Elyse Sullivan: And now we can get started with today's talk. So thank you so much for joining our session on Rigor and Reproducibility: Back to Basics. My name is Elyse Sullivan. I'm your moderator for today's 45-minute session, and presenting today, we have Dr. Patricia Valdez. Dr. Patricia Valdez is our Extramural Research Integrity Officer, and our format today will include our presentation followed by some time for Q&A with Dr. Valdez. We do have our colleague on the back end who can be answering some of your questions as they're coming in in the chat during the presentation, as well, so thank you for joining us. Patricia, you can take it away.

Patricia Valdez: Okay, great. Thanks so much and welcome to Rigor and Reproducibility: Back to Basics. Well, hopefully, I can move the slides here. Okay. It moved onto your side. It's not moving. Okay. Let me see.

Elyse Sullivan: It didn't actually … Oh, there you go [Indistinct].

Patricia Valdez: Okay, got it, okay.

Elyse Sullivan: All right.

Patricia Valdez: Okay, so I'm going to be talking about a couple of different things today. So first we're going to talk about, why are we concerned about reproducibility? Then I'm going to talk about the NIH response, including application updates that we made, and again, that will be addressing rigor in grant applications, and then we'll talk about training and resources at the very end. Okay, so the reproducibility challenge now, this is something that we've been hearing across the media, as well as by … amongst our researchers. The initial interest in this or, I guess, concern with reproducibility came about, I would say about 2011 to 2013. There were a couple of drug companies that were trying to reproduce data in order, of course, then to go on to develop drugs, and what they found is that they … For a large number of the studies that they attempted to reproduce, they were unable to. And so we had a lot of publications came out about the issues, drug targets sliding away and trouble in the lab. So you see that this is really … It became very pervasive at that point. And one thing I'll mention is that a lot of the concerns were around preclinical research. And one thing that I will mention about, there's studies that the pharmaceutical companies that were attempting to reproduce the studies in the … in journals was that we didn't really know exactly what studies they were not able to reproduce or replicate. We don't have a really good sense of how many exactly were they talking about. So I would say that those studies were not very transparent in themselves so … now ... So the NIH was actually concerned about this issue even before this all came out in the media in 2011, 2013. So around 2002, there were several studies that reported about a drug called minocycline. This drug was shown to, in preclinical animal models, shown to increase survival of SOD1 mice, and this is a model for ALS. Now ... So based on those preclinical data, NINDS funded a clinical trial and enrolled hundreds of patients. They were given the drug minocycline and followed, and basically they had no improvement. Nothing happened. And so at that point, NINDS decided to go back and try and figure out what happened. Why did this trial fail so miserably? And so when they went back and looked at those 2002 papers, they found that a lot of those papers actually didn't … were not very transparent in reporting. They didn't indicate whether or not the animals had been randomized, if there was blinding. In some cases they didn't report the sex of the animal, or they didn't report the transgene number, copy number of those mice. So there were some issues there, and so in response, in 2012, they got a group together, and they published this article which is basically a call for transparent reporting to optimize the predictive value of preclinical research and really outlined a need to be transparent when you report preclinical work including, as I mentioned, including information on whether things were … the animals were randomized, whether there was blinding, how the data were handled. Now ... So there are challenges to rigor and transparency and reporting science. Now, we often think of science as being self-correcting. So eventually we'll get to the right … the correct piece of data or the correct information. And so does that mean that science is immune from reproducibility problems? Probably not. So the principle does remain true over the long-term. So we will eventually get to the true answer or closer to the true answer, but in the short and medium-term, there are these interrelated factors that will short-circuit that self-correction, even maybe extend that time frame, and this is what leads to the reproducibility problem. And in addition, there's a loss of time, money, careers and public confidences. There's a lot of collateral damage when things cannot be reproduced. So what are some of the factors that might short-circuit self-correction? So what is poor training? So it's possible that an individual may not have been properly trained in experimental design. There could be inappropriate use of statistics, so if an individual didn't learn how to properly use statistics. There's something called p-hacking, where you tag the data, and then you basically take the data, try and, I guess what I say is torture it enough, so you get your p-value to be at the right value that you want it to be, so really manipulating the data at that point. There could also be incomplete reporting of resources used or unexpected variability in resources, and so this means, for instance, if there's a cell line that is being used in a study that's later found to actually be misidentified cell line, and so I'll talk more about this in a second. So it's possible that you may be using a reagent or a cell line that you think is one thing but is actually another. Other factors that can short-circuit your self-correction are publication practices. So we all know there's a difficulty there's … in publishing negative findings. There's also an overemphasis on the exciting big picture findings that leaves out necessary details, and so we've seen this for many years. We saw that the method sections of papers were shrinking and shrinking, and ultimately we're starting to reverse that trend. There's also the current hypercompetitive environment. Now, we know there's historically low funding rates, and also grant review and promotion decisions really depend too much on those high-profile publications, and so someone who is trying to get a grant or trying to get a promotion may tend to take shortcuts. Now ... So in 2014, NIH published a couple of papers. These are perspectives and plans on how we might want to address, need to address reproducibility. Now ... So this first one came out again in 2014, and it laid out our plans to update grant applications with language that would further allow us to be able to determine whether or not the proposed research could be very robust and reproducible. And the one thing I want to note is this quote here. It says, "Efforts by the NIH alone will not be sufficient to effect real change in this unhealthy environment." And this is really important because, again, this … We really need everybody working together to solve this issue, researchers, institutions alike, as well as funders. Now, in that same year, another paper came out. This was from an NIH paper. It is a perspective really telling the community that we were planning to make updates to grant applications to balance sex in animal studies and really in all the studies. And so, as I said, this is over the course of fiscal year 2015. We rolled out policies that require applications to address inclusion of both sexes in biomedical research, and because we know that males and females can react differently to drugs. They may have diseases that look different, for instance, heart disease, and so it's really important that we are paying attention to those differences, and that we are not only using one particular sex in certain studies. And another … The third paper that came out, this perspective that came out in 2014 was by NIH, was this one here you see. So it made a couple of points all dealing with the problems with misidentified cell lines, so some of the points are here. So since the 1960s, more than 400 widely used cell lines worldwide have been shown to have been misidentified, and a 2011 study of 122 different head and neck cancer cell lines revealed that 37 or 30 percent were actually misidentified. So this is a big problem, and so we want to make sure that researchers are regularly checking their cell lines to make sure that they are working with the cell lines that they believe they are and so this informed part of the policy that I'm going to describe now. So our guiding principles for rigor and transparency, when we rolled out this policy, where first we wanted to clarify our long-standing expectation regarding rigor and transparency in applications. And so we don't think that we're funding applications that were not rigorous in the past, but we wanted to clarify this need and make sure that we do get applications that properly described their research. We also wanted to raise awareness and begin culture shifts in the scientific community. We also wanted to improve the way that applicants describe their work to provide sufficient information for reviewers. So reviewers need to know more details in order to determine whether or not it looks like a proposal that could be successful. And, as always, we want to ensure the NIH is investing in the best science and minimizing unnecessary burden. Okay. All right. So there were four areas of clarification. So the first area is called rigor of the prior research. Previously, it was called scientific premise, but many researchers, I think they … There was a misunderstanding on them for work premise, and so we call it now rigor of the prior research. Now, the second one is scientific rigor of the proposed research, and then the third one is relevant biological variables, such as sex, that we want to consider those, and then the fourth area is the authentication of key biological and/or chemical resources, okay? And this all came out with … in 2016, for applications that came in in 2016. Okay. Now this is an important chart. This is really showing you where in the application are each of these elements addressed. And so we have, on the left side you see the element of rigor, and you see rigor of the prior research. Now, rigor of the prior research, if you look at the section ... So it's in the research strategy. It's scored under significance, and it does contribute to the overall impact score. Now, rigor of the prior research is the only element that is actually scored in two different places. So we have it under the research strategy, where it's scored under approach, as well, and so this is … I'll talk more about this in a second, but this is really … If you identify any problems in the rigor of the prior research, you would then tell us how you're going to address them, okay, and this contributes to overall score. And then we have scientific rigor, and that's under research strategy. It's scored under approach, and it contributes to the overall impact score. And then we have consideration of relevant biological variables, such as sex, which is under research strategy, scored under approach and contributes to the overall impact. And then finally we have authentication of key biological and/or chemical resources. This is actually an attachment. It's an additional review consideration. It does not contribute to the overall score, but reviewers will mark it as unacceptable or acceptable. Now one thing with authentication, the authentication plan is that if it's marked as unacceptable, that doesn't mean that the application won't be funded. The program official will then work with the PI and the institution to come up with an acceptable plan. Okay, so now I'm going to go through each of those elements in a little bit more detail and address some of the questions that we've had about them. As I mentioned, rigor of the prior research is addressed under significance and then under approach. So under significance, we ask that you, the PI, addresses the strength and weaknesses and the rigor of the prior research that serves as the key support for the proposed research project. Now, when you're looking at the prior research, again, prior research can include some observations, the preliminary data or published literature. So you're going to assess the strength and weaknesses of that data. And then under approach, we ask you to describe plans to address any weaknesses in the rigor of the prior research that serve as the key support for the proposed project. So again, so in the significance, you tell us about the strengths and weaknesses of the prior research, and then under approach, you tell us how you're going to address any weaknesses. Okay, so one question that we often get is … Excuse me. What do I include when describing the rigor of the prior research? Now ... So when you're assessing the rigor of the prior research, you could consider whether or not there was an appropriate sample size in the prior research, whether the prior research … whether they stated there was randomization or blinding. Did they use adequate positive or negative controls, they used appropriate statistical tests, and do they consider relevant biological variables? So maybe they did all of the studies in male mice, and maybe they should have also looked in female mice, as well. Authentication of key resources, for instance, if the … If previous studies used a misidentified cell line, that could be considered a weakness, and then you might want to address that in your … in the approach. Okay, so the second element is scientific rigor. So we defined scientific rigor as the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting and results. So in this section, this is under approach, we expect that you will describe the experimental design and methods proposed and how they will achieve robust and unbiased results. So one question we get around scientific rigor is, how much detail should I include to address this? So we tell applicants to succinctly state what's planned. So you want to include information on sample size estimation, effect size, whether you're not … whether you're going to blind the study, how you're going to blind the study, randomization, physical analysis. This is also where you're going to describe your experimental animal numbers and include your power calculation. Sometimes people will include that in the vertebrate animal section, but we do ask that you include that under approach. And you should be transparent about your plans for analysis and, of course, stay within page limits. Okay, so the third element is consideration of relevant biological variables, such as sex. So we understand that different biological variables can affect health or disease, and those include sex, age, weight and any underlying health conditions. So in the application, we asked that you explain how relevant biological variables, such as sex, are factored into research designs and analysis for studies in vertebrate animals and humans. So this applies to, again, both vertebrate animals and humans. Now, you can propose to study one sex, but you will need to provide a strong justification from the scientific literature or some preliminary data or other relevant considerations if you're going to do that. Okay, so the FAQ or the frequently asked questions around this is, "Will I have to double my animal numbers? So I was previously doing all my studies in male mice, and now do I need to have male and female?" So you may not need to power your initial study to detect sex differences because we're not … We don't want to make everyone start to become a sex-differential researcher, but we ask that you begin to collect data on sex for early-stage research. So again, we think of research as a continuum, where you have the early stages, and then you go into later stages. We really want to start understanding that … the differences between males and females early on, and by the time you reach a late stage, you may have more information about whether or not what you're setting is more relevant for males or females, and then you can make a decision to study only one or the other. So then the justification should be provided in the application if you're proposing to study one sex. Now, some of these justifications could be if you're studying a sex-specific condition or phenomenon, for instance, ovarian or prostate cancer. If you're using an acutely scarce resource, for instance, if you have a complicated genetic cross to get these mice, and maybe the genotype of the mice is very rare, their interest is very rare, that could limit you as far as using both males and females as equal numbers. And also ... So you could make a sex-specific hypothesis if you already know that there's differences between the males and the females. So again, that's another justification that you could provide. Cost and absence of known sex differences are inadequate justifications for not addressing sex. Okay, so then the last element of the enhancing reproducibility through transparency is authentication of key biological and/or chemical resources. So we know that the quality of the established resources is critical, and again, this policy applies to established resources, not resources that you are developing, or you're proposed to develop, okay? And these include cell lines that are already in existence, antibodies, chemicals or mice, et cetera. And so for this part, we ask in the application that you provide a plan to regularly authenticate and ensure the identity and validity of your resources, and each investigator will determine which resources are considered key. Okay, so what are … So we did publish a subsequent reminder because we wanted to make sure that people understood what are we looking for here. So again we ... for the defined … repeated their definition of key biological and/or chemical resources and provided examples, like cell lines, chemicals, genetically modified animals or cells. And specifically in the authentication plan, we said, "Do not include any plans for authentication of datasets, databases, machinery or electronics." Okay, and these are only for biological and/or chemical resources. Do not include plans for the development of an authentication of new key biological and/or chemical resources. Again, that should be described in the application itself under approach. The authentication plan is only for established resources. Do not include plans for authentication of standard laboratory reagents that are not expected to vary, and don't include the authentication data or any other data in the authentication plan because you will risk the application being returned because you added information in places where it shouldn't be. So make sure that you're not adding authentication data there in the authentication plan. Okay, and then I just want to quickly remind you that when you're submitting your progress reports, we are still looking at those progress reports with an eye for research rigor. So when we ask, "What was accomplished under these goals?" you'll have to provide more information how you … steps you have taken to ensure robust and unbiased results, and then when we're asking what you're going to plan to do … What are your plans for the next reporting period? You're going to include efforts to ensure that the approach is scientifically rigorous and results are robust and unbiased. So make sure that you don't ignore the rigor when it comes to the RPPR, the progress report. And I wanted to mention that one of the newest, I guess, developments is that we've implemented training in rigor last year. So that means now … So this applies to institutional research training and institutional career development grant applications. And so we ask those applicants to describe how the program and faculty will provide training and rigorous research design and relevant data science and quantitative approaches. These applications need to also include a plan for instruction and methods for enhancing reproducibility, okay, and all these things will contribute to the overall impact score. And in addition, for fellowships and individual career development, starting last year they now are required to address as applicable any new research skills that they expect to acquire in the areas of rigorous research design, experimental methods, quantitative approaches and data analysis and interpretation. So ... And again that also contributes to the overall score. Okay, and then I just want to point you to some resources here. So this is the NIGMS Clearinghouse for Training Modules to Enhance Data Reproducibility. We … NIGMS, along with other ICs, came together to fund modules that were created by the extramural community, and really the idea was that these modules would be useful and used by institutions as they're developing their training plans, or they need to incorporate rigor into their training plans. Okay, and this is our extramural websites on Enhancing Reproducibility through Rigor and Transparency. You'll find a lot of resources here. So if I were to scroll down, you would see the guidance. You would see the resources here which include the scientific rigor examples, resources and tools for rigorous experimental design, authentication plan examples and more. And the training is here, as well, and then notices. These are some of the items that you can find here, including this infographic, and I won't go through this in detail. Also this chart really describes to you the four areas, the four elements, and where they're addressed, and how they should be addressed in applications. And then we also posted this reviewer guidance. This is what reviewers were given to evaluate sex as a biological variable, and it's kind of this flowchart where it says, "Does the study involve vertebrate animals or humans?" If no, then no further consideration. If it's yes, then go on to the next question. Is the study intended to test for sex differences? If yes, then you want the design … Then the next question is, "Is design adequately rigorous to test for sex differences?" So we thought that it would be very helpful for applicants to really be aware of the guidance that we are providing to reviewers, as well, when it comes to sex as a biological variable. Okay, and that's it, and I will take questions now. So we do have a mailbox: reproducibility@nih.gov. We welcome your questions so ... and I welcome your questions now, too.

Elyse Sullivan: Wonderful, thank you so much, Patricia.

Patricia Valdez: Thank you.

Elyse Sullivan: We're going to take some questions that have come in over the course of the presentation. I think you've shared some really, really great materials that people can take home and further flesh out all of their references, but I'll hit you with some questions.

Patricia Valdez: All right.

Elyse Sullivan: So the first one is, how should we handle rigor and reproducibility in proposals that are maybe more process- based versus hypothesis-based, so things bioengineering and technique development? Are there sort of different ways you can … you should be thinking about rigor and reproducibility in that … with that lens?

Patricia Valdez: For process-based, well, I will say that definitely what you'll want to look at, the funding announcement that you're applying to because if it's a special funding announcement developed by the IC, it's possible they could change or kind of edit some of the language as far as what the reviewers will be looking at. So really the rigor and transparency policy is really geared towards research really than the conduct of research, and so I think, if … You may not be able to address sex as a biological research, so it doesn't mean that will be not applicable. If you don't have any biological variables, then you just say, "Not applicable." But I think you can probably still describe scientific rigor and other parts of the premise … the rigor of the past research.

Elyse Sullivan: So some questions about the rigor of the prior research here. Is it … a couple questions here, is it limited … Should you really focus on your prior research or the entire field? And if we're focusing on the entire field, there's a lot of prior research, right? How much detail? How do you balance the entire field of research that came before you?

Patricia Valdez: Yeah, so the idea is that you want to focus on the key, key research that's supporting your proposal. So it doesn't have to be the entire field, but you can pick a few key studies that you are using to support your proposal and focus on those. Again, we didn't expand page limits. So you can only go so far as to what you're going to describe as [Indistinct] weaknesses and the strengths. But again it's up to you to determine what are those key … What are the key pieces of data that are important? So that's … but again, don't … Definitely don't do a review of the entire field. That would not help.

Elyse Sullivan: Right. And then when discussing the rigor of your proposed research, are there any recommendations on integrating this into your research strategy? Should you incorporate it aim by aim, or do you recommend having a separate kind of description? Sort of overall, what do reviewers want to see?

Patricia Valdez: Yeah, that's interesting because I've seen it done both ways, incorporated in aim by aim and then another section of … saying, "This is my section on scientific rigor." And I will say that having these sub-headlines do bring the reviewer's attention to that area. So if someone is … If a reviewer is looking to score and make a comment about your scientific rigor or whether you paid attention to consideration of biological … consideration of sex, for instance, or other biological variables then … so I think it … I feel like it's always good to point it out and draw people's attention to it. But again, there's no set rules on either way, but I think that can be helpful.

Elyse Sullivan: Great. So are you allowed to point to or refer to other parts of your application for some of these details, like my statistical analysis are going to be described elsewhere in some of our supplemental materials, or must all of the items you describe be contained within your research strategy?

Patricia Valdez: They should be contained in the research strategy. I will say that reviewers do know that you may include that information in the vertebrate animal section, for instance, if you're working with animals. So if it's not there, then it's not … You don't get scored on it because it's not necessarily missing because they know where to look for it, but I think ideally you'll want to keep that information in the research strategy if possible.

Elyse Sullivan: That's great. So onto sex as a biological variable, for human cells or cell lines, is sex something we need to consider if it's not about sex differences? Should we state that it's a cell line is all of the same sex and whatnot?

Patricia Valdez: Right, and this is a question now that comes up a lot, and I think you really … We would really want you to tell us more about sex as a biological variable if you're using primary cells, understanding that cell lines that have been in culture for many, many years are ... They can get all kinds of weird, funky things happening, chromosomal irregularities. So I feel like … So at that point, we're not as focused on the sex of those types of cells, but if you're using primary cells, you're culturing primary cells taken directly from an animal or human, then that's when … That's where you would want to consider sex as a biological variable.

Elyse Sullivan: Great. So another question about powering initial studies for detect sex differences or not. You mentioned that you may not have to power your studies. You may not have to double your animals to really detect those, but yet it looks like the review criteria are … They are looking for, "Are you in a position to explore this?" So what is … What's really the balance there?

Patricia Valdez: Yeah, so I think the balance, so if you're at the early stage and this is … you're just starting to … maybe no one has looked at this in the past, and your group is just starting to kind of consider sex differences. In the application, you … It's not required again that you're going to power this study to detect the sex differences, but you can say that we're starting to collect data on sex differences. The other important part is you want to explain that when you analyze the data, you're going to disaggregate the sexes. So that way, you're going to be able to determine any differences so make sure that ... That's an important point that I think I've heard people leaving out of their applications. It's like they say they're going to use it, but then you've got to make sure that you also say that you're going to disaggregate and actually look to see if there's any differences there. And I completely understand. It's kind of a push and pull. It's a difficult … It's not easy. I know, but I think the idea is that we want to collect as much data as we can, so eventually you can make that hypothesis on a single sex, if that's what you can do, what you're able to do.

Elyse Sullivan: Great. And so if the initial application, if the initial studies are actually revealing a potential sex difference that we didn't really know about, are you … Can you apply for more money for higher budgets to actually power your subsequent years, your subsequent studies to really explore that?

Patricia Valdez: Yeah, that's interesting. You'd have to talk to your program official to get a good answer. I know that ORWH was providing some supplemental funds at one point to study sex differences. I don't know if they're out now, but you can definitely check the NIH guide to see if there's any funds available for that, but no. I think if there's a certain field that looks promising, I think it's worth talking to your program official about the supplements or what else could be done.

Elyse Sullivan: Great. And with regards to the training requirement, is there any specific guidance for what folks should include in those training plans, and how it is or is not different from the responsible conduct of research training that we had previously?

Patricia Valdez: Yeah, that's a really interesting question because I know that, in anticipation of rigor training requirements, a lot of institutions started incorporating training in rigor into their RCR or responsible conduct of training … conduct of research training, and I think that's fine. We really haven't … I don't … we haven't really nailed down exactly what … These are the elements that you need to do. Kind of like with the RCR notice, you probably remember the 2009 notice, it does lay out, "These are some of the elements that are important." I think they list like nine of them, and for rigor, I think it's … I think data science is one part that's important, quantitative research. So look at the instructions, and it's not as cut and dry, I would say, or as what's listed in the RCR guide notice, but there is some information there. But again, it's more general because you really understand that the training needs for each department or type of research is really going to vary, and so that's what makes it difficult for us to say, "Okay, this is exactly what you need." So again, I think it's pretty general for that reason.

Elyse Sullivan: With regards to the authentication plans, if you're using an established resource such as a cell line or a mouse strain that are purchased sort of directly from Jackson Labs, do you need to have a plan for separately verifying that, or does that not sort of count under that scope?

Patricia Valdez: Right, and so we … You do need to have a plan for verifying that, and that's really … We want to make sure people understand that. That authentication plan requirement is really for established resources, including resources that you're purchasing. So have some plan to make sure, for instance, if you buy an antibody, that it does react to the antigen that you think it does in the assay that you think it does. So those are the kinds of things we really are concerned about is, again, even if it comes from the company, you definitely want to just continue and make sure you have an authentication plan. And we don't want to … So one thing I'll mention, too, is, don't attach the product sheets. We're seeing that, too, the product sheets because, really, the authentication plan, we say, "Try to limit it to one page." So if you can do that, that's ideal. We don't need a lot of additional information, especially not the company product pages so …

Elyse Sullivan: Great. So I think that it's about the time that we have. I think we got to a lot of good questions. Thank you so much, Patricia, for your time, and thank you, all, for attending. As we stated, the slides are available, and a recording of this presentation will also be posted within a day or so in the conference platform. I would encourage you to continue to ask questions, visit our exhibit booths, book some one-on-ones and please give us some session feedback. Let us know what you liked about the sessions you've been to, what we could do better. Each session in the auditorium where you joined, there will be an individual session feedback link, so please go ahead and give us that feedback. We really want to know what you all thought. And thank you so much, enjoy the rest of the conference.

Patricia Valdez: Thank you.