Understanding the NIH Sex as a Biological Variable (SABV) Policy and the Importance of Sex & Gender in Research

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Rajeev Kumar Agarwal, PhD: As Darryl mentioned, I'm going to give you an overview to understand NIH policy on sex as a biological variable, which we call SABV, and the importance of sex and gender in biomedical research. Next, please. Before we begin, I wanted to share good news that we just celebrated seventh anniversary of Sex as a Biological Variable, or I might be using SABV, Policy in January, and it was enacted in January, 2016. Next, please. In 2014 .. . Oh, next slide. In 2014, in "Nature" journal, Janine Clayton and Francis Collins unveiled NIH policy to ensure that preclinical research considers both females and males. Next, please. This "Nature" publication led to publication of NIH landmark.. . landmark policy, Sex as a Biological Variable, which set new expectation for applicants. Next, please. To begin, I would like to introduce you to the Office of Research on Women's Health, or ORWH. ORWH is the first public health service office dedicated specifically to promote women's health research within and beyond NIH scientific community. ORWH was established in September 1990. The mission of the office is to enhance and expand women's health research, include female and minority groups in clinical research and promote career advancement for women in biomedical careers. ORWH crafts and implements the NIH's strategic plan for women's health research in partnership with NIH institutes, centers and offices, and cofund research on the role of sex and gender on health. This strategic plan helps the NIH vision, which calls for sex and gender to be integrated into biomedical research, every woman to receive evidence-based care, women in science careers to reach their full potential. The study of how sex and gender influence health and disease is central to the NIH mission of enhancing health, extending life and reducing illness for all people. Together with others in the NIH community, ORWH has committed to setting the example across scientific research that consideration of sex and gender is critical for rigorous and responsible science and for establishing a future in which every person can receive safe, effective and evidence-based medical care. Next slide. In the next few slides, I will explain why the Office of Research on Women's Health and why it was established. Next, please. Next. Next. Next. So ORWH is committed to understanding influences of sex and gender on health and disease at every level from preclinical to translational to clinical, research studies or clinical trials. From sex-specific data analyses, education and to animal studies and sex-specific reporting, health policy and health care. Next, please. So it becomes important to understand, is there any difference between sex and gender, and what are the sex and gender, and why do they matter? It is critical to understand the importance of sex and gender in human health and disease. Although many times sex is incorrectly, or sometimes synonymously, used as gender, in fact both terms describe different but connected constructs. Sex and gender shape health independently as distinct factors, as well as interactively through the many ways in which they intersect and influence each other. It is important to understand the differences and interaction between sex and gender to better understand how they affect health and why they are important in medical practice and biomedical research. Based on National Academies of Science, Engineering and Medicine, NASEM, report of 2022, sex is multidimensional biological construct based on anatomy, physiology, genetics and hormones. These components are sometimes referred as sex traits. Whereas gender can be broadly defined as multidimensional construct that encompasses gender identity and expression, as well as social and cultural expectations about the status, characteristics and behavior as they are associated with certain sex traits. The study of how sex and gender influence health and disease is central to the NIH mission, and ORWH is committed to setting the example across biomedical research. That consideration of sex and gender is essential for rigorous and reproducible science. For more information about sex and gender, please visit the ORWH website and look for the Sex & Gender section. Next, please. So why does it matter? Next. So sex has effects at multiple levels of biology. Next, please. Whether it is cells, genes, intracellular processes. Next, please. Or at the system level, for example, immune system which affects and it is affected by other systems. Next, please. Or organism as a whole. So differences in disease manifestation to response to prescriptions. And all levels interact and influence each other simultaneously. Next, please. Sex factors are important because sex-specific factors govern differences in the prevalence to disease, how women and men present with disease, the course and outcome of disease. As you can see, they may start at a different point. They will go overlap at one point, and then they go in different direction. Next, please. Women and men differ in numerous parameters, whether it is physical, emotional, biological or something else. Among others, women have a lower total body weight, a higher proportion of body fat, a lower body surface area, a lower muscle mass, a smaller organ size, lower glomerular filtration rate and lower gastric acid excretion. These factors may influence drug disposition, physiological differences such as hormonal fluctuations during the menstrual cycle may also influence drug pharmacokinetics, or PK. Menstrual cycle variations do occur in renal, cardiovascular and hematological system with the potential to impact protein binding and volume of distribution. Similarly, hormonal changes during menopause, pregnancy and hormonal contraceptives therapy are likely to have the same effects. The problem is that many drugs are developed and optimized in men using 70 kilogram male as a standard. In fact, in 2000, the GAO, which is Government Accountability Office, examined several drugs that were approved by FDA for widespread use and then later pulled for safety issues. Eight out of 10 of these drugs posed more of a threat for women. Understanding the mechanisms of sex differences in drug therapy is critical for optimal dosing in both sexes. Evaluation of sex differences in PK, pharmacokinetics, of drugs will further enhance understanding of sex-based differences in the safety and efficacy of drugs and minimize therapeutic adverse events. PK differences are the most common sex differences, and early detection of these differences during drug development can lead to clinical trial design that will use sex-based dosing and better individualization. Because men and women may differ in a specific drug PK, it is essential to understand those sex differences in drug disposition and responses as in turn they may affect drug safety and effectiveness. As an example, lipophilic drugs, like diazepam, nitrazepam and others, have slower clearance, higher tissue accumulation and exposure-related adverse reactions in women. Next, please. So three big changes that go hand to hand to advance the health of women. Number one, from focus of reproductive health to health over the life course and from head to toe. Next, toward a multidimensional framework that addresses all factors affecting health. And, the last one, the study of sex as a biological variable. Next, please. Next.

Woman: It's not moving. Give me one second.

Rajeev Kumar Agarwal, PhD: Okay. Thanks. So as I said, NIH published in 2015 its landmark study Sex as a Biological Variable Policy. Next, please. In the policy, NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies. Next, please. Giving you an example that one size does not fit all. Susan Cheng, who is at Cedars-Sinai Hospital in LA, she is one of our grantees, and she published this landmark study. So, we all know that blood pressure guidelines state that women and men have same normal healthy range of BP, which is systolic upper limit of 120 millimeter of mercury, and above threshold is associated with risk for heart attack, heart failure, stroke, et cetera. Susan Cheng showed that women have lower normal systolic blood pressure range compared to men. A study found increasing cardiovascular disease beginning at lower threshold of systolic blood pressure for women than for men. Because the current .. . Why this is important, this finding? Because the guidelines do not account for sex differences, they may be detrimental to women's health. So it is important to revisit hypertension treatment guidelines that do not account for sex differences. Next, please. Until recently, basic and preclinical biomedical research has focused on male animals and cells from male animals, and over reliance on male animals and cells from males may obscure understanding of key sex influences on health processes and outcomes. NIH expects that Sex as a Biological Variable to be factored into research designs, analyses, and reporting in vertebrate animal and human studies. A strong justification from scientific literature, preclinical data, or other relevant consideration must be provided for applications proposing to study only one sex. Accounting for SABV begins with the development of research questions and study design. It also includes data collection and analyses of results as well as reporting of findings. Consideration of sex may be critical to the interpretation, validation, and generalizability of research findings. Adequate consideration of both sexes and experiments and desegregation of data by sex allows for sex-based comparison and may inform clinical interventions. Appropriate analyses and transparent reporting of data by sex may therefore enhance the rigor and applicability of preclinical biomedical research. Next. So NIH SABV policy: what are the achievements so far? So 7 years is a brief period in the world of biomedical research. As I mentioned in my second slide that we just celebrated the seventh anniversary, but in the last 7 years since NIH enacted this pioneering policy on SABV, there has been a lot of activities including impressive research findings, a marked increase in media and attention by scientific journals on sex differences and influences creating enthusiasm from researchers and many questions and requests from assistant. I am pleased to announce that ORWH has developed many resources. ORWH has added multiple resources. I'll come to that. Next slide, please. So few more example. What more needs to be done? Next, please. So Woitowich and colleagues performed a meta-analysis of 10 year publication data, from 2009 to 2019, of sex inclusion in biological science and observed increases in consideration of sex and gender. Next, please. Next. Next. Oh, go back, please. Okay. Next. Oh, it's going .. . Okay, so go back. Something is not... . Go back, please. So there are significant increases in the field, such as neurology, immunology, endocrinology and physiology. And, yes, happily, the number of the studies that provided an evidence-based rationale for a single-sex study increased also, consistent with the SABV policy. Unfortunately, when it comes to sex-based analyses, that is part of SABV policy, we see that only one field .. . Is there any way .. . Next. Oh, yes. Next. Next. Yeah, just there. Only one field, pharmacology, has shown improvement in sex-based analyses when you compare the studies done in 2009 with the studies done in 2019. Actually, when looking across all disciplinary studies, the percentage of articles that perform sex-based analyses went down from 2009 to 2019. The publication and other similar studies highlight and confirms the need of continued education, awareness and advocacy for the inclusion of sex and gender, including the consideration of SABV in biomedical research. Next, please. I just want to give you some data on COVID-19 pandemic. The data is from Global Health 50/50, and you will see that there are still gaps, even though we have seen in the media as well as in scientific reports that more men are dying because of this, but it has significantly affected the female population. So there is definitely a gap in COVID-19 trials, and still the data has not been reported based on sex or desegregated. So zero stratified subjects by sex in their design. One stratified data by sex in an after-the-fact analysis. So we have a number of missing things here, and this is a publication also from Schiffer, et al. So you can see on the left-hand side is the data that there is sex-based differences. Next, please. Some journals have taken proactive steps to enforce changes in reporting practice in addition to the development of the SAGER guidelines. This is from Canada. In 2019, Judy Regensteiner and her colleagues published an article in "Lancet" advocating integrating sex and gender consideration in research education.. . educating the scientific workforce without changes in publishing practices. Even when we make changes in policy, we won't experience the full benefit of this change, and our ability to improve the health of women and men will be limited. A number of societies and associations are having their own platform sessions on this topic showing a high level of enthusiasm for uptake of policy, and there was also a publication in "Science" recently in September in where the authors have published a framework for sex, gender and diversity analyses in research. Next, please. I will give you some programs how ORWH advances study of sex and gender and the health of women through collaboration across NIH. Next, please. So we have an R01 program, which is Intersection of Sex and Gender Influences on Health and Disease, and 11 NIH institute centers and offices participate in this initiative. Next, please. We have another one, which is a SCORE, Specialized Centers of Research Excellence. It's a cooperative agreement supported as U54, and eight ICOs are are participating. This is the only disease- agnostic centers program at NIH. Next, please. We have administrative supplements program, Sex and Gender administrative supplement as well as Understudied, Underrepresented and Underreported, which we call U3 administrative supplement program, and 26 ICs participate in these administrative supplement programs. Next, please. And we have BIRCWH, which is Building Interdisciplinary Research Careers in Women's Health, supported as K12 mechanism, and seven ICOs partner in this initiative, and it's a mentored career development program. Next, please. So ORWH, as I briefly mentioned, has developed many resources, and here are some of those e-learning programs which can be utilized for your further advancement. So one is Bench to Bedside: Integrating Sex and Gender to Improve Human Health. The other one is Sex as a Biological Variable Primer and Introduction to the Scientific Basis of Sex and Gender-Related Differences. As of August 2022, a total of 19 -- more than 1,900 individuals have registered for these courses. And out of it, 1,190 individuals have completed the Bench to Bedside course, while more than 700 individuals have completed the SABV Primer course. And when we look, some characteristics of these investigators, 81 percent were females, 16 percent were male, 1 percent was transgender and 2 percent none of the above. They declined to disclose. And when we look for ethnicity, 11 percent of learners reported Hispanics. Eighty-one percent reported non-Hispanic. And 8 percent declined to answer, and out of those, 62 percent were white. Fourteen percent were Asian, and 11 percent were Black or African American. And most of the learners are in academia or university sector, and some were also patient retired or self-employed or unemployed. And employment status, most of them were researchers, but we also had 18 percent students, and patient care investigators also, approximately 14 percent. Next, please. So this is, again, if you are interested in learning these, go ahead and register. Next, please. Using this link for the Primer and some more information on the Primer as well as the video link. Next, please. I'm happy to inform that media has shown a great attention to SABV. So CNN has published "Blood pressure may need to be monitored differently, according to a new study," the one which I highlighted in my presentation. "New York Times" also reported, "Women report worse side effects after a COVID vaccine." "Morning Consult," NPR, and we also had a congressional briefing, and scientific journal, like "Nature," "Neuroscience" and "Drug Monkey Blog," they published "Considering sex as a biological variable will require a global shift in science culture." "Endocrine News," "Biological Psychiatry," and ORWH staff has been invited to update Dr. Chyren Hunter about the progress in considering sex as a biological variable. So this is good news. People are getting more aware of it. Next, please. So Shansky and Murphy call for global shift in science culture and what they call, "What we consider rigorous must be a body of work that includes males and females in all experiments, except those that cannot be done in one sex." So it's an important publication, and I will suggest you to read it. Next slide. I will highlight some funding opportunity announcements which ORWH has active. The first one is a NOSI, which is Notice of Special Interest, Administrative Supplement to Promote Research Continuity and Retention of NIH Mentored Career Award. And the next one is Administrative Supplement for Continuity of Biomedical and Behavioral Research Among First-Time Recipients of NIH Research Projects and Grants. And another is the NOSI also, Research on Gender Measurement. And then we have the Intersection of Sex and Gender Influences on Health and Disease. I talked about R01 program. And then there's SCORE, which is Specialized Centers of Research Excellence on Sex Differences. Next, please. Some important upcoming events, I will suggest you to register for this Diverse Voices Virtual Talk session, and then we have our 58th meeting of the NIH Advisory Committee on Research on Women's Health, which will be a virtual event. And then we have seventh annual Vivian Pinn Symposium on May 16th, and the topic is Menopause and the Midlife Woman. Then we have SCORE annual meeting. This will be closed, but the keynote address will be open, and then BIRCWH annual meeting. Next. With this, I will stop and just highlight other ORWH resources. You can subscribe for "The Pulse," which is a monthly newsletter or any other regular e-mails you will get. And next, please. Thank you so much.

Darryl: Okay. So thank you very much, Dr. Agarwal. So I am viewing some of the questions here in our Q&A. And once again, if anyone has any questions, please submit them through the Q&A box. So one of the most popular questions here so far is, what is the NIH policy for transgender, gender-nonconforming individuals born as one sex, but have taken hormones to transition?

Rajeev Kumar Agarwal, PhD: Wonderful question. I will suggest you to look the website for SGMRO office as part of NIH Office of the Director. They have provided extensive data on this, and the whole office is dedicated to transgender or nonconforming individuals. Please look at the website, and if necessary, please feel free to discuss with Dr. Karen Parker, who is the director of the office. Next, please.

Darryl: Okay. You have another question here. It says, "Despite the noted difference between sex and gender, it seems like the term women is being used to only refer to cisgender women. An example: those assigned female at birth and identify as women. How to transgender men assigned female at birth, identify as men, and transgender women assigned male at birth, identify as women, fit into the SABV framework.

Rajeev Kumar Agarwal, PhD: Very good question again, and we are working with the SGMRO office, which deals with this issue, as well as with IC leaders how to incorporate those transgender human beings as part of the big SABV policy. So we are working on it. Next, please.

Darryl: Let's see. I have another one here. It says, "What questions" .. . Excuse me, "What guidelines currently exist for recording sex as a biological variable in human studies, which may include transgender and intersex individuals whose .. . excuse me, anatomical, physiological, genetic and hormonal characteristics may not fit neatly into binary male and female categories? For example, a transman on HRT may have their sex recorded as female due to their anatomy and sex assigned at birth, but their hormonal and physiological characteristics are likely to resemble more closely those of people typically designated male. What steps are being taken to ensure individuals with divergent biological sex characteristics are being included and considered in clinical research?"

Rajeev Kumar Agarwal, PhD: Same. It's a wonderful question, and it's on the same topic which we have discussed in the previous two questions. So we are getting the data as we speak, and SGMRO is leading major role in how to get the data. So they have issued a number of funding opportunity announcements, including NOSIs, which is Notice of Special Interest, to encourage investigators to look at those transgender animals or transgender human beings and get the data so we can see where exactly the science is going. And based on the data we'll be happy to incorporate or include them in other studies. So this is still growing up, or this is a little bit a little nascent field, you can say. So we are getting data. We are providing money to encourage investigators to look for those changes. Next, please.

Darryl: Would it be possible to share the PowerPoint slides? I would like to read someone .. . Excuse me. I would like to read some of the articles mentioned, but the slides went by too fast to write the citations.

Rajeev Kumar Agarwal, PhD: So, Darryl, I think the slides will be available, if I remember.

Darryl: That is correct. The slides will be available.

Rajeev Kumar Agarwal, PhD: So they can always look for those, and if you have any questions, feel free to contact me or anyone at NIH, and we'll be happy to help you. Next, please.

Darryl: Okay. Next one. "Is the NIH working with medical professionals to make the changes to training programs so that PCPs, primary care physicians, can implement these new findings about biological female differences?"

Rajeev Kumar Agarwal, PhD: Yes. We are working with the scientific community as well as the health practitioners, and we're giving seminars as well as developing these resources, and as I mentioned, those e-learning courses, we had a good response from the caretakers. Either they are involved in hospitals or clinical trials, as well as those clinicians. So people are getting aware by having those sessions as well as the media is reporting also. So it is getting .. . Or I should say the community is getting more aware of these differences. Next, please.

Darryl: Will the future research in pharmakinetics ensure, enforce the later phase trials be conducted with specific categorical determinants, like sex or gender, for future compliance with FDA approval? What is the NIH doing to encourage this in a real way?

Rajeev Kumar Agarwal, PhD: Great question. So we have been working, because FDA is a sister organization of NIH. We are part of HHS. We had.. . had multiple workshops and ongoing discussions to resolve this issue and how to proceed further. We just had a workshop in .. . I think in April where we discussed with the FDA, BARDA, ORWH and NIAID discussed sex differences in radiation research. And so we are working very closely with other organizations of HHS how to implement sex and gender in broader perspective. Next, please.

Darryl: Are there any funding opportunities to have patient-recorded gender and sex in electronic medical records?

Rajeev Kumar Agarwal, PhD: Okay. So the sex and gender administrative supplement program, which we had for a number of years, which started before the NIH SABV policy. It started in 2013. The due date was January 26th, so you just missed it. I don't know whether the program will continue, but there it was open for investigators to request the additional money from NIH to look for the medical records or anything to look for sex and gender. And I will suggest you to get in touch with the SGMRO office because they do have administrative supplements program where they will give you additional money to look for this gender or whether binary or nonbinary, that kind of research proposals. Next, please.

Darryl: Okay. Yes. "What is the point of distinguishing between sex and gender at the onset but not considering this distinction in the data presented?"

Rajeev Kumar Agarwal, PhD: Not exactly sure what the person is asking.

Darryl: And that is the last of the questions that I have at this time. Just double checking to make sure there's nothing else. Yes, that is all the questions I have at this time.

Rajeev Kumar Agarwal, PhD: Okay.

Darryl: If anyone else has any additional questions, please use the Q&A box to submit your questions.

Rajeev Kumar Agarwal, PhD: And the PowerPoint of this presentation has been posted. Please feel free to download it.

Darryl: Okay. So I do have additional questions at this time.

Rajeev Kumar Agarwal, PhD: Okay.

Darryl: Does NIH want to see all results supported by NIH separated by sex?

Rajeev Kumar Agarwal, PhD: Answer is yes. Unless or until you are working on one sex, diseases. For example, cervical cancer, prostate cancer, but then the gender part will come in, but, yes, it should be desegregated.

Darryl: Okay. And then here's another. Looks like comment. It says, "Not a question, but just want to amplify the need for transgender and nonbinary inclusion in biomedical research. It is so important."

Rajeev Kumar Agarwal, PhD: Agreed.

Darryl: Another comment here. It says, "Thank you, Dr. Agarwal, for presenting this. It's interesting and important."

Rajeev Kumar Agarwal, PhD: Thank you.

Darryl: And here's another. "Can SABV be considered if only women are enrolled in a trial?"

Rajeev Kumar Agarwal, PhD: So it depends. Is it a trial related with gynecological disease, or is it related with pancreas? If it is pancreas and only female are involved, it is not right because men should also be .. . Sex as a Biological Variable Policy is not only to account for women but both men and women. As I mentioned in my presentation, majority of the research are being done using male animals or cells from males. So that's why we are saying include females. But if you are using only females, you have to use males. So you can see, is there any difference whether the dosing will be okay? What will be the PK, PD for the drug? So, yes, you have to include both.

Darryl: Thank you. All right. Let's see. "For clarity, if we have more specific questions about how this policy applies in our work, should we be contacting the program officers in the individual IC that our work fits into?"

Rajeev Kumar Agarwal, PhD: Absolutely. You should always be in touch with your program officer. That is your primary contact, but feel free to contact our office if you have some uncertainty, or you are not sure how to move, or you are not getting any answer, which I doubt, because ICs and ORWH work in collaboration as a team. It's not like they are doing their own work. Yes, we are doing our own work, but we work as a team, and we educate each other, whether it is a policy or a scientific question. Ultimately, our goal of all the program officers or grants management, especially, is our goal is to improve human health, and everyone has its own role and responsibilities, but ultimately we represent NIH.

Darryl: I have another question here. "What about limitations in funding? For example, with R21s, we're including sex as a biological .. . Excuse me, sex as a variable, but double the number of mice needed to reach sufficient power."

Rajeev Kumar Agarwal, PhD: So R21 is exploratory grant. You don't have to have a lot of preliminary data as well as, yes, it is for 2 years. You may limit the scope of the aims what you are proposing, but you have to use SABV in R21 or even R03 grants, which are even smaller than R21. So all the RPG grants or centers grant, like BU, you have to include SABV. And regarding the doubling of the cost, it will not really double the cost. Sure, there will be .. . There may be some increase, but you put the project accordingly as well as what is scientifically needed. And of course, the peer reviewer will comment on it because they're also in the same boat. They're also trying to make sure that NIH gives the money for the best proposal and which are accounting for both SABV, sex and gender and everything in their research. So it will not really be a doubling, and ultimately the question is, you are working and we are working to improve the health of human beings.

Darryl: And it looks like another question has been revisited with a little more detail that says, "Can SABV be considered if only women are enrolled in a trial? It is an intervention that is appropriate for women, an example, estrogen, but not men?"

Rajeev Kumar Agarwal, PhD: Yes, so as I said before, in this case the question will come here, are there any transgender women? And so when if you are looking for SABV policy, right now we are only say SABV, Sex as a Biological Variable, but we want to have sex and gender part also. So this will be important for enrolling or accounting SABV. Ultimately, you want to have sex and gender. Even though it is a women study, you are looking for estrogen effect. But there will be .. . Unless all the women said they are all cis, then it is different, but if there are transgender women, you may want to have representation. Next.

Darryl: I believe that that is all I have at this time.

Rajeev Kumar Agarwal, PhD: Okay.

Darryl: If there are additional questions, once again, please submit into the Q&A box. Nothing additional. Looks like we have looks like 2 minutes remaining. Let's see.

Rajeev Kumar Agarwal, PhD: I wanted to thank all the audience for their wonderful questions and listening for the presentation. Great questions, and I really enjoyed giving this presentation. Thank you.

Darryl: All right. Do you have time for one last question, Dr. Agarwal?

Rajeev Kumar Agarwal, PhD: Yes, please.

Darryl: Okay. Last question. It says, "Are there any transgender, intersex and/or gender-nonconforming NIH employees included on the committee developing these SABV policies?"

Rajeev Kumar Agarwal, PhD: We do not ask people their sexual preferences in any of those committees, but if anybody .. . The best example here will be Dr. Karen Parker, who is leading the SGRMO office. She has been invited in all those committees and working groups, either she or her staff, and they do bring sex and gender or the gender perspective in those discussions. So answer is yes and no because people have not identified themselves. And if they do, or if they did, we do not discriminate based on sex and gender orientation. Everybody is welcome on the table, and especially Dr. Karen Parker has been advocating the gender orientation in all those research proposals.

Darryl: All right. Thank you very much, Dr. Agarwal.

Rajeev Kumar Agarwal, PhD: Thank you.