is a free service of the National Library of Medicine, and at the moment it contains about 23 million references to biomedical information. In my experience, with both IACUC members and researchers, there's sometimes confusion about [the difference between PubMed, MEDLINE, and PubMed Central]. People don't know what the difference is between those three, so let's clear that up really quickly.

PubMed is the overarching umbrella database. It includes all of these 23 million citations. MEDLINE is a subset of PubMed, and all the results that are in MEDLINE have been indexed with medical subject headings; they have been filed into one of those areas, those categories [that we discussed earlier]. MEDLINE represents about 90% of the articles that are in PubMed. PubMed Central is another portion of

PubMed that includes only articles that are open access – articles that are freely available. I'm guessing many of you may have had to deposit work into PubMed Central as a requirement of a funding agency. But let's just quickly go through that terminology that you may see as a reviewer showing up in the narratives, so you know the difference between the different areas of the database.

I think it would be most helpful to talk about PubMed by doing some searches. We'll begin with a search geared more toward replacement, just to get our feet wet with the database and see how it's operating, and then we'll segue into a discussion of some more refinement-related searches. We'll start with a very broad search and look at how quickly to focus our results to more on-topic information. I'm going to pretend that I'm a researcher using a mouse model to investigate the role of apoptosis in neurodegenerative disorders.

If I were not very familiar with literature searching, I may enter something like this into the search box: "apoptosis neurodegenerative disorders mouse alternative." And let's see what our results list looks like: all right, a whopping 42 results. Let's think about why I'm retrieving such a limited results list here. Let's think about what exactly is going on in this search. All of these terms in the search box, including this word "alternative," have to show up in the searchable fields. Now the information that I am finding – it's quite possible that there are many other articles that would be helpful that don't mention, for example, this word "alternative". This really limits the search. One of the red flags that some IACUCs actually use is including this word "alternatives" in the search. So let's change our search and try to do things a little bit differently. I'll put my researcher hat back on here and pretend that I'm remembering some of my Boolean logic and some of my literature searching tips, and let's try "apoptosis neurodegenerative disorders NOT mouse." When I do this search, I have the opposite problem going on. I have way too many results. So at this point in the search, I would have a couple of options.

I could use some of the general search strategies that we discussed earlier, such as quotation marks or subject headings to narrow things down, but when we do that, we can actually lose some of the features that make PubMed really such an amazing resource. We're going to take a side trip here and look and see how PubMed is interpreting our search and look and see what it's doing behind the scenes. So if I scroll down this somewhat busy screen – if you're not used to seeing results in PubMed, this may seem a little bit busy of a results list. But down here on the right-hand side, there's something called "search details." And if I click on the "see more" option, I can see what PubMed is actually doing with my search. So this box here, the translations shows in the first column what I actually wrote in, and then the second column is what PubMed is actually doing for me without me having to do much work on my end.

Let's look at how this term "neurodegenerative disorders" [was interpreted].You can see that the database is first going to map it – I'll try to highlight here – to a medical subject heading, an appropriate MeSH term. This is the controlled vocabulary that PubMed is using, and it's a very powerful way to get on-topic results efficiently. This is really pretty amazing; it automatically is mapping what I put in as a keyword to an appropriate subject heading. It's automatically doing that. And then it goes on to search our keywords separately here, and then also here in quotation marks, as a phrase. And then it decides, oh, I should probably decide that I should go ahead and [search] for that term "disorders," too, that was actually typed in.

You can see another example of this expansion here with the term "mouse," it's automatically looking for the medical subject heading, and then it's also looking for the singular and the plural versions. This is one of the reasons, like I said before, that PubMed is such a powerful database, but it's also one of the reasons why on that results list that I just got – I have such a large number of results. I can use these medical subject headings, these MeSH terms, as a way to focus my results, and that's what we're going to look at next.

When I search PubMed – I'm going to scroll up here – I usually use this "advanced" search box [located under the regular search box]. I'm going to now put on my librarian hat and search here using the advanced search. I like to use the advanced search because it allows us to access different fields and indicate where we want our search terms to appear; as well as it keeps this nice search history down here at the bottom of the screen that will allow us to combine [our] searches in different ways.

So let's do the search again here. I'm just going to keep my research-related keywords on one line: ["neurodegenerative disorders apoptosis"]. And rather than actually searching it, I'm going to add it to my history so it appears down here in the bottom of my [search history] list. Now I can see – okay – that's how many results there are in PubMed that match this search. And then I'm going to use this drop-down menu to [search] those MeSH terms that we were talking about. [After selecting MeSH terms in the dropdown; I'm going to type animals into the first search box and select the Boolean operator "not" from the next dropdown menu. On the next line, I'm going to select MeSH terms again and type the word "mammals" into this search box, making this part of the search be "animals [MeSH] NOT mammals [MeSH]." I will then add it to my history and hopefully I will see that there's quite a few articles that match that indexing. I can then use the search builder to combine these two different searches: (neurodegenerative disorders apoptosis) AND (animals [MeSH] NOT mammals [MeSH]). I will add them to my history; and get this nice preview of the number of results that I have. I can then review those 106 items that match this search.]

That was a window into PubMed, a little introduction through a replacement search. Let's turn our focus now to searching for more refinement related searches, searching for alternatives to potentially painful procedures and for ways to minimize animal pain and distress. These types of searches, as you are aware, can be challenging. Using these MeSH terms can help with some of the problems. So we saw just now how to use the advanced search to get to some of those MeSH terms, but you can also search this controlled vocabulary directly, which has some benefits. And I do like to do that sometimes – I can change [the dropdown menu at the top of the PubMed screen to search the MeSH list directly], then I'm going to modify my search to look at ways to minimize pain and distress – and construct a search that I could do that with.

When you're searching the MeSH thesaurus directly, remember that you're looking for the names of subject headings. Often these would be broader than what you might think of with a keyword search. We'll be very broad here and [search for a MeSH term related to "pain."] I can see on this results list that there are a total of 60 headings, or 60 categories of information, that have to do with pain. Some of them are very specific, and the specificity is one of the reasons that PubMed, again, is a very powerful database. For this search we're going to keep things general. [When I select the category called "pain,"] I have a nice definition, and I also have access to seeing all of these subheadings that have been associated with this term.

Here in this subheading, I can see that I can select "prevention and control," and then there's also a "veterinary" subheading. I can then add these [subheadings] to my search builder, and you can see it's looking for "pain/prevention and control [MeSH]" OR "pain/veterinary [MeSH]." Then I can [do the same thing for the idea of stress and distress]. Again, keeping it very broad; [I will begin by searching MeSH for the term "stress"]. You can see there are many more subject headings that incorporate this idea, but the one that is most useful, I think, for our types of searching is physiological stress. So that's number 9 here on the list. You can read the definition to make sure that's what we're after. And then here we have the same subheadings: "prevention and control" and "veterinary" might be useful. I can then add these to the search builder.

Then I want to come over here and actually look at the search builder, and this is where speaking about that Boolean logic earlier comes in handy. Right now [the search will look for (pain/prevention and control [MeSH] OR pain/veterinary [MeSH]) AND the stress terms.] In order to be really broad, I probably would want to change that "AND" to "OR," so I'm looking for pain or stress. So in this search, you could go ahead and [run this search] in PubMed and combine it with a particular laboratory procedure, or a particular outcome, or as I'm going to do for this example, I could just continue to build the search [within the MeSH database].

Just to show you [an idea of] what exists on this topic and to show you that the subject heading exists, I'm going to look within MeSH for the category "laboratory animals." And there are subheadings [associated with that term], but I'm just going to add [the general term "laboratory animals [MeSH]"] to the search builder to look at the body of literature that exists about pain and stress in laboratory animals in general. Again, you have to come over and adjust your search builder to make sure that it's searching for exactly what you want it to, and then that search is ready to be performed in PubMed. And this is a pretty narrow set of results.

Many librarians have created some sample, prepared searches that could be good jumping-off points for this type of searching. And you can see some of these sample searches here on a research guide that we've created at the University of Denver [Research Guides: Alternatives Searching]. Just look at those since they're all in one place. This research guide you can see is set up according to those same steps [in the overall strategy] that we talked about earlier. This area is talking about MeSH searches. It refers specifically to PubMed and [provides] some sample searches. These are some MeSH terms that might be useful. And then here are those prepared searches other librarians have come up with and [published] in the literature for searches that might be helpful.

Now, these are good starting points, but just as every research project is unique, each alternative search is also going to be unique, guided by the specific project at hand. These [prepared searches] would be ready to be combined with some of your more specific keywords and terms from your projects. I'd also like to point out here on this guide, as I'm going to be referring to it later, is the area for refinement considerations, where I'll be discussing some resources and some challenges related to refinement searching in particular, and I just wanted to point that out also in case you wanted to explore it on your own.

Let's hop back over here to PubMed. Here is my results list. I went through a lot of work to create that search, and there's often a lot of up-front work to crafting a good alternative search. The good news is, there are tools within databases like PubMed to help make these searches easier in the future; and this is especially true if you have a continuing protocol and will be running the same searches in the future. One way to do that is to use this "save search" option [located underneath the search box]. If I click that underneath there, I'll be taken to my [personal] area of PubMed. So I have a MyNCBI account. You can see my user name is up here [in the righthand corner of the screen when I am logged in]. If you do not have a MyNCBI account, you'll be taken, instead, when you click that "save search" button, to a log-in screen where you can create a user name and password. Once you do have that personal space here within PubMed, you can save searches. So I could save this search, and then I could also ask for e-mail updates when something new

is added to the database that fits within my search. I can also specify how often I want to see those results, even on which day, if I want to get that picky. This is a real big timesaver because rather than going out and proactively searching the database, I can have that information pushed to me.

That was a very, very brief introduction to doing some of this searching in PubMed, but I just really wanted to give you an idea for how the database works so that it's easier to do some of these searches, and also for IACUC members so you have more of an idea of what you're seeing in those narratives. We're going to hop back to the slides now and discuss some of the challenges that go along with alternatives searching.

Slide 10 (Challenge: Managing Databases and Free Databases)
PubMed, as I said, is just one database, and although we spent our time talking about it today, researchers will need to use more than one resource to be comprehensive. In fact, many IACUCs will actually use searching in only one resource as a way to red flag a protocol. It can be challenging for both investigators and IACUC members, in particular, to know which databases should be used when, and what are the little quirks for each database. Perhaps it's more challenging for IACUC reviewers, who may or may not have expertise with searching some of these discipline-specific resources. I created these tables, which are based on something similar in the Animal Welfare Information Center's training materials to reflect how our free and fee-based databases work for our IACUC [at the University of Denver]. In these tables, IACUC members have a quick reference for the primary subjects of a database, the type of information included, and also unique strategies or quirks, that are specific to that database. This subject list is not comprehensive, it's just an overview to get [reviewers] started.

Slide 11 (Fee-based Databases)
Then we did the same thing for our fee-based databases, subscription databases that our library pays to have access to. This list would be different for your particular institution, depending on what databases your library subscribes to.

Slide 12 (Databases by Subject)
At the request of our IACUC, I modified these tables a little bit so that they could be consulted by subjects, as you can see here. Again, some of this information will be different for every institution, depending on what databases you have access to. But if you're interested in seeing something similar, I recommend that you contact your librarian or your information professional at your institution for assistance in creating a similar cheat sheet – if you're interested.

Slide 13 (Other Databases)
And just for your reference, there are a few other databases here. These we do not

have access to at DU, but they might be databases that you use or that you've seen reported in narratives, and then UC Davis has this wonderful bibliography listing the databases by subject that could also be an important resource for IACUCs and researchers [http://www.lib.ucdavis.edu/dept/animalalternatives/databaseapproach.php].

Slide 14 (Challenge: Refinement Searches)
Let's move on to talking about my next challenge, and that's the challenges we face when doing those refinement searches. While there's some research on the pain and distress caused by specific procedures, the effects of every procedure have not been investigated. And while there may be some information that was considered during the investigator's own alternative search, it's often not reported in the literature with the level of detail that we may hope for, that might be useful. This is one of the reasons it can be very challenging to locate and evaluate alternatives to potentially painful procedures.

When you're searching, there are some general guidelines to think of that can help to frame the search and to get the information you need. The first step would be to begin by listing all of the procedures in the protocol and really determining if they have the potential to be painful. Once that has been done, rather than just searching on a particular procedure, consider each procedure as an avenue to a goal. Searching on the end result can help to identify other alternative procedures. For example, if you're planning on using a catheter to monitor blood pressure, try searching for terms related to blood pressure monitoring. This could yield techniques that would not have been retrieved if you had [included] the word "catheter" in the search.

It's also important not to be too narrow when searching. If there are multiple techniques that are going to be used in a protocol, search each technique separately rather than combining them into a long search string. Again, begin by casting a very wide net, and then narrow down the results bit by bit. The same procedure, of course, could often be used in different research fields and with different animal models. So in the beginning of the search, consider not restricting the information to a particular discipline or to a particular species. This could give you insight into different information that you otherwise would not have seen. As you proceed, you may want to add those more specific terms. But, again, starting very broadly will help you to retrieve a wider amount of information that can be potentially useful.

Slide 15 (Challenge: Identifying Potentially Painful Procedures)
Added to these challenges here, with actual searching, is the challenge that researchers face in even identifying all of the potentially painful procedures in a design. This may seem intuitive to researchers, but in informal conversations that

I've had with some veterinarians and IACUCs, the concern has been raised that not all of the potentially painful procedures are always identified. Policy 11 in the Animal Care Resource Guide, of course, provides us with a legal definition that what is painful to humans should be considered to be painful to animals. But, as is pointed out in some of the literature on pain identification, no matter how similar animals are to humans, they are still not human, and certain things may be painful or stressful to them that are not to humans. I've spoken with librarians who do alternative searching or serve on IACUCs, and many of them take this approach and that's the approach that all procedures have the potential to cause pain and to search accordingly.

There are also numerous resources on pain scales, pain assessment, pain severity indices that can be consulted, some of which are listed on that research guide that I highlighted earlier. But, there are often problems with these also. Many of these assessments rely on observation of animal behavior and physiology, which, of course, implies that some experimentation is necessary to first determine if a procedure is potentially painful. And, of course, observations are also subjective, and they may depend on – they do depend on – the observer. There is an older resource that I found that's listed on that guide that has a table of potentially painful procedures, but the date is somewhat worrisome, because it's older, and we can assume that newer procedures have been developed since it was first produced. The bottom line is, if there's any doubt as to whether a procedure is potentially painful or not, consult with a veterinarian before conducting the literature search.

Slide 16 (Improved Reporting?)
From a librarian's perspective, some of these challenges, specifically with refinement searching, could be improved with changes to the ways the information about the 3R's is reported. Every researcher working with animals needs to do this type of searching in order to meet the legal requirements, and yet, when reading the literature, it's rare to see a discussion of the consideration of alternatives. Not that I want to encourage any more paperwork or reporting on the researcher's side, but it does seem to me that if alternatives information was even briefly documented in the actual literature, it would make the alternatives searching and the alternatives consideration for future projects easier. Of course, in order for that to happen, journals would actually need to change. They would need to provide a way for this documentation to occur and a means to encourage it. In the past, as I'm sure you're well aware, journals have been loath to include extra material because of space limitations. But in today's digital world, space limitations are perhaps not that big of an issue and questions could be asked like: Could this [information] be added into a separate section, or perhaps as supplementary material?

There have been steps taken to improve the reporting in general, and you may be aware of some of these. For example, the ARRIVE guidelines, which are part of an NC3R's initiative, have been published in PLoS Biology and have been endorsed by a long list of other journals. These guidelines provide specific tips on how to incorporate information about the 3R's within the existing framework of a paper; no additional sections, just within the existing body of information. If more information about these 3R's considerations are included in the literature, this would enhance discoverability, both through keyword searching, and it would also give librarians more information which could lead to deeper levels of indexing or even perhaps new subject headings, which would all hopefully lead to simpler, more comprehensive searches. But that's enough of my librarian soap box.

Slide 17 (Challenge: Evaluation Questions to Ask)
Let's talk about the final challenge that I'm going to address in this type of searching, and that's the challenge of evaluation. This is a challenge that both IACUCs and investigators face; so I thought I would present these evaluation strategies and tips from two different standpoints. First, IACUC members may find it helpful to ask themselves these questions when reviewing protocols.

Are the right databases being used? Do these make sense topically? Perhaps some of those tables that we saw earlier might be helpful when asking those questions. What keywords and subject headings are being used? Is there a combination of terminology related to the 3R's and to the specific research at hand? Are there any general search strategies being used, such as Boolean logic, phrase searching, or the use of subject headings? And what is the time period covered in the search? Was it the last five years, the last 20 years? And then when was the search performed? Was it performed with enough advance notice to actually inform the process?

Slide 18 (Evaluation Red Flags)
From an investigator's standpoint, this list of red flags produced by the Animal Welfare Information Center may be helpful. It addresses the same concepts that I discussed there on the last slide, but just from a little bit of a different lens.

As we all know, the search for alternatives can be complicated and complex; and hopefully some of these strategies and resources that we discussed today can give you some insight into how best to approach the examination of alternatives.

Slide 19 (References & Resources)
My next slide has some references and resources that I used in the presentation and that I mentioned.

Slide 20 (Questions?)
And I think we have some time for questions scheduled, but if you do have any questions that you think of later, please feel free to submit those questions for the next two weeks and we'll work on getting them answered for you. If you have any questions about alternative searching for your specific protocols, your specific research projects, I really encourage you to contact your local librarian or your information professional and sit down with him or her and work through your alternatives searches together.

>> *Babcock:* Thank you, Kathleen, for an excellent presentation. And, yes, we do have some time for some questions. We'll start with questions that participants submitted before the webinar, and then move to those received during the webinar. Please submit your questions through GoToWebinar question box on your screen. As Kathleen mentioned, specific questions about your individual projects are best directed to your local librarian. But we will welcome your questions and comments on more general aspects of this topic. We will accept questions for up to two weeks and amend these to the transcript of the recorded webinar. So as you think of them, go ahead and submit them at a later time. Susan Silk will be joining us with the live questions that are being received in the OLAW offices.

Slide 21 (Question 1)
First question: **It is not obvious to me what details are considered adequate for documenting the consideration of alternatives. I think there are four items to include in the search: databases, date of search, range of search, and key words.**

However, for consideration of alternative searches to, for example, intracranial injections of tumor cells into adult mice under anesthesia, there are many kinds of alternatives: alternative models, alternative species, alternative technical procedures, alternative ways to set up the experiment, alternative anesthetics, and analgesics, and more.

Our researchers are leaders in the field and are aware of the best models to answer their scientific questions. They also know the resources and expertise we possess and get technical guidance from our veterinary staff.

I think the kinds of searches that are required are unlikely to produce useful references, so we want to strike the best balance between burden and benefit. Our IACUC prefers that the requirement would have potential for producing something useful, rather than meaningless, regulatory exercise.
>> *Gregory:* So, you're right, the alternatives search can be approached in many ways. The key point here is to remember that the goal is to look for ways to

minimize pain and distress. And this can be done by finding those alternative approaches to potentially painful procedures. The search for these alternatives, again, you're right, requires a variety of expertise. Your researchers and vet staff bring their expertise to the table, but there's also valuable knowledge that can be gained from other research, both within a discipline and outside of it, and that knowledge is often documented in the literature. So these literature searches really do have the potential to be a valuable resource, not just a hoop to jump through, if they are executed effectively.

Slide 22 (Question 2)

>> Babcock: The next question: **If the point of alternatives is to reduce the potential for pain in animal subjects, should "pain" be included as a key word?**

>> Gregory: If you include the word "pain" as a keyword, you need to be cognizant of how this is going to affect the results. Only items that have that term "pain" in the searchable fields are going to be retrieved. So while this can be a useful approach, think of that example search we did using the MeSH thesaurus during our live searching, the potentially painful effects of every procedure, as we mentioned, have not been documented. So while this can be an important part of the refinement search, it should not be where you stop. It should not be the only part. Other strategies that we discussed, like searching on the outcomes of specific procedures rather than just the name of a procedure to get ideas of different methods, should also be incorporated.

Slide 23 (Question 3)

>> Babcock: Okay. The next question: **If the institutional librarian does the alternative search instead of the PI, what is the estimated average length of time required for a skilled medical librarian to handle this and send in the search results to the investigator? Do you know if librarian-conducted searches have been shown to produce more useful information to researchers or to the IACUCs?**

>> Gregory: I wish I could give an exact time, but the turnaround time for a search conducted by a librarian or an information professional is really going to depend on a variety of different factors. It would depend on the topic of the research. It would depend on the familiarity of the librarian with alternatives searches and the requirements in general. It could even depend on the relationship between the researcher and the librarian or the IACUC and the librarian.

I think in order for this approach to be most effective, the PI should plan on meeting with the librarian for an initial consultation – we do consultations, research consultations for about an hour – in order to make sure that he or she completely understands the research, to brainstorm different protocol-related keywords, and also to highlight any potentially painful procedures in the protocol, that the

researcher has already identified. And then after that initial consultation, the search process should be, I think, fairly smooth, should be more smooth than without a consultation, but the turnaround time for getting that information back to the researcher is going to depend – it's going to depend on those factors that I discussed. It's also going to depend on the librarian's workload and her skill.

If you are interested in pursuing that type of option, I recommend that you contact your institutional librarian to really develop set work flows and expectations, and if time is an issue, that you work together to come up with a turnaround time that would be appropriate for both parties.

And to answer the second part here of the question, I don't really know of any research that's been undertaken to compare librarian-conducted alternatives searches to those conducted by researchers, but I think that's definitely an interesting research question that could be pursued and looked into.

Slide 24 (Question 4)
>> *Babcock:* Okay. The next question, question 4: **What is the appropriate range of dates that should be included in the literature search?**
>> *Gregory:* My answer is similar to my last answer. I think this depends. It depends on the research protocol and the research that's being done. I tend to cast my net very broadly and just include the widest possible date range, as I mentioned before and then narrow things down. But for some newer areas of research, that may not be necessary if newer procedures that are being used. If a researcher is working in a new field, though, it's important to remember that the older literature from other disciplines that potentially use similar procedures could also be useful. So it's important to keep that in mind.

Slide 25 (Question 5)
>> *Babcock:* All right. Question 5: **It takes time to index an article with medical subject headings in PubMed. What is the best way to search the newest information before it is indexed?**
>> *Gregory:* That's a really good point. As I mentioned, 90% of the content in PubMed has had the MeSH terms added to it, and then the remaining has not been indexed yet. So it does take some time to index that material. The best way to access the latest articles there would be to create keyword searches that you could use either stand-alone [searches] or combine them with some of the MeSH searches, but using those keywords to get at that newest information [is key]. I spoke with a researcher who actually has two different search alerts set up; one, just keywords to get the latest information, and then one that is relying on incorporating those MeSH terms to get the more on-topic information. So those keywords are really important to getting the latest information as it's added.

Slide 26 (Question 6)

>> *Babcock:* Okay. Question 6: **The search for alternatives to pain and distress is a USDA requirement. Does OLAW require an alternative search also?**

>> *Silk*: Hello, everyone. This is Susan Silk. I'm going to jump in with the questions directed at OLAW and also the ones coming in to the OLAW office. So yes, George, OLAW does require compliance with the USDA requirement. There's a footnote in the PHS Policy. It shows up first as Footnote 2 on page 9, but it's repeated several times in the Policy. And this footnote states: This Policy requires that Assured institutions base their programs of animal care and use on the *Guide for the Care and Use of Laboratory Animals* and that they comply with the applicable regulations (9 CFR, Subchapter A) issued by the U.S. Department of Agriculture under the Animal Welfare Act. The *Guide* may differ from the USDA regulations in some respects. And here's the important part. Compliance with the [applicable] USDA regulations is an absolute requirement of the PHS Policy.

Slide 27 (Question 7)

>> *Babcock:* Thank you, Susan. **Does OLAW expect investigators to conduct alternatives searches for non-regulated species?**

>> *Silk:* OLAW considers it a best practice to conduct a search for alternatives to painful and distressful procedures. Alternative searches can provide refinements that improve both animal welfare and the science. However, implementation of this best practice is determined at the institutional level.

>> *Babcock:* Thank you. Kathleen, I'd like to follow up with a general, practical question on your overall presentation. [Question 8] **As your examples, in one example you had, you started out broad and you had 800 and some thousand hits, and then it went to 1500, and then you narrowed it down. Obviously, nobody is going to read 800,000, and if you get down to six or five or maybe even 20, that may not be enough. But how do you know exactly when you've really accomplished an adequate search? You could pick a point and you can read all the articles, but that only gives you the ones that you got during your search. And sometimes the next step up is a huge number, or huge increase in number. So when can the investigator feel confident that they probably have done an adequate search?** I know that's a very open-ended question.

>> *Gregory:* No, that's fine. You know, one point to recognize or to look for when you're looking for an end point in your search is when you start to just see the same articles over and over and over. That is indicative that you have really looked at the body of knowledge. However, having said that, if your results list that you're looking at has only 50 results on a results list, then that point might happen sooner rather than later. So as I mentioned earlier, it's really important to start broad and

then narrow down bit by bit. And with every bit that you use to narrow your search, I tend to kind of keep an eye on the top results that are on my list, to use that as a gauge for the relevancy. If, when I refine my search even further, if I tweak my search even further, I lose some of those potentially relevant studies, then that may be a sign that I'm too narrow. So it's the constant process of adjustment there, keeping an eye on the search results as you're making those narrowing steps, and then that second bit of, once you start to see the same studies, that same body of information, again and again and again, and nothing new, as you use different strategies and as you use different resources, then that shows that maybe you're nearing the end of the search.

>> *Babcock:* Thank you.

>> *Silk:* Well, now we have some questions that have come in live to the OLAW office. [Question 9] **Please comment on the requirement for the narrative to include the key word searched, versus the search strategy. Are both required for the search to meet regulatory standards?**

>> *Gregory:* And this is a question for me?

>> *Silk:* Yes.

>> *Gregory:* So the keyword search and the search strategy, to me – and I would have to look at the actual regulation there – are the same thing. So the search strategy is a documentation of the keywords that you used, of the [subject headings that you used], and how you used them together. That's how I interpret that. Susan, do you know any more about a separate requirement there for keywords and search strategy?

>> *Silk:* I don't know, Kathleen. George, do you know?

>> *Babcock:* No. I think – we interpret it the way Kathleen does. They're one and the same, but …

>> *Silk:* Here, [Question 10] **Can you provide resource options for alternatives to using animals in teaching?**

>> *Gregory:* In terms of databases to look at?

>> *Silk:* Yes.

>> *Gregory:* I would think the same types of databases [would be appropriate]. I think PubMed also would index some of that information. There are also some alternatives specific resources that may have some of that information, some of which are listed on the research guide that I mentioned earlier, that may index some of that information. It's also possible, although not quite as likely, that more education types of resources might index some of that. But again, I think those resources that we just discussed [would also be a good place to start].

>> Silk: [Question 11] **My institution does not maintain a USDA registration, but it does have an Assurance agreement with NIH. What requirement for alternative searches pertains to our institution?**
This is very similar to the question that I answered earlier. And I'm assuming that since you don't have a USDA registration, you're not talking about USDA-covered species. And so, although we do require compliance with the Animal Welfare Act, since you don't have covered species, it's not required. But we think it would be a best practice to conduct a search for alternatives to painful and distressful procedures. Alternatives searches can provide refinements, as I said before, that improve both animal welfare and the science. However, how you implement this would be up to your institution. And Pat is asking me to read U.S. Government Principle Number 3: The animals selected for a procedure should be of an appropriate species and quality, and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and in vitro biological systems should be considered. And of course we expect you to apply the U.S. Government Principles to all of your research conducted under an NIH Assurance.

>> Babcock: It would be very difficult to find those without doing a search, I would think.

>> Silk: Okay. We're coming to the end of our time together, and we don't have any more questions, so if you think of some, get them in to us within the next two weeks, and Kathleen, George, and I and the staff at OLAW will work on answering those and amend them to the recording of the – to the transcript of this recorded session. And, George, I'll hand the podium back to you now.

Slide 28 (Upcoming OLAW Webinars 2014)
>> Babcock: Okay. I'd like the thank Kathleen and the participants from OLAW. Our next webinar will be Thursday, September 18th, 2014. We've had a change of plans regarding this webinar. We are currently working on the topic for the September webinar and will notify you soon by our listserv and RSS feed. The following webinar will be held on December 4th, 2014, on IACUC review of aquatic species. So thank you very much.
>> Silk: Bye, everybody.
>> Gregory: Goodbye. Thank you.
>> Babcock: Bye.

Additional Submitted Questions Not Addressed During the Webinar

Question 12: **Are there any examples you could provide of an appropriate narrative the PI could provide to support the search?**

[Gregory:] The purpose of the narrative is to give the IACUC enough information to determine that a good faith effort has been made in the search for alternatives. When I am reviewing a narrative, I like to have a very detailed account of the search strategies that are used. It is important to remember, though, that the terms that are used and the databases that are consulted are specific to individual protocols. Below is an example of the type of reporting that I would find useful when evaluating a literature search.

Sample Narrative: To determine that applicable alternatives are not available, the following literature searches were performed.

Search One
Date: July 17, 2014
Database: PubMed
Time Period Covered: 1990-2014
Search Strategies: (*The search strategies are the meat of the narrative; I would list all strategies that produced useful results in your consideration. Remember that the search strategy that you include in your narrative will be specific to your protocol; the below example is NOT comprehensive.*)
1. neurodegenerative disorders AND (("Models, Theoretical"[Mesh] NOT "Disease Models, Animal"[Mesh]) OR "Computer Simulation"[Mesh] OR "Cadaver"[Mesh] OR "Culture Techniques"[Mesh] OR "Cells, Cultured"[Mesh] OR "In Vitro"[MeSH])
2. mice AND ("Central Nervous System Depressants"[Mesh] OR "Sensory System Agents"[Mesh] OR "Anesthesia and Analgesia"[Mesh])
3. ...
4. ...

Search Two
Date: July 18, 2014
Database: BIOSIS Citation Index
Time Period Covered: 1990-2014
Search Strategies:
1. ("blood pressure" NEAR/3 monitor*) AND (mouse OR mice)
2. ...
3. ...

Comment 13: **It was surprising that you used "stress" rather than "distress" as a search term. Stress is generally considered an acute or short term mental/emotional state that is difficult to assess in people other than oneself let alone in animals but is probably unavoidable with animal experimentation. According to the *Guide*, and consistent with its common usage with people, distress is an unabated, long-term state of anxiety,**

which might be avoidable so would be a legitimate and appropriate search term.

[Gregory:]This distinction is important. In the search that I demonstrated, I chose to use the term "stress," as I was utilizing the medical subject headings in PubMed. The current set of MeSH terms does not include a general heading for the type of distress that would have been appropriate. There are headings specific to particular types of syndromes that incorporate the term "distress," e.g. Respiratory Distress Syndrome. There are also headings that list the term "distress" as an effect or in the description of the heading itself; many of these are very narrow, however. While these concepts may be useful in some research, they may be too specific to be of general help. (List of MeSH terms mentioning "distress": http://www.ncbi.nlm.nih.gov/mesh/?term=distress).

The MeSH term for Physiological Stress is described as "The unfavorable effect of environmental factors (stressors) on the physiological functions of an organism. Prolonged unresolved physiological stress can affect HOMEOSTASIS of the organism, and may lead to damaging or pathological conditions." This seems like a better, broader choice when using the MeSH terms. When doing keyword searches, outside of the MeSH terms, it would be more appropriate to use the term "distress" in conjunction with other research-related keywords. However, it is important to note that while keyword searching may produce some useful results, it will most likely also produce results that mention the term distress in different contexts

Question 14: **Might we be able to use the "jumping off point" to PubMed from the University of Denver?**
[Gregory:] Of course. This is a freely available resource and is a compilation of much of the work that has been done by librarians in this area. Feel free to use this and distribute it to your colleagues!

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