JOURNAL OF WOMEN'S HEALTH
Volume 30, Number 10, 2021
Mary Ann Liebert, Inc.
DOI: 10.1089/jwh.2020.8997

Biomedical Researchers' Perceptions of the NIH's Sex as a Biological Variable Policy for Animal Research: Results from a U.S. National Survey

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Abstract

Background: In 2015, the National Institutes of Health (NIH) established a policy on sex as a biological variable (SABV) in an effort to address the overrepresentation of men and male animals in biomedical research and the lack of attention to sex-based responses to medical treatments. However, questions remain regarding how U.S. biomedical researchers perceive the impact of the SABV policy on their own research and on translational science more broadly.
Materials and Methods: A national survey of U.S. scientists who use vertebrate animals in their research was conducted. Respondents were asked how they select and use animal species as model organisms as well as how they perceive the impact of the SABV policy on their research practices.
Results: Almost all respondents reported that they had previously heard of the NIH SABV policy, and over one-third had altered their study designs to comply with the policy. There were robust differences in perceptions of the SABV policy based on researchers' primary species of model organism. However, there was no significant difference in the likelihood of researchers analyzing their results by sex based on whether they had received recent NIH funding.
Conclusions: While many researchers report adhering to the SABV policy requirements, more work needs to be done to ensure that the policy is being evenly applied to researchers using all types of animal models and that researchers adhere to the policy after receiving NIH funding, particularly in terms of reporting on and analyzing SABV in their study findings for publication.

Keywords: sex as a biological variable, policy, preclinical research, women's health, National Institutes of Health, animal research, survey

Introduction

In 2015, the National Institutes of Health (NIH) released a policy on sex as a biological variable (SABV) in an effort to address the overreliance on men and male animals in biomedical research and the lack of attention to sex-based responses to medical treatments.[1] The policy requires researchers seeking NIH funding to consider SABV in their research questions and study designs and to provide justification if one sex is excluded from the research.[2] Proponents argue that such a requirement will improve the rigor of research, save money by identifying sex differences earlier in the translational pipeline, and improve women's health outcomes by identifying sex-based differences that may have otherwise been missed in the safety and efficacy of novel therapies.[3–9]

Few empirical studies have investigated biomedical researchers' perceptions of the SABV policy and its implementation. In a survey of NIH grant review Study Section members, an increase in grant applications addressing SABV since the onset of the policy was reported, but not all grant reviewers ''accepted'' the policy or agreed on how to evaluate SABV in grant applications.[10] In addition, qualitative interviews with scientists who use animals in their research and Institutional Animal Care and Use Committee (IACUC) members revealed that levels of support for the SABV policy varied among animal research community members.[11]

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Importantly, that study indicated that independently of their level of support for the policy, researchers and IACUC members identified challenges to the policy's implementation, particularly regarding the lack of funding to support the inclusion of two sexes in research studies. Findings such as these raise questions about the extent to which U.S. biomedical researchers have integrated SABV into their work as well as how they perceive the importance of NIH's policy for advancing biomedical research. The purpose of the current study is to survey U.S. biomedical researchers who use vertebrate animals in their research to examine their perceptions of the impact of the SABV policy on their own research and on translational science more broadly.

Materials and Methods

Survey instrument

A survey was developed to investigate how biomedical researchers think about the selection and use of live vertebrate animals as model organisms in research. The survey included 45 questions, which were organized into the following themes: research experience, translational science issues, research oversight and welfare issues, SABV policies and practices, societal views of animal research, and participant demographics (see Supplementary Data for instrument). The survey was administered via Qualtrics, an online platform, and was available to respondents over a 6-week period from late-March 2020 to early-May 2020. The study was determined to meet the criteria for oversight exemption by the Biomedical Institutional Review Board at the University of North Carolina at Chapel Hill.

Study participants and recruitment

A list of potential respondents was created by conducting targeted web searches of U.S. universities and nonacademic public and private institutions to identify biomedical researchers who use live vertebrate animals in their research. The search included the top 100 colleges and universities from *U.S. News and World Report*'s 2019 rankings that were also 2018 Carnegie R1 doctoral research institutions as well as the 10 top ranked historically black colleges and universities that were not already included in the list. It also included the top 20 highest earning pharmaceutical companies, as well as nonacademic public and private institutions that are well-known hubs of biomedical animal research.

Next, each institution's website was used to identify individual researchers. The inclusion criteria specified that researchers must hold a PhD, MD, DVM, or other equivalent degree, conduct biomedical research with live vertebrate animals, and have a publicly available email address. At universities, the search was targeted to include departments most likely to support biomedical animal research, such as biomedical engineering, genetics, neuroscience, pathology, and psychiatry. Individuals' research profiles and publications were used to determine whether they met the inclusion criteria. These web searches generated a list of 4910 eligible U.S. biomedical researchers.

To request participation, researchers were sent an email describing the study with a unique link to the survey. Follow-up emails were sent 1 week and 1 month after the initial email only to those individuals who had not yet completed the survey or opted out of the email campaign. Respondents were offered an incentive of entering a drawing to receive 1 of 20 $100 Visa gift cards for completing the survey.

Analysis

The results from the SABV section of the survey are the primary focus of this analysis, which was conducted in Stata (version 16.1). In addition to descriptive statistics, regression analysis was used to identify factors that are associated with outcomes of interest, holding all other relevant variables constant. For each model, variables were selected for inclusion based on evidence from prior research and other published studies on SABV. Because of small sample sizes, participants who did not hold an MD, PhD, or DVM, participants from nonacademic public institutions, and participants who identified as genderfluid were dropped from regression analyses that included those variables. Some animal response categories available to respondents were aggregated for analysis. ''Other rodents'' include rats and other rodents. ''Other mammals'' include cats; dogs; pigs, cattle, sheep, and/or other livestock; ferrets or other weasels; opossum and/or other marsupials; and rabbits. ''All other animals'' include fish, amphibians, and reptiles, along with all write-in responses.

For any two covariates with a correlation coefficient greater than 0.5, the covariate with the clearest theoretical rationale was selected for inclusion. The only two covariates that were highly correlated were age and years of experience as a biomedical researcher, and age was retained because it was a continuous variable, whereas years of experience was categorical and 55% of the sample were in the most experienced group (*i.e.*, 20 or more years). Logistic regression (logit) was used for binary outcomes. Multinomial logistic regression (mlogit) was used for categorical (nonordinal) outcomes. For ordinal outcomes, the proportional odds assumption was tested, and if it was met, ologit was used. If it was not met, gologit2 was used with the option autofit, which fits the model by testing the parallel odds assumption for each covariate. The results of logistic regressions are presented as odds ratios (ORs), where a value greater than 1 indicates higher odds and a value between 0 and 1 indicates lower odds.

Results

Demographics

Of the 4910 biomedical researchers contacted, 1234 (25.13%) participated in the survey with a completion rate of 96.19%. Participant demographic characteristics are outlined in Table 1. The median age of respondents was 52, and over half (55.14%) had more than 20 years of experience with animal research. A majority of respondents (64.36%) identified as men. Almost all (94.17%) had a PhD, and most (66.16%) worked at a public academic institution. In terms of research funding, 71.96% said they had received NIH funding as a principal investigator in the past 5 years, and 24.39% said they had been funded as a principal investigator by industry within the same time period. A majority of researchers (68.16%) identified mice as the primary animal species used in their research, and 73.63% said they primarily use both male and female animals in their research.

Awareness of the SABV policy

Table 1 provides descriptive statistics of respondents' attitudes and opinions about the SABV policy. Almost all

Table 1. Descriptive Statistics

N = *1187 who completed the survey*	%
Age, median (interquartile range)	52 (44, 61)
Years of experience with animal research	
1–5 Years	3.88
6–10 Years	9.44
11–20 Years	31.53
20+ Years	55.14
Gender	
Men	64.36
Women	34.97
Genderfluid	0.34
Degree[a]	
MD	12.42
DVM	4.39
PhD	94.17
Other	1.35
Institution type	
Public academic	66.16
Private academic	29.62
Nonacademic public	0.59
Industry/nonacademic private	3.63
Funding source	
Industry-funded PI in past 5 years	24.39
NIH-funded PI in past 5 years	71.96
Primary animal	
Mice	68.16
Other rodents	16.26
Other mammals	5.73
Primates	4.30
All other animals	5.56
What sex of animals do you primarily use?	
Both female and male	73.63
Female	11.71
Male	14.66
Reasons for selecting animal sex for research[a]	
Specific research questions	55.07
Differences in animal behavior by sex	31.17
Compliance with funding policies	31.08
Use of that sex or those sexes in prior studies	26.78
Availability of animals	22.63
Females' hormonal fluctuation interferes with research	20.01
Cost of animals	8.44
Males' hormonal fluctuation interferes with research	7.01
Availability of housing	5.15
None of the above	10.56
Heard of NIH sex as a biological variable policy	92.15
Altered study design in response to NIH policy	
Already meeting policy expectations	44.77
Altered study design to meet expectations	34.65
Will likely affect future studies	7.76
NIH policy allows use of one sex	5.73
Not NIH funded or planning to be	7.08
Sex differences are relevant to my research	65.04
Why are sex differences not relevant? (*among those who responded no above*)[a]	
Difficult to classify by sex	6.52
Disease only affects one sex	11.35
My pilot studies show no differences	35.02
Other people's studies show no differences	15.46
There is no evidence to suggest differences	45.17
None of the above	24.94
How often do you report the sex of animals?	
Always	76.39
When I think it is relevant	18.13
Only when asked by reviewers	1.77
Never	2.28
How often do you analyze findings by sex? (*among those who use male and female animals*)	
Always	50.74
Sometimes	41.70
Never	7.56
Sex as a biological variable will improve reproducibility	
Yes	52.88
Unsure	24.45
No	22.67
Sex as a biological variable will improve translation to humans	
Yes	47.51
Unsure	34.77
No	17.72
Importance of analyzing by sex	
Equally important in animal and human studies	73.23
Most important in human studies	19.52
Most important in animal studies	2.97
Not important	1.27
Extent to which animal studies are accurate predictors of therapeutic safety	
Small	9.92
Moderate	68.22
Great	21.86
Main issue with poor rates of drug success	
Problems with animal models	48.55
Problems with study design	37.39
Some other problem	14.05
View of reproducibility ''crisis''	
Exaggerated problem	17.22
Unsure how important	9.11
Important problem	73.67
Biggest contributors to reproducibility problem in animal research[a]	
Differences across animal housing/husbandry environments	43.46
Differences in personnel	20.17
Lack of rigor in design of studies	65.15
Variability in animals used	51.90
Insufficient details on methods in published reports	61.69
Falsification of published results	12.07
Commercial interests biasing the design or analysis of studies	8.78
Some other issue	11.48
Effect of SABV on number of animals needed	
Number unaffected	5.62
Increased but less than doubled	30.38
Doubled	47.49
More than doubled	16.51

[a]Respondents could select multiple responses.

NIH, National Institutes of Health; PI, principal investigator; SABV, sex as a biological variable.

(*continued*)

respondents (92.15%) indicated that they had heard of the NIH SABV policy. A majority of respondents (65.04%) reported that sex differences were relevant to their research, and most (73.23%) said that analyzing by sex was equally important in animal and human studies. In terms of the policy's effects on their study design, fewer than half (44.77%) of the respondents said they had already been meeting the expectations of the policy, and a third (34.65%) said they altered their study designs to meet policy expectations.

Table 2 provides the results of the logit analysis identifying factors associated with having heard of the SABV policy. Compared with respondents at public academic institutions, researchers who worked in industry or other nonacademic institutions were much less likely to have heard of the SABV policy, holding all other variables constant (OR: 0.192, 95% confidence interval [CI] 0.0884–0.4185). Similarly, those who had not received NIH funding in the past 5 years were much less likely to have heard of the policy than those who had received NIH funding (OR: 0.124, 95% CI 0.0717–0.2148). Researchers who primarily used animals that fell into the ''all other animals'' category were also much less likely to have heard of the policy than those who primarily used mice (OR: 0.297, 95% CI 0.1392–0.6334).

Table 2. Regression Analysis of Who Previously Heard of the National Institutes of Health Sex as a Biological Variable Policy

	Had you previously heard of the NIH's SABV policy?
Observations	1108
Model type	Logit
Statistics	ORs/95% CI
	Yes vs. no
Age (continuous)	0.983 0.9621–1.0048
Gender (reference: man)	
Woman	1.065 0.6385–1.7779
Degree (reference: no)	
MD or equivalent	2.655 0.8989–7.8426
DVM or equivalent	1.232 0.4461–3.4017
PhD	1.723 0.5589–5.3145
Institution (reference: public academic)	
Private academic	0.817 0.4641–1.4381
Industry or other nonacademic private	0.192*** 0.0884–0.4185
NIH-funded PI in past 5 years (reference: yes)	
No	0.124*** 0.0717–0.2148
Industry-funded PI in past 5 years (reference: no)	
Yes	0.737 0.4134–1.3144
Ever served on an IACUC (reference: no)	
Yes	1.368 0.7715–2.4251
Primary animal (reference: mice)	
Other rodents	1.039 0.5086–2.1219
Other mammals	0.94 0.3589–2.4625
Primates	0.376 0.1363–1.0388
All other animals	0.297** 0.1392–0.6334
Constant	61.116*** 11.4529–326.1353

*$p<0.05$, **$p<0.01$, ***$p<0.001$.
CI, confidence interval; IACUC, Institutional Animal Care and Use Committee; OR, odds ratio.

Reporting and analysis by sex

When asked how often they report in publications the sex of animals used in their studies, more than three-quarters of respondents (76.39%) indicated that they always report sex, fewer than one-fifth (18.13%) indicated instead that they report sex when they think it is relevant, and a small number selected that they reported sex only when asked by reviewers (1.77%) or never (2.28%) (Table 1). Factors associated with likelihood of reporting the sex of the animals used in studies and analyzing findings by sex are reported in Table 3. Holding other variables constant, women were more likely than men to report in their publications the sex of animals used (OR: 1.831, 95% CI 1.2662–2.6482). Researchers with an MD were less likely to report the sex of animals compared with those without an MD (OR: 0.497, 95% CI 0.3057–0.8096). Respondents who primarily studied rats and other rodents were more likely than those who studied mice to report the sex of animals (OR: 2.728, 95% CI 1.5435–4.8215). Compared with those who claimed that their research already met the expectations of the SABV policy, respondents were more likely to report the sex of animals in publications if they had altered their study designs to comply with the policy (OR 1.601, 95% CI 1.1086–2.3128) or if they thought that the policy allows for the use of only one sex in their studies (OR 4.023, 95% CI 1.5190–10.6527). Researchers who thought that analyzing results by sex was most important in animal studies were more likely to report the sex of animals (OR 4.581, 95% CI 1.0571–19.8491), and researchers who thought analyzing by sex was most important in human clinical trials were less likely to report the sex of animals (OR 0.635, 95% CI 0.4311–0.9347), both compared with those who believed that analyzing by sex is equally important in animal and human trials.

In terms of differences among researchers in how often they analyze their findings by sex, about half (50.74%) of researchers said they always analyze their results by sex and 41.70% said they sometimes do (Table 1). Odds of moving up one level from never to sometimes/always or never/sometimes to always are presented in Table 3. Holding other variables constant, respondents who primarily studied rats and other rodents were more likely than those who studied mice to analyze findings by sex (OR 1.557, 95% CI 1.0076–2.4070). In contrast, compared with those who studied mice,

Table 3. Regression Analysis of Reporting by Sex and Analysis by Sex

	How often do you report the sex of your animals in publications?	*How often do you analyze your findings by sex?*	
Observations	1056	818	
Model type	Logit	Ordered logit (gologit2)	
Statistics	ORs/95% CI	ORs/95% CI	
	Always vs. when relevant (others excluded)	*Sometimes/ always vs. never*	*Always vs. sometimes/never*
Age (continuous)	1.005 0.9899–1.0208	0.991 0.9670–1.0160	1.017* 1.0038–1.0314
Gender (reference: man)			
Woman	1.831** 1.2662–2.6482	1.215 0.8939–1.6518	1.215 0.8939–1.6518
Degree (reference: no)			
MD or equivalent	0.497** 0.3057–0.8096	1.199 0.7462–1.9260	1.199 0.7462–1.9260
DVM or equivalent	0.948 0.3881–2.3146	1.789 0.8476–3.7742	1.789 0.8476–3.7742
PhD	0.467 0.2090–1.0427	0.956 0.4726–1.9355	0.956 0.4726–1.9355
Primary animal (reference: mice)			
Other rodents	2.728*** 1.5435–4.8215	1.557* 1.0076–2.4070	1.557* 1.0076–2.4070
Other mammals	1.88 0.8092–4.3683	0.417** 0.2200–0.7905	0.417** 0.2200–0.7905
Primates	0.783 0.3624–1.6932	0.352** 0.1715–0.7240	0.352** 0.1715–0.7240
All other animals	0.521 0.2483–1.0950	0.110*** 0.0545–0.2207	0.376** 0.1967–0.7190
NIH-funded PI in past 5 years (reference: yes)			
No	1.395 0.8968–2.1690	1.092 0.7483–1.5941	1.092 0.7483–1.5941
Heard of NIH sex as a biological variable policy (reference: yes)			
No	0.55 0.2769–1.0939	0.727 0.3852–1.3725	0.727 0.3852–1.3725
Altered study design in response to NIH policy (reference: already meeting policy expectations)			
I have altered how I design studies to comply with these expectations.	1.601* 1.1086–2.3128	1.73 0.8248–3.6273	0.635** 0.4607–0.8758
It hasn't affected my research yet, but I expect it will when I apply for my next grant.	0.942 0.4988–1.7795	0.453* 0.2397–0.8557	0.453* 0.2397–0.8557
The NIH policy allows for the use of one sex, and I believe I can justify continuing to do so.	4.023** 1.5190–10.6527	0.299* 0.1098–0.8149	0.299* 0.1098–0.8149
I am neither funded by the NIH nor plan to seek funding from NIH.	1.127 0.4981–2.5491	0.523 0.2575–1.0629	0.523 0.2575–1.0629
View on importance of analyzing by sex (reference: it is equally important in animal and human trials)			
It is most important in animal studies	4.581* 1.0571–19.8491	0.328 0.0897–1.1954	1.853 0.7180–4.7840
It is most important in human clinical trials	0.635* 0.4311–0.9347	0.353*** 0.2414–0.5154	0.353*** 0.2414–0.5154
It is not important to do so	0.689 0.1701–2.7897	0.121** 0.0275–0.5299	0.121** 0.0275–0.5299
Constant (cut 1/main)	4.464* 1.3373–14.9017	43.342*** 8.8633–211.9410	0.632 0.2222–1.7967

researchers who primarily studied primates (OR 0.352, 95% CI 0.1715–0.7240), other nonrodent mammals (OR 0.417, 95% CI 0.2200–0.7905), or all other animals (OR 0.110, 95% CI 0.0545–0.2207) were less likely to analyze findings by sex. Compared with those who had already been meeting the expectations of the SABV policy, respondents were less likely to analyze their findings by sex if they indicated the SABV policy had not yet affected their research (OR 0.453, CI 0.2397–0.8557) or that the SABV policy allows for the continued use of only one sex in their studies (OR 0.299, 95% CI 0.1098–0.8149). Researchers who thought it was not important to analyze findings by sex (OR 0.121, 95% CI 0.0275–0.5299) and those who thought analyzing by sex was most important in human clinical trials (OR 0.353, 95% CI 0.2414–0.5154) were less likely to analyze animal findings by sex than those who believed that analyzing by sex is equally important in animal and human trials.

Broader impacts of the SABV policy

Respondents were asked whether they thought that the emphasis on including SABV would improve the translation of animal research to human clinical trials. Just under half (47.51%) of respondents said SABV would improve translation, about one-third (34.77%) said they were unsure, and less than one-fifth (17.72%) said SABV would not improve translation to humans (Table 1). Factors associated with the perception that the SABV policy would improve translation are presented in Table 4. Respondents were more likely to think SABV would improve translation if they were women (OR 1.362, 95% CI 1.0516–1.7643) or if they primarily studied rats or other rodents compared with mice (OR 1.459, 95% CI 1.0472–2.0330). In addition, the more the respondents thought animal studies are accurate predictors of how safe therapies would be in humans, the more likely they were to think SABV would improve translation (OR 1.567, 95% CI 1.2525–1.9617). Respondents were also more likely to think that SABV would improve translation if they had also reported that the reproducibility ''crisis'' in science is an important problem for the research enterprise or were unsure about the extent to which reproducibility is a problem compared with those respondents who thought the reproducibility ''crisis'' frame is an exaggeration of the problem (OR 1.443, 95% CI 1.0473–1.9872; OR 1.781, 95% CI 1.0976–2.8904).

Barriers to implementing the SABV policy

Very few respondents believed that implementing the SABV policy would not affect the number of animals required in studies (5.62%), and the majority (64%) believed that it would require doubling or more than doubling the number of animals used compared with protocols using only one sex of animal (Table 1). Factors associated with respondents' views of the effects of the SABV policy on number of animals required are presented in Table 5. Holding other variables constant, respondents with a PhD were more likely to think that animal numbers would need to be increased to implement the policy compared with those without a PhD (OR 1.968, 95% CI 1.1545–3.4152). Compared with researchers who primarily studied mice, those who studied primates, other nonrodent mammals, or all other animals were all the more likely to think that implementing the SABV policy does not affect the number of animals needed (OR 0.213, 95% CI 0.0879–0.5140; OR 0.181, 95% CI 0.0852–0.3829; OR 0.239, 95% CI 0.1037–0.5519). Finally, researchers who did not think it is important to analyze findings by sex in either human or animal trials were less likely to say that the SABV policy would require increasing the number of animals used compared with those who thought it was equally important to analyze sex in animal and human trials (OR 0.109, 95% CI 0.0277–0.4265).

Holding other variables constant, respondents who believed that implementing the SABV policy requires increasing the number of animals used in a research protocol were more likely to think that insufficient funding is a legitimate barrier to policy implementation (OR 2.257, 95% CI 1.9070–2.6722). However, researchers who worked in industry or for other nonacademic private institutions were less likely than those at public academic institutions to endorse funding as a legitimate barrier to SABV policy implementation (OR 0.471, 95% CI 0.2354–0.9432). Similarly, those who had not received NIH funding in the past 5 years were less likely to select funding as a legitimate barrier to implementation than those who had recently received NIH funding (OR 0.552, 95% CI 0.4173–0.7314).

Discussion

This article describes the findings from a national survey of U.S. biomedical researchers using live vertebrate animals in their research, exploring researchers' knowledge of the NIH's SABV policy, their related scientific practices, and their perceptions of the impact and broader scientific significance of the policy. The key findings are summarized in Figure 1. These findings indicate that there are important differences among researchers in the degree to which they address SABV in their own research, the manner in which they do so, and their perceptions of the policy's significance. These differences are discussed in detail below.

Overall, the results indicate that the SABV policy is having its intended impact.[12] While nearly half of respondents said they had already met the expectations of the policy before the SABV requirements, over one-third said they altered their study designs to comply with NIH's expectations. In addition, almost one-third (31.08%) of respondents specifically noted that compliance with funding policies contributed to their choice of sex(es) of animal to use in their studies (Table 1). However, even 4 years after the policy went into effect, only about half of the respondents report always analyzing their study results by sex.

While some scholars have called for the SABV policy to extend beyond NIH-funded research to encourage more scientists to design and analyze their studies to capture potential sex differences,[13] this survey reveals there is no significant difference in the likelihood of analyzing results by sex between researchers who have and who have not recently received NIH funding. Despite likely being subject to the SABV policy, almost half of surveyed recent recipients of NIH funding are not conducting sex-based analysis of their findings for all of their studies. Potential explanations for this researcher subset include diverse funding sources for individual research portfolios or the fact that some studies meet allowable exemptions for the NIH's SABV policy—a

Table 4. Regression Analysis of Impact of Sex As a Biological Variable on Translation

	Do you think that the emphasis on including sex as a biological variable will make NIH-funded animal research translate better to human clinical trials?
Observations	1103
Model type	Ordered logit (ologit)
Statistics	ORs/95% CI
	Yes vs. unsure vs. no
Predictive power of animal models for safety in humans	
Small/moderate/great extent	1.567*** 1.2525–1.9617
Cause of poor predictive value	
Problems with study design	1.125 0.8679–1.4588
Some other problem	0.97 0.6697–1.4046
Views on reproducibility ''crisis''	
I think this is an important problem for the research enterprise.	1.443* 1.0473–1.9872
I'm not sure about the extent to which this is a problem.	1.781* 1.0976–2.8904
Reasons for reproducibility failures (*choose up to 3*)	
Differences across animal housing/husbandry environments	0.965 0.7210–1.2914
Differences in personnel	1.25 0.8870–1.7612
Lack of rigor in design of studies	1.36 0.9975–1.8530
Variability in animals used	1.209 0.9058–1.6127
Insufficient details on methods in published reports	1.233 0.9258–1.6427
Falsification of published results	0.608* 0.4056–0.9128
Commercial interests biasing the design or analysis of studies	0.803 0.5176–1.2456
Some other issue	0.783 0.5070–1.2095
Primary animal (reference: mice)	
Other rodents	1.459* 1.0472–2.0330
Other mammals	0.992 0.5850–1.6811
Primates	1.057 0.5771–1.9351
All other animals	0.928 0.5476–1.5719
View on importance of analyzing by sex (reference: it is equally important in animal and human trials)	
It is most important in animal studies	0.865 0.4166–1.7965
It is most important in human clinical trials	0.236*** 0.1755–0.3180
It is not important to do so	0.167** 0.0522–0.5313
Age (continuous)	
Age	0.999 0.9877–1.0099
Gender (reference: man)	
Woman	1.362* 1.0516–1.7643
Degree (reference: no)	
MD or equivalent	1.148 0.7646–1.7224
DVM or equivalent	0.69 0.3734–1.2747
PhD	0.802 0.4547–1.4138
NIH-funded PI in past 5 years (reference: yes)	
No	1.097 0.8360–1.4388
Constant (cut 1/main)	4751.330*** 32.3986–7.0e+05
Constant (cut 2)	3.1e+04*** 209.8326–4.6e+06

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

limitation of the policy that some biomedical researchers criticize.[11] Another interpretation of this finding is that a lack of buy in about the importance of the SABV policy among some researchers leads them to not always analyze their findings by sex. Supporting this explanation is that survey respondents who thought sex-based analysis was not important or was more important in human trials were less likely to analyze their own data by sex compared with respondents who thought that analyzing by sex was equally important for human and animal studies as well as those who thought SABV would improve translation. Because these findings show that scientists are responsive to funding policy shifts with regard to SABV, it is likely they would additionally respond to shifts in journal policy, such as requiring researchers to report animal sex in publications and to provide a justification regarding why sex-based analyses were not conducted.

Table 5. Regression Analysis of Beliefs About Animal Numbers Required by Sex As a Biological Variable and Beliefs About Funding As a Legitimate Barrier to Sex As a Biological Variable Implementation

	How would the inclusion of both sexes affect the number of animals used?			*Insufficient funding is a barrier*
Observations	1099			1155
Model type	Ordered logit (gologit2)			Logit
Statistics	ORs/95% CI			ORs/95% CI
	Less than doubles/ doubles/more than doubles vs. does not affect number	*Doubles/more than doubles vs. does not affect/less than doubles*	*More than doubles vs. does not affect/less than doubles/doubles*	*Yes vs. no*
Effect on number of animals required (ordinal)	—	—	—	2.257***
	—	—	—	1.9070–2.6722
Age (continuous)	0.991	0.991	0.991	—
	0.9803–1.0010	0.9803–1.0010	0.9803–1.0010	—
Gender (reference: man)				
Woman	1.221	1.221	1.221	—
	0.9593–1.5541	0.9593–1.5541	0.9593–1.5541	—
Degree (reference: no)				
MD or equivalent	0.98	0.98	0.98	—
	0.6680–1.4366	0.6680–1.4366	0.6680–1.4366	—
DVM or equivalent	1.56	1.56	1.56	—
	0.8829–2.7550	0.8829–2.7550	0.8829–2.7550	—
PhD	1.986*	1.986*	1.986*	—
	1.1545–3.4152	1.1545–3.4152	1.1545–3.4152	—
Institution (reference: public academic)				
Private academic	0.926	0.926	0.926	0.816
	0.7216–1.1879	0.7216–1.1879	0.7216–1.1879	0.6205–1.0724
Industry or other nonacademic private	0.847	0.847	0.847	0.471*
	0.4480–1.6015	0.4480–1.6015	0.4480–1.6015	0.2354–0.9432
NIH-funded PI in past 5 years (reference: yes)				
No	0.932	0.932	0.932	0.552***
	0.7096–1.2244	0.7096–1.2244	0.7096–1.2244	0.4173–0.7314
Heard of NIH SABV policy (reference: yes)				
No	0.743	0.743	0.743	—
	0.4694–1.1765	0.4694–1.1765	0.4694–1.1765	—
Primary animal (reference: mice)				
Other rodents	1.038	1.038	1.038	—
	0.7603–1.4180	0.7603–1.4180	0.7603–1.4180	—
Other mammals	0.181***	0.425**	0.749	—
	0.0852–0.3829	0.2472–0.7290	0.3448–1.6251	—
Primates	0.213***	0.65	0.723	—
	0.0879–0.5140	0.3522–1.1984	0.2980–1.7557	—
All other animals	0.239***	0.831	0.974	—
	0.1037–0.5519	0.4689–1.4745	0.4604–2.0601	—
View on importance of analyzing by sex (reference: it is equally important in animal and human trials)				
It is most important in animal studies	0.929	0.929	0.929	—
	0.4856–1.7771	0.4856–1.7771	0.4856–1.7771	—
It is most important in human clinical trials	0.795	0.795	0.795	—
	0.5973–1.0593	0.5973–1.0593	0.5973–1.0593	—
It is not important to do so	0.109**	0.979	1.632	—
	0.0277–0.4265	0.2873–3.3370	0.4303–6.1932	—
Constant	23.450***	1.751	0.174***	0.019***
	9.8149–56.0252	0.7713–3.9733	0.0760–0.3970	0.0070–0.0489

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

	Summary of Findings
How often do you report the sex of your animals in publications?	• Researchers most likely to report the sex of their animals in publications include: o Women o Non-MDs o Those who used rodents other than mice in their studies • Researchers reporting sex: o Were more likely to have altered study designs or could justify using only one sex o Stated that analyzing findings by sex is more important in animal studies than in human trials
How often do you analyze your findings by sex?	• Researchers most likely to analyze their study findings by sex include: o Older researchers o Those who used rodents other than mice in their studies • Researchers analyzing findings by sex were: o Less likely to have altered their study design as a result of NIH policy o Much less likely to believe that analyzing results by sex was not important to do or is more important in human trials than in animal studies
Do you think that the emphasis on including sex as a biological variable will make NIH-funded animal research translate better to human clinical trials?	• Researchers most likely to believe that the SABV policy would improve translation of animal findings to human trials include: o Women o Those who used rodents other than mice in their studies • Researchers who believed the SABV policy would improve translation: o Were much less likely to believe that analyzing results by sex was not important or is more important in human trials than in animal studies o Reported that animal models are good predictors of safety issues in humans o Thought that the reproducibility crisis is an important problem in science
How would the inclusion of both sexes affect the number of animals used? (From doesn't affect numbers to more than doubles)	• Researchers with PhDs were most likely to believe that including two sexes in research would increase the number of animals needed. • Researchers less likely to believe they would have to increase the number of animals used include those who used: o Primates o Non-rodent mammals o All other animals • Researchers who did not believe analyzing findings by sex was an important thing to do also did not think they would need to increase the number of animals used in their studies.

FIG. 1. Summary of main findings.

Gender also affected how researchers perceived the value of the SABV policy and their related science practices. Women were more likely than men to think that the SABV policy would have a positive impact on the translation of animal research to human medicine, and women were more likely to report the sex of animals used in their research studies. However, there were no statistically significant differences in whether men and women researchers analyzed their findings by sex. This conflicts with a 2017 study by Nielsen et al. that found that in over 1.5 million medical research articles, women's authorship was positively correlated with sex and gender being included in analyses.[14] The results of the current survey might differ because the SABV policy has had its intended effect and may, therefore, be motivating more men to analyze results by sex. Future research should investigate through publications the possible impact of the SABV policy on men's analysis of animal studies by sex.

The animal species used by researchers also impacted perceptions of the SABV policy and actions related to SABV. For instance, while researchers primarily using mice and those primarily using other rodents did not differ in whether they had heard of the SABV policy, nonmouse rodent researchers were nonetheless more likely than mice researchers to report and analyze their findings by sex. They were also more likely to think the SABV policy will improve the translation of animal research compared with those who primarily use mice, perhaps reflecting the additional finding that the SABV policy was more likely to have changed their research practices. These differences suggest that researchers who use rats and other (nonmouse) rodents may be more on the forefront of SABV research, signaling the possibility that mice are not the chosen species among researchers most interested in model organisms for sex-based differences in biomedicine. Alternatively, these differences may be a result of the complications in studying SABV introduced by genetic modification and sex-specific inheritance patterns, which are more frequently studied in mouse models. Because questions about specific uses of animal models were not asked, this possible explanation cannot be ruled out. Beyond rodent

research, researchers who used other vertebrates, including mammals, in their research were more likely to never analyze their study findings by sex compared with mice researchers. In addition, researchers who used animals that fell into the ''all other animals'' category, which largely comprised nonmammalian vertebrates, were less likely even to know about the policy compared with mice researchers. These differences across species of model organisms used are a robust finding, suggesting that the SABV policy may be failing to reach certain researchers because of the work they do or the animal models they use.

Finally, degree type appears to have influenced perceptions of the SABV policy. Specifically, researchers with PhDs were more likely to think that the number of animals used in each protocol must increase to enact the SABV policy. However, this perspective has been rejected as misinformed by scientists specializing in sex-based research.[5,6] Significantly, a perception that SABV research requires increasing the number of animals used in studies explains why insufficient funding was most frequently selected (24.42%) as a legitimate barrier to using two sexes in research. These findings thus support the call for additional training of all scientists who use animals in their research on how to best implement the SABV policy into protocol design.[15]

This study has limitations. There is no available database inclusive of all biomedical researchers in the animal research community, so the sample was drawn from a national list of U.S. scientists who use vertebrate animals in their research that was generated through web searches of public and private research institutions. Older and more experienced researchers as well as those who work for public academic institutions are likely overrepresented in this sample due to their more prominent web presence. The time period of the survey at the beginning of stay-at-home orders for COVID-19 may have impacted some researchers' ability to complete the survey if they had to perform additional childcare work or attend to other responsibilities. In addition, this survey elicited self-reported information on issues relating to the SABV policy, including whether researchers were meeting the policy's expectations of including two sexes in research designs. However, this survey does not reveal how well two sexes are included in studies or whether analyses by sex are performed correctly. Finally, data about individuals' specific research fields or scientific areas of inquiry were not collected. Thus, how fields differ in their opinions about or degree of compliance with the NIH SABV policy could not be examined. Nonetheless, this survey provides an important snapshot of current perceptions and practices regarding the integration of SABV into the research enterprise.

Conclusion

NIH announced its SABV policy in 2015 and required researchers to include consideration of SABV in their extramural research proposals beginning in January 2016. This survey of a national sample of U.S. scientists using live vertebrate animals in their research aimed, in part, to explore how biomedical researchers perceive that policy and their own research practices surrounding SABV. These findings indicate that there is a broad awareness of the policy and that many researchers report adhering to its requirements. Nonetheless, more work needs to be done to ensure that the policy is being evenly applied to researchers using all types of animal models and that researchers adhere to the policy *after receiving NIH funding* when reporting on and analyzing their study findings for publication. These results underscore the importance of training so that researchers can better understand how to best integrate SABV into their research, potentially with limited grant budgets and without needlessly increasing the number of animals used in their studies. With greater adherence to the SABV policy, NIH-funded research will be better positioned to enhance public health by improving women's health outcomes.

Acknowledgments

The authors are grateful for the research assistance of Molly Green, Ryan Joseph Kramer, Lisa McManus, and Megan Wood for conducting the biomedical researcher search to generate the survey distribution list. In addition to assisting with the biomedical researcher search, Julianne Kalbaugh also programmed and administered the survey. They are also grateful to the individual biomedical researchers who piloted the survey instrument and to the additional members of their research team who offered feedback on the survey questions. Teresa Edwards also provided helpful input on the survey instrument.

Authors' Contributions

M.W., J.A.F., and R.L.W. made substantial contributions to the conception and design of the work. J.A.F. and R.L.W. designed the survey. M.W., J.A.F, K.W.S., and R.L.W. contributed to the analysis plans and interpretation of the findings. K.W.S. conducted the statistical analysis, and M.W. drafted the article. M.W., J.A.F, K.W.S., and R.L.W. contributed to the writing and revising of the work for important intellectual content, give final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

Research reported in this article was supported under a grant from the National Institute of General Medical Sciences and the Office of Research on Women's Health (National Institutes of Health) through an administrative supplement for research on sex/gender influences made as part of award number R01GM099952, ''Healthy Volunteers as Model Organisms: Comparative Research Ethics and Policy for Phase I Trials'' (principal investigators: J.A.F. and R.L.W.).

Supplementary Material

Supplementary Data

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