Including Diverse Populations in NIH-funded Clinical Research

>> Dawn Corbett: Hi, I’m Dawn Corbett, the NIH Inclusion Policy Officer and today I'd like to talk to you about including diverse populations in NIH funded clinical research. The current times really bring into focus the importance of including diverse populations in NIH research. The disproportionate effects that COVID-19 has had on individuals based on sex, race and ethnicity and age have become very apparent in recent months. Dr. Francis Collins and Dr. Eliseo Pérez-Stable the director of the National Institute for Minority Health and Health Disparities, recently published a blog about COVID-19 disparities. And Dr. Francis Collins mentioned, “With the bright light now shining on this important issue, it's time to talk about the role research can play in reducing the disproportionate burden of COVID-19, as well as improving the health of all people of our great nation.” It's within this framework that I'd like to talk to you about NIH’s efforts on including diverse groups in our research.

NIH has a long history of ensuring the inclusion of women, minorities and individuals across the lifespan in the research funds. This goes back to 1986 when NIH established a policy encouraging women to be included in NIH funded research studies. In 1993, the 1993 Revitalization Act required that women be included in NIH funded clinical research, and furthermore required that minorities be included in NIH clinical research. And then in 1998, NIH issued a policy requiring the inclusion of children in NIH funded clinical research. And that policy was updated more recently in 2015, when NIH changed the definition of a child from an individual under 21 to an individual under 18, which better aligns with the age of consent to research in most states. And then in December of 2016, the 21st Century Cures Act was passed and with this Act came a number of new requirements for inclusion. NIH has been implementing these over the last few years. In 2017, we published a notice amending the inclusion of women and minorities policy. And we now require that phase three trials report results of inclusion analyses and Clinicaltrials.gov. And then most recently, just last year, our inclusion across the lifespan policy came into effect, which requires that individuals of all ages be included in NIH funded clinical research.

So let's take a look and look at these policies and a little more depth. First, let's talk about the NIH policy on the inclusion of women and minorities in NIH research. The NIH policy requires that women and minorities be included in all NIH funded clinical research unless there was a compelling rationale for exclusion. So what's a compelling rationale? Well a compelling rationale meet maybe a condition doesn't occur in a certain group. So for example, if you're doing a study on prostate cancer, you may not be expected to include individuals whose sex at birth is female. What is not a compelling rationale, cost is something that NIH generally would not consider to be a compelling rationale. And in fact, the 1993 Revitalization Act specifically stated that cost was not an acceptable reason for exclusion. NIH funded phase three clinical trials have some additional requirements, they must be designed to permit analyses by sex or gender, race and ethnicity. And if they're applicable clinical trials, they also need to report the results of these analyses to Clinicaltrials.gov. Note that these analyses don't necessarily have to be powered, but they are predefined analyses and they should, at a minimum, be able to stratify their results by these variables. And then finally, NIH is required to support outreach efforts to recruit and retain women, minorities and their sub populations.

So let's talk a little bit about our policy on inclusion across the lifespan. The inclusion across lifespan policy replaced the inclusion of children policy and became effective for applications submitted for due dates January 25, 2019 or later and for contracts, solicitations issued and intramural studies initiated after that date. So as I mentioned, this policy now requires that individuals of all ages be included in NIH funded clinical research unless there are scientific or ethical reasons not to do so. And I should note there may be scientific or ethical reasons not to include individuals of a certain age, but these do need to be specified, included in the justification. So a reason maybe, for example, you're doing a study on Alzheimer's research and you will not include children because children do not get Alzheimer's disease, it's appropriate to exclude them from the study. However, there are other reasons simply because for example, individuals may have comorbidities would not be considered an acceptable reason for exclusion without further justification.

The policy also requires that investigators submit individual-level data on participant age at enrollment and progress reports. So for quite some time investigators have been submitting data in the aggregate on sex or gender, race and ethnicity. However, this policy requires an additional variable age at enrollment be included and also that the information can be provided at an individual-level data to help us understand the intersections between these variables. So this slide shows an example of what those data might look like, the data are submitted in a CSV file. And for each participant, you can see the race, the ethnicity, the sex or gender, the age at enrollment and the age unit are provided. Something to note we do ask for age at enrollment as opposed to date of birth to help protect the privacy of the participants. So let's do a quick knowledge check. True or false? Cost is an acceptable reason to exclude women from an NIH Clinical Research study. What do you think? Put your answer in the chat? Okay, it looks like most of you got it right. The answer is false. The 1993 Revitalization Act specifically mentions that cost is not an acceptable reason to exclude individuals from NIH funded research.

So let's move on to talk about what's required when applying for NIH funding. If you're applying for NIH funding, you're going to need to include plans for the inclusion of women and minorities. If you're doing an NIH defined phase three clinical trial these plans must include your plans for analyses by sex or gender, race and ethnicity. You also need to include an inclusion enrollment report. So this is a table that specifies the demographics of the population that you'll be including, including data on sex or gender, race and the ethnicity of the sample. Depending on the design of your study, you may provide planned which most applications will provide or actual for example, if you're doing a secondary analysis study looking at an existing data set. You'll also need to include plans for inclusion of individuals across the lifespan and you'll specify the age limits of those participants, if applicable and provide a justification for those age limits. This information is going to be provided on the PHS Human Subjects and Clinical Trials Information form. This form was introduced a couple of years ago by NIH and consolidates all the human subjects information in the application into one form. It includes five sections, the inclusion information is entered in section two, study population characteristics. And as you can see on the slide, this is where you will specify those age limits indicate a minimum or a maximum age if you have one, it's okay not to have a minimum or maximum age, you can specify not applicable. And then you'll include your plan for inclusion of individuals across the lifespan and inclusion of women and minorities. You'll also submit an inclusion enrollment report in this section. The inclusion enrollment report has two different parts. The first part has a few fields that you'll fill out about your study. And then the second part includes a data table. In this first part a new feature that was recently introduced as we now require a title for each inclusion enrollment report so there should be a unique title that helps identify one report from another. You'll need to specify whether you're using an existing data set or resource. So for example, if you're using existing samples, or you're doing a secondary analysis, you would put yes here. If you'll be recruiting prospectively, then you generally would put no on this question and you'll specify the enrollment location type, either domestic or foreign. Important to note if you're going to be doing recruitment both within the US and outside the US, you will need to provide separate tables for each of those groups. The data tables that you provide include both planned or actual depending on the design of your study and specify the sex or gender and the race and the ethnicity of the participants in the aggregate. They're quite similar the only difference is for actual data, you will have the opportunity to use the field unknown or not reported for any individuals who did not identify their sex or gender, their race or their ethnicity.

So after you've submitted your application, it will go under peer review. In peer review is going to look at your inclusion plans as part of its evaluation of the application. They'll also specify whether the inclusion plans are acceptable or unacceptable. And you'll see the results of the review and the summary statement. So for example, in this summary statement, you can see that there are gender, minority and age codes listed. The codes have two components. The first part is descriptive, it just lists the population that's included. And the second part of that code, the letter is either A or U and indicates whether it's acceptable A or unacceptable U. So in this example, you can see that peer review found the gender and minority inclusion was acceptable but they found the age inclusion unacceptable. In this case no children were included and they found that was scientifically unacceptable.

So how do we avoid these unacceptable codes and make a good inclusion plan? Well, a good inclusion plan has several components. The first is that it's complete. The plans must include plans for the inclusion of women, minorities and individuals across the lifespan. Something peer review sometimes sees is that investigators will address one or the other or maybe two but not all of these. So make sure you address all of these in your application. You'll also need to make sure you include inclusion tables for each study. Your plan also needs to be scientifically appropriate. So you'll want to consider the external validity. What is the scientific question that you're asking? And what population are you trying to answer this question in? And that should drive the individuals who will be on your study. If you're planning any subgroup analyses, you want to make sure those are adequately powered. And if you're excluding any groups, make sure those exclusions are well justified. So you want to justify your minimum and your maximum age range. As I mentioned, if you don't have one, you can just enter NA. And make sure any exclusions that you do mention are based on scientific or ethical reasons, not simply convenience alone. So just because the individuals may not live near you, maybe they don't go to the clinic from which you'll be recruiting, this wouldn't be considered to be acceptable, you will need to establish an outreach plan, if needed. And that gets us to the last bullet, which is that the recruitment needs to be realistic. So you may have proposed a wonderful plan but maybe that plan really doesn't seem to be very feasible, peer review would pick up on this and they may consider your application to be unacceptable, if they think that it's not realistic. If you will not be able to recruit the individuals that you need in the study within your local area or at your local clinic, then you may need to think about outreach plans, collaborating with others in your area or outside of your area in order to have appropriate inclusion.

Some points to consider when developing your inclusion plan, think about the demographics of the source population, who are the people who typically go to these places from which you're trying to recruit? Who have you historically been able to recruit through these channels? Think about your inclusion and exclusion criteria and the effect they may have on the population you're trying to recruit. If you exclude people with comorbidities, you may be disproportionately excluding individuals who are older, you may be disproportionately excluding individuals based on race and ethnicity, because the incidence of those comorbidities may be higher in those groups. So you need to think through how that may affect your recruitment. Literacy requirements are another one that may affect who you may be able to include. Is there something else you can do? Can you provide literacy support? Are those criteria necessary? And if so, how can you still make sure you have a diverse sample? Cognitive abilities, now, sometimes you may have to exclude individuals based on cognitive abilities but we would always encourage you first to think about how you can design your study to offer supports for those who may need those supports. Is that something that you can do? So we want to make sure that all of your inclusion and exclusion criteria are necessary and also consider the effect that they're going to have on different groups.

You'll also want to consider a participant burden. And so every study has some burden for the participant to be able to be a part of that study. Some burden may be harder for some groups than others. So things like multiple visits, how are they going to get to and from your study? Are you able to provide any support for that? Is it affordable for them to participate in the study? Will they have to take time off of work? Are you able to provide childcare? Are they going to have to find childcare? How will they navigate your protocol? Are there supports needed for that? So those are all things to think about? Also think about the role of family and community? In some cases, family members may be a part of the study, they may help individuals consent. How can we engage the community in this study as well? Think about language and participant communication. How will you participate? How will you communicate with participants? Both in your interactions, in the study also with the consent forms, do they need to be translated into different languages? Do you have the language supports that you need? What is the expertise of your staff? Do they know how to work with the various groups that you'll be working with? If not, how will you get that expertise? Do your staff need training? Do you need a consultant? So these are all things to think about.

And then also, you'll want to think about how are you going to evaluate your recruitment and retention strategies. So inevitably, recruitment rarely goes exactly as planned. It's important that you take a look at your recruitment throughout the study and adjust when needed. How are you going to do that? What are your time points in what you're going to check in? And what are those check ins look like? And all of this needs to be thought of in the context of the budget. Certain groups may require more time, maybe they'll be more expensive to recruit, maybe not. But we need to think about that, anticipate that early as we're writing the budget and make sure that our budget has accounted for any supports we might need.

Okay, now, I'd like to take a moment and have you play the NIH peer reviewer for a while and take a look at a few case studies that we have. These are some example, snippets of inclusion plans, I'd like you to look at each of them and tell me if they're acceptable or unacceptable by giving me a thumbs up or thumbs down. And you can put your comment in the chat box. So case study one, a researcher proposes a study to determine the efficacy of a novel treatment for prostate cancer. The study excludes individuals whose sex at birth is female, thumbs up or thumbs down? Okay, this is an easy one. We mentioned this before. If a condition does not occur in a specific group, it's okay to exclude that population. So, because individuals whose sex at birth is female are not going to have a prostate, they will not need to be included in the study. So I'd give this one a thumbs up. Let's move on to the next case study. A researcher proposes a study to examine the use of a smartphone app to improve glycemic control and diabetic individuals. The study excludes children and older adults due to generational differences and use of technology that may affect the statistical power of the study a thumbs up or thumbs down? What do you think? So I have some concerns about this one. The study says that it's going to exclude children and older adults due to generational differences in use of technology. We know that the condition that they're looking at diabetes occurs in both children and older adults, they haven't provided a lot of information about these supposed generational differences, or how they may affect the study. Generally, a recommended method would be to design your study with knowledge that those differences may exist. And then they also mentioned that it could affect the statistical power of the study. So we do see this a lot that, you know, bringing these groups in would introduce variability. But the bottom line is we're not going to know how the interventions work in these groups if they're not included in the studies. So without additional information, I'm going to give this one a thumbs down. Okay, let's move on to the next case study. Case Study three: A researcher proposes a study in individuals 18 to 60. The study indicates children are excluded because the legal age to consent to research is 18 in the state where the research will be conducted. Individuals over 60 will be excluded because of the likelihood of comorbidities and this group. What do you think thumbs up or thumbs down? So I have some concerns about this one as well. The study indicates children are excluded, because the legal age to consent to research is 18 but they don't mention any way that they may accommodate individuals under 18. In many states, for example, a legally authorized representative may be able to provide consent and they don't explain why that's not a feasible option here. In addition, they indicate that individuals over 60 will be excluded because the likelihood of comorbidities, they don't explain why people with comorbidities can't be included, which comorbidities those might be and why they're making the assumption that anyone over 60 would have these comorbidities. So a couple questions I would ask is, is there a safety reason? You know, what are those comorbidities? Is there a safety reason why those individuals shouldn't be excluded or shouldn't be included in the study? And then also, could you just exclude people with those comorbidities rather than just excluding everyone over 60, on the assumption that they have those comorbidities. So this one needs a little work, I'm going to give it a thumbs down.

Let's move on to talk a little bit about requirements for just-in-time. So after your application goes through peer review, for applications that score within a fundable range, they'll be asked to provide some additional information during just-in-time. For inclusion generally, there's not a lot that you'll need to submit however, if you did receive one of those U codes and peer review found that inclusion was unacceptable, then you'll have to work with institute or center staff to resolve those concerns during this period. You'll also provide any information that may be requested such as adjusted or new inclusion or enrollment reports if they were missing any updated information to your plans that may be a result of either peer review or programmatic adjustments. And then, once your grant is awarded, there's still some things that you'll need to do to monitor inclusion. The first thing you'll need to do is to provide actual inclusion enrollment data and progress reports. And we talked a little earlier, if you're under the inclusion across the lifespan policy, those data will look like that CSV file that we showed. For those that were funded prior to inclusion across the lifespan, they'll be submitting the inclusion tables. And then if you're doing an NIH defined a phase three clinical trial, you'll need to report the status of any analyses by sex or gender, race and ethnicity. You'll update these in each report. If they're in progress, that's okay but still give us an update. And then if you're doing an applicable NIH defined phase three trial, you'll also need to make sure that you report the results of your analyses by sex or gender, race and ethnicity within one year of the primary completion date. And those need to be submitted to Clinicaltrials.gov. And then, finally, if you are doing any delayed onset studies, those are studies that you couldn't describe at the time of application, maybe you had to do some pilot work initially but now you can describe, you will need to provide full information, including inclusion information for any of those. And that needs to happen before they get started.

So we talked about providing the inclusion data and progress reports on this slide, I just want to show you where you'll be providing that data, you'll provide them in the human subject system, which is in the eRA Commons status module that shows you an example of how you would upload the participant-level data. You first will need to download the participant level data template, which gives you the format in which data are to be submitted, then modify that template with your data and then upload it into the system. Once you do that, you'll see your data that populated in the table that's displayed. So let's do one more quick knowledge check. If funded NIH recipients will need to provide data on participant race, ethnicity, sex or gender and date of birth. True or false. Okay, I'm glad you were listening. That's right, this is false. You will need to provide data on participant race, ethnicity and sex or gender but you don't need to provide data on date of birth, you need to provide data on age at enrollment, which we require rather than date of birth to protect the participant’s privacy. So thank you very much. I've really enjoyed the chance to talk to you about inclusion today. If you would like to see additional information you can look at our websites. We have one on inclusion of women and minorities and another on inclusion of individuals across lifespan. And you can also reach us via email at the email address on the slide. Thank you.