

Evaluating the National Institutes of Health's Sex as a Biological Variable Policy: Conflicting Accounts from the Front Lines of Animal Research

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Abstract

Background: Since the National Institutes of Health (NIH) Revitalization Act of 1993, focus on the equitable inclusion of women in clinical research has been ongoing. NIH's 2015 sex as a biological variable (SABV) policy aims to transform research design, analysis, and reporting in the preclinical sphere by including male and female organisms in vertebrate animal research as well as human studies. However, questions remain regarding how researchers and members of research oversight committees perceive the value and need of the SABV policy.

Materials and Methods: Based on 62 interviews with animal researchers and oversight personnel, we analyze what the animal research community knows about the policy and sees as the benefits and challenges of implementation.

Results: We found that the 62 interviewees disagreed about the need for the policy, with some being supportive and others questioning whether the policy is based on science or is politically motivated. There were also tensions in how interviewees conceptualized the challenges to and resources needed for implementing the SABV policy. For instance, while some thought implementation would require a significant increase in numbers of animals used for each study, others explicitly rejected this claim.

Conclusions: We conclude by discussing the practical and social implications of our findings about the views of members of the animal research community regarding the SABV policy.

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

Introduction

SINCE THE NATIONAL INSTITUTES OF HEALTH (NIH) Revitalization Act of 1993, which requires that women and members of minority groups be included in clinical research, programs to promote the equitable inclusion of women in clinical research have expanded.¹ Furthering this effort, the NIH released a policy in 2015 on sex as a biological variable (SABV), calling for researchers to factor sex into research designs, analyses, and reporting of both human and vertebrate animal studies. If NIH-funded researchers propose studying only one sex, they must provide "strong justification from the scientific literature, preliminary data, or other relevant considerations."²

NIH's SABV policy was established to address the underrepresentation of and lack of robust data about women and female animals in biomedical research.³⁻⁵ In biomedical re-

search, the male body has historically been thought of as normative, leaving female bodies to be seen as a "demographic subpopulation" because their menstrual cycles and reproductive potential mark them as different.⁶⁻⁸ Much research has excluded women and female animals as a result of this convention, the idea that their inclusion requires more complex research designs, and the assumption that results from male animals would apply to female animals.⁶⁻¹¹ However, research based on male bodies can translate poorly to female human populations as men and women may metabolize drugs differently, experience different adverse effects, and can "manifest, progress, and react" differently to some diseases.¹² The SABV policy was designed to address these translational issues, according to NIH's Francis Collins and Janine Clayton, and "ensure that the health of the United States is being served by supporting science that meets the highest standards of rigour."¹³

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To date, little empirical research has been conducted about researchers' and research oversight committees' perceptions of NIH's SABV policy. A recent survey of NIH Study Section members found that grant reviewers perceive that more applications now address SABV, indicating that implementation of the SABV policy is improving.¹⁴ Yet reviewers' perspectives on how to evaluate the execution of SABV when reviewing grants differed, and some had "negative attitudes toward the policy."¹⁴ Particularly absent is information regarding how the animal research community perceives the value of investigating sex effects during preclinical research as required by the SABV policy. In this article, we report on what animal researchers and Institutional Animal Care and Use Committee (IACUC) veterinary and leadership members articulate as the value of the SABV policy as well as challenges to its implementation.

Materials and Methods

We conducted semi-structured interviews with 62 U.S.-based animal researchers and key IACUC members to explore views about animal welfare and research oversight, research design methodological choices, and translational science challenges. One section of the interview guide (Table 1) focused on NIH's SABV policy and respondents' perceptions of the importance of sex-based methodologies during preclinical research. As is typical of semi-structured interviewing, the interviewer adapted questions to best fit the experience of the respondent and asked follow-up questions probing relevant topics that emerged during the interview.¹⁵ All interviews were conducted by telephone and lasted ~75 minutes. The institutional review board of the University of North Carolina approved all procedures.

We identified eligible participants for our study through web searches and snowball sampling, focusing on biomedical researchers who used vertebrate animals and worked in academia or the private sector. Our recruitment strategy aimed for a national sample of scientists with institutional and participant demographic diversity, so we capped active recruitment to two people per institution and adjusted outreach efforts to have representation by gender, race, and ethnicity. Recruitment began in September 2018, and interviews were completed by December 2018. In total, we e-mailed 250 animal researchers and IACUC members. Only 9.2% explicitly declined participation, and the interview response rate was 24.8%.

All interviews were transcribed in full. To facilitate analysis, we (M.W., J.A.F., and R.L.W.) created memos summarizing key findings from the interviews.¹⁶ Relevant to this article, we memoed interviewees' perspectives on NIH's SABV policy using the following questions as guides: "What does the informant know about the SABV policy? What do they say are the benefits of the SABV policy? What do they report as reasons why the policy might be problematic?" We also memoed the interviewees' current scientific practices regarding the SABV policy, such as how they reported applying SABV to their work and any difficulties they encountered. For interviews with IACUC members, we also documented any concerns or changes in IACUC practices that had arisen from the policy. All authors used these memos to identify themes that emerged regarding the SABV policy across all interviews, and we discussed these themes together to prioritize how to focus the analysis. After organizing these themes, the lead author (M.W.) returned to the transcripts to identify in more fine-grained detail what interviewees said about the SABV policy. We summarize our findings

TABLE 1. INTERVIEW GUIDE QUESTIONS PERTAINING TO SEX AS A BIOLOGICAL VARIABLE

Animal researcher interviews

- One area of translation that has received attention lately has been in the inclusion of sex and gender variation as part of the design of research protocols and analysis of study findings. The NIH now has guidelines encouraging the inclusion of sex as a biological variable in animal studies and we are curious what information is actually out there.
 - What have you heard about NIH's guidelines? [If heard about]
 - What do you understand NIH to be encouraging researchers to do with their new guidelines?
 - What do you think is their justification for including sex and gender variation?
 - Tell me a little [more] about how sex is taken into account in your work? (probe: research questions, protocol design, data collection, analysis)
 - How have the NIH guidelines changed your approach to considering sex as a biological variable? [If not heard about]
 - The NIH has implemented a guideline, effective in 2016, that requires the use of both sexes in vertebrate animal research unless the use of only one sex is adequately justified.
 - What are your thoughts on this approach?
 - Tell me a little about how sex is taken into account in your work? (probe: research questions, protocol design, data collection, analysis)
- [All interviewees]
 - Opinions vary about the importance of requiring the use of female organisms in research, how important do you think it is? (Why?)
 - What are the challenges for including female organisms in nonhuman animal research? (Why?)
 - How have these challenges impacted your own personal experience?

IACUC interviews

- The NIH has new guidelines encouraging the inclusion of sex as a biological variable in animal studies, and we are curious what information is actually out there.
 - What have you heard about these NIH guidelines?
 - How do these guidelines change the work that you do? (probe: selection of animals, protocol renewals)
 - Why do you think NIH has developed these guidelines?
 - Opinions vary about the importance of requiring the use of female organisms in research, how important do you think it is? (Why?)
 - Based on your conversations with researchers or your deliberations as a committee, what are the challenges to including female organisms in nonhuman animal research? (Why?)
 - What challenges are there to implementing NIH's guidelines on sex and gender at your institution? (Why?)

NIH, National Institutes of Health; IACUC, Institutional Animal Care and Use Committee.

below using illustrative quotes to represent the diverse perspectives within the animal research community on the SABV policy.

Results

Sixty-two members of the animal research community were interviewed: 15 in the oversight role and 47 in the researcher

TABLE 2. DEMOGRAPHIC CHARACTERISTICS OF INTERVIEWEES (N=62)

Variable	Frequency	Percentage
Gender		
Man	29	46.8
Woman	33	53.2
Age, years		
30–39	9	14.5
40–49	15	24.2
50–59	17	27.4
60–69	14	22.6
70–79	6	9.7
Did not report	1	1.6
Race		
Asian	4	6.5
Black or African American	2	3.2
More than one race	3	4.8
White	52	83.9
Did not report	1	1.6
Ethnicity		
Hispanic or Latino	3	4.8
Not Hispanic or Latino	58	93.5
Did not report	1	1.6
Education		
DVM	14	22.6
DVM, PhD	6	9.7
MD	2	3.2
MD, PhD	1	1.6
MPH, PhD	2	3.2
MS	1	1.6
PhD	35	56.5
PhD, RN	1	1.6
Time in the field, years		
2–5	3	4.8
6–10	8	12.9
11–20	14	22.6
20+	37	59.7
Institution type		
Private academic institution	16	25.8
Public academic institution	37	59.7
Institution other than academic	9	14.5

role. Interviewees' self-reported demographic characteristics are presented in Table 2. Our sample included 29 men (46.8%) and 33 women (53.2%). Most (83.9%) identified as White. Interviewees held at least one graduate or professional degree in a scientific field of study, such as human or veterinary medicine, pharmacology, neuroscience, immunology, genetics, and biology. Over half (59.7%) had worked in their field for over 20 years. Most (85.5%) were associated with academic institutions, primarily public academic institutions (59.7%). Our sample was geographically distributed throughout the United States, with 45% working in the East, 34% in the Midwest, and 21% in the West. Our findings are explicated below; and main points are summarized in Table 3.

Familiarity with NIH's SABV policy

When asked whether they had heard of NIH's SABV policy, most interviewees said that they were familiar with it from receiving NIH extramural funding and/or serving on NIH study sections. However, some held misunderstandings about

TABLE 3. SUMMARY OF KEY THEMES

Key themes

- Varied levels of support for the SABV policy
 - Most interviewees were supportive, emphasizing its importance for translational purposes.
 - Others questioned the need for the policy. They noted that including both male and female animals was important for human trials but less necessary for preclinical research.
 - While some questioned whether the policy was needed for scientific purposes or was politically motivated, others critiqued it for not being stringent enough in its mandate by only asking scientists to “consider” sex.
- Differing views about implementation challenges
 - Some thought that implementation would require a significant increase in numbers of animals used for each study and, as a result, increase research costs. Others explicitly rejected this claim saying that the policy does not require doubling of animal numbers.
 - Some thought that female animals' estrous cycles introduced problematic variability in research protocols. Others disagreed about the degree to which the estrous cycle creates problems for research, and others still argued that the estrous cycle—and the variability it can introduce—proves the importance of including females in research.
 - Some deemed the policy to be an unfunded mandate, which without adequate resources could inhibit researchers' ability to study two sexes.

SABV, sex as a biological variable.

the policy. One animal researcher (AR02), for instance, thought that the SABV policy referred only to human clinical trials and not preclinical research, and other interviewees misused the terms “sex” and “gender” when talking about the policy. By conflating sex and gender, interviewees demonstrated their lack of familiarity with the distinction between the terms, particularly the social construction of gender.¹⁷

Views on the importance of the SABV policy

Interviewees expressed various opinions about the SABV policy's importance. Some supported the policy, regardless of its impact on their work, whereas others questioned the need for it altogether.

Articulations of support

Many interviewees said that the policy was important because scientists should be using two sexes in their research unless the condition being studied is sex-linked. Some noted that animal selection has been “male biased.” Others argued that studying only one sex—regardless of which one—is a “limitation” because researchers leave out “half of the population” who may react differently to the drug or condition under investigation. As an IACUC member (IA10) commented, “I think that particularly from a translational perspective, if you're interested in what your results in these animal models mean for the human population, it's a pretty large percentage of the population that you're ignoring if you're only looking at one sex—whether it's just males or just females.” Similarly, an animal researcher (AR16) stated, “If you want to improve the translation of your study from

preclinical to clinical, you need to pick an animal that is most representative of your target population. Why you would pick a male mouse [only] is a mystery to me.”

Some researchers thought that the SABV policy addresses these translational science problems. For example, one animal researcher (AR11) argued, “If we don’t know anything about females, that minimizes our capacity to translate to humans. Now that we know these things, and have a richer picture, I think that improves overall translation of the data.” By including two sexes, researchers noted that studies may catch differences not previously observed. One researcher (AR36) explained that he began to study two sexes because of the policy and found that “it wasn’t necessarily that one sex wasn’t affected. It’s just that they were affected in different ways, which I think is more interesting, to be honest ... We’re discovering things that we’ve previously sort of missed.”

Researchers also noted that the policy helps inform research questions, which can improve the rigor of research. One animal researcher (AR14) said that “ultimately, until you ask the question, you don’t know” if sex differences may exist. Another researcher (AR10) asserted, “Sometimes there is no sex difference, and it is okay to pool that data. But you can’t find out there is no difference if you don’t include both [sexes] ... People are wasting a lot of effort if they move to a human study but didn’t know things reacted differently by sex.” Interviewees also suggested that by shifting which research questions are asked, historical perceptions of the “normal” body as the male body are altered, which some considered an important goal of NIH’s policy. An animal researcher (AR12) stated that the policy is needed because “the male organism is not the default organism. Period. I think [two sexes] should be required.”

Some interviewees supportive of the policy even critiqued it for not being stringent enough in its mandate. One researcher (AR20) said, “At least what I have witnessed is now researchers are giving it lip-service in their grant applications and proposing some sort of strategy for addressing what the NIH wants you to address, but I don’t know if the follow-through is there yet.” One component underlying this concern is that the policy requires scientists only to “consider” sex.² Interviewees suggested that this language means investigators can “get away with” using only male mice, which some had experienced in the grant review process (AR20).

Supportive but unaffected by the SABV policy

In addition to expressions of support, some interviewees noted that the policy would not impact their own work. Animal researchers who did not receive NIH funding were most obviously exempt from the policy. Among those with NIH funding, some had already been investigating sex effects, whereas others were studying a sex-linked disease. Additionally, researchers who used large animal models stated that the animal models themselves made it difficult to adapt to the policy. An animal researcher (AR03) studying nonhuman primates said that the numbers of primates studied are often small, so “if we’re just going to test something in two monkeys, whether you have two males, two females, or one male and one female, you won’t really be able to tell if there’s any difference anyways. We usually try to do our best to comply to it [the policy], but sometimes it is just not really feasible.”

IACUC members held the position that the SABV policy would not change animal research oversight because of IACUCs’ limited ability to enforce such a policy, particularly when not all the research they oversee is funded by the NIH. The primary perceived limit to their involvement in the SABV policy, as one IACUC member (IA06) explained, is the fact that IACUCs do not comment on the scientific merit of investigators’ research. While she personally believed that the SABV policy is “absolutely critical,” she saw the policy as outside the scope of IACUC review because: “I see that as essentially part of scientific merit, and so that’s not something that we would see as within our purview ... We would never ask a researcher to perform an experiment that they couldn’t fund.” Similarly, another IACUC member (IA04) said that whether a researcher was using two sexes “would not be our call ... I don’t think it would be our place to say you need to go back and redesign this experiment to include females. Again, we don’t oversee any experimental design. We are looking at the welfare of animals.”

Questioning the need for the SABV policy

Not all interviewees were convinced of the value of NIH’s SABV policy. While these individuals typically thought considering sex was important in human trials, they thought that the study of sex in preclinical research is unnecessary. For instance, an IACUC member (IA09) understood the reason for developing the guidelines as “that women were underrepresented” but “that is primarily in human studies as opposed to animal studies. I don’t really know in terms of animal studies if there’s a real bias.” Other interviewees questioned whether the policy was needed for scientific purposes or if it was politically motivated. One animal researcher (AR32) observed, “I think you would be questioned now if you just said, ‘Oh, I bought male mice.’ And that was your only justification for why you did that. I think people would say that was unacceptable and that you should study both. But whether that’s sort of trying to be inclusive and politically correct or actually based on science, I’m not sure that that’s clear.” When asked why the NIH instituted the SABV policy, another animal researcher (AR23) replied, “If you ask me that question after I’ve had a glass of wine, I’d say politics!” Similarly, a researcher (AR01) commented that while “gender [sic] is an extremely important variable,” the consideration of sex in research “has gotten politicized.” He continued saying, “I think NIH in their sort of blanket ruling on this may have hurt research a bit because, you know, there’s only a certain amount of resources and money to study things, and for many questions, there may or may not be a gender bias. But I’m not sure you have to study it upfront ... So, personally, I don’t like to have this dictated.”

Challenges to implementation

Beyond the various views on the SABV policy’s importance, there were tensions in how interviewees conceptualized how the policy works in practice. Regardless of their level of support for the policy, some interviewees cited challenges to its implementation, including increased animal numbers, cost, or biological variability. Other interviewees explicitly countered these claims.

Animal numbers and cost

A perceived increase in numbers of animals needed per study, and the associated costs and housing problems, were commonly mentioned challenges to enacting the policy. Some interviewees claimed that studying two sexes doubles the animal numbers. One researcher (AR11) stated, “If you’ve only been studying one sex forever and you bring in a second sex, it doubles the cost of your study. ... And so NIH is going to have to acknowledge that if you double your sample size, that that has costs associated with it.” Costs relate to the purchase and housing of animals. Some relayed that animals can be particularly expensive to procure because of demand or their use in breeding. Interviewees noted further that sex-specific housing is required to prevent pregnancies that may impact study outcomes, but it doubles the number of cages. One researcher (AR46) said that this can add expenses “because oftentimes we get charged [by animal husbandry] by the cage, not the animals.” Another (AR42) commented that researchers may not have “the infrastructure to keep these animals separate.”

Undergirding some interviewees’ concerns was their perception that the SABV policy was tantamount to an unfunded mandate. An animal researcher (AR34) declared that “if you want us to study sex, we are really happy to do it. But we would love to have a little bit more money to do it ... Sounds like complaining, but for me this is a practical issue.” Another researcher (AR15) noted that the NIH has not done a good job of “putting their money where their mouth is.” She worried about researchers conducting underpowered studies if they must use two sexes, but their budget is inadequate for the research question. Another researcher (AR13) took the point further and argued that studying sex differences is more resource intensive compared with conventional treatment efficacy studies:

You really have to do that study a lot. You’d really have to do it two or three times in female mice and two or three times in male mice. That’s a huge investment in animal testing when you could have done six experiments with six different drugs and try to find out which is the best drug instead of focusing on one [drug] and seeing the difference between males and females.

Researchers noted that an increased number of animals have implications not only for financial costs but also for animal ethics concerns. One researcher (AR26) observed, “There’s also the idea from a humanitarian perspective that you want to reduce the number of mice that you’re using ... So, then suddenly we’re told that we need to do everything with both male and female mice, you’re doing the opposite of reducing.” Another (AR22) echoed this by emphasizing the “wasted” animals: “Generally speaking, about 80 percent of the research you do is probably going to be trashed. This is basic research [I’m talking about] now. There’s just a lot of failure that precedes right guesses. If the NIH is saying [to] do everything twice, that’s going to create, in my mind, a lot of waste.”

While many interviewees believed that the SABV policy leads to increased animal numbers and cost, others did not see these as challenges *per se*. One researcher (AR29) countered the idea of using two sexes as wasteful by saying that before the policy, his laboratory studied male animals and discarded female animals. They now include female animals and have

realized that “throwing away half the population is wasting a lot of mice in the first place.” Another (AR05) noted that the policy does not require researchers to double their animal numbers as “there’s very easy ways to quickly figure out if you have any kind of robust effect of sex. But people tend to kind of hide behind that [argument].” Others indicated that using two sexes is important to discover sex-based differences early in the research process to save time and resources later. As one IACUC member (IA02) said, “I think that the studies just need to be done properly. They need to have the appropriate number of animals. If that means you have to have more animals to study this drug because you’re gonna look at both sexes, that’s just what needs to be done.” Similarly, an animal researcher (AR41) said, “I get that it’s harder and more expensive to do this other work [on sex differences], but we’ve got to face up to the fact that the way we’re doing things right now [on only one sex] isn’t necessarily working all that well. When the translation rate is 10%, I think it’s time to rethink the strategies.”

Variability and the estrous cycle

Interviewees noted another problem with the inclusion of two sexes in research: the introduction of variability in studies. Summarizing this challenge, an animal researcher (AR09) said that using more than one sex “introduces another variable into an experiment that may make it more difficult to test your hypothesis ... And if you split between two sexes, and if there is a difference between sexes, you’re going to lose statistical power to find the outcome that you’re testing because you’ve introduced more variance in your population.” However, other interviewees did not see variability as a negative feature of the inclusion of two sexes. Instead, they saw it as important for translational purposes, as evidenced by a researcher (AR46) who commented:

In science, we’re taught to control for as many variables as possible so you’re focused only on a certain thing ... If your female subjects are responding differently than your male subjects, that becomes a confounder and makes your data less clean. But ... if that is indeed the outcome that your female subjects are behaving differently than your male subjects, that’s something that’s potentially important to know for when you want to translate these findings into humans.

Related to the potential introduction of variability is how participants perceived the role of the estrous cycle in studies. Some interviewees framed the estrous cycle as a problem, contending that researchers now working with female animals need to learn how to take consistent measurements given fluctuating estrogen levels. However, others disputed the position that estrous cycles present a challenge for research studies. One researcher (AR41), who thought that male animals are studied because of “inertia,” avowed, “It’s part of the standardization. It’s ‘Oh, you know, females have all of these fluctuating hormonal cycles and they’re so messy and complicated.’ ... I don’t think this is free of any gender issues.” Another researcher (AR36) pointed out, “Males also have fluctuations over time as well as hormonal cycles, so the males aren’t constant either. We just tend to emphasize females as being inconstant due to hormones.” Other interviewees professed that the estrous cycle is a reason that female animals should be studied. As one researcher (AR37) asserted, “The wording was that menstrual cycle might skew

the results. I'm going to flip it and say the menstrual cycle plays a role in the results, and therefore it should be part of your study.”

Discussion

We have described how some members of the animal research community view NIH's SABV policy, as well as what these stakeholders see as the challenges to implementing it. Interviewees voiced varying levels of support for the policy, with most emphasizing its importance for translational science. In fact, even when interviewees questioned the need for such a policy, most conceded that it is “reasonable” to ask the question of whether sex differences exist for drugs or disease trajectories.

Stakeholder support for the SABV policy, however, did not equate to an uncritical stance on its implementation. Many animal researchers and IACUC members identified logistical challenges, most related to additional costs. By studying two sexes, some interviewees said that the cost of research increases or even doubles due to the need for more animals and housing. Furthermore, when taking sex-based variability into account, studies might need to be repeated. For some, the perceived increased number of studies and animals required by the SABV policy also raised ethical concerns by contradicting efforts to reduce animal use in research.

Despite these challenges, many interviewees contended that the long-term payoff of studying two sexes is valuable. Implementation challenges are, therefore, a necessary component to improving research, which echoes what others have argued about the SABV policy and highlights the importance of curricular efforts to train researchers on how to incorporate SABV.^{3,17–22} Identification of sex differences early in the translational pipeline instead of during human clinical trials may ultimately save money and time. More importantly, the rigorous examination of potential sex differences may prevent women from experiencing disproportionately harmful adverse effects when drugs reach the market.^{1,19}

This is not to say, however, that the short-term challenges of implementing the policy should be ignored. Deemed by some as an unfunded mandate, inadequate funding to conduct rigorous sex-based preclinical research may prevent or dis-incline even the most ardent supporters of the SABV policy from implementing and/or enforcing it. Furthermore, lack of clarity around stringency and enforcement of the policy may lead researchers to find other justifications for their use of only one sex in research to balance their budgets. This lack of clarity may have the unintended consequence of reproducing the environment that necessitated the need for the policy in the first place. Yet such ambiguity in the SABV policy also has the benefit of allowing interpretation of the mandate based on the proposed science. Furthermore, the existence of the SABV policy itself encourages and enables researchers to find sex differences they may not have found otherwise. Consequently, some commentators recommend that the SABV policy be more comprehensively incorporated into the research enterprise so that all animal researchers, not just NIH-funded investigators, are encouraged to consider how sex might be important to their research questions.²³

The limitations of this study should be considered when interpreting these findings, including that we did not collect standardized information about when and if interviewees had

received NIH funding or served as NIH grant reviewers. Additionally, semi-structured interviewing does not allow for quantitative reporting of findings or subgroup analyses in terms of demographic differences among interviewees. These limitations highlight the value of conducting a survey to identify the potential influence of such factors within the animal research community.

Conclusions

More broadly, policy is a way of enacting social change.²⁴ By addressing the logistical challenges raised by our interviewees, the NIH has the opportunity to transform how researchers ask questions, design studies, analyze their results—and perhaps think about sex and gender. Our findings suggest that there is still work to do in dismantling frameworks that view the male sex as the norm and the female sex as “other.”⁶ While broader social change is not an explicit goal of the SABV policy, it is a necessary condition to ensure that the scientific enterprise is better equipped to address the questions that matter most to women's health.

Authors' Contributions

M.W., J.A.F., A.D.L., and R.L.W. made substantial contributions to the conception and design of the work. M.W. and J.A.F. contributed to the analysis and interpretation of the data for the work and drafted the article. M.W., J.A.F., A.D.L., and R.L.W. contributed to the writing and revising of the work for important intellectual content, gave final approval of the version to be published, and agreed 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.

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