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rpth research & practice in thrombosis & haemostasis

EDITORIAL

Sex Matters: Policy on Reporting Sex as a Biological Variable at Research and Practice in Thrombosis and Hemostasis

One of our favorite bits of party trivia (you can tell who we hang out with) is to ask folks to guess when the National Institutes of Health (NIH) started to require the inclusion of women in clinical research. Most people guess sometime in the 1960s, occasionally the 1970s. The correct answer is 1993. In this editorial we discuss the importance of sex as a biological variable (SABV) in research, both laboratory and clinical, and will discuss what Research and Practice in Thrombosis and Haemostasis (RPTH) is doing to help and encourage authors to report on this important factor.

As with all discussions of sex and gender it is critical first to establish definitions.

- Sex refers to a set of biological attributes in humans and animals. It is primarily associated with physical and physiological features including chromosomes, gene expression, hormone levels and function, and reproductive/sexual anatomy. Sex is usually categorized as female or male but there is variation in the biological attributes that comprise sex and how those attributes are expressed [1].
- Gender refers to the socially constructed roles, behaviors, expressions and identities of girls, women, boys, men, and gender diverse people. It influences how people perceive themselves and each other, how they act and interact, and the distribution of power and resources in society. Gender is usually conceptualized as a binary (girl/woman and boy/man) yet there is considerable diversity in how individuals and groups understand, experience, and express it [1,2].

Both sex and gender are critical determinants of health [3] yet there remains serious evidence gaps on the role of these factors in health. This gap adversely affects quality of care for patients who identify as anything other than the cis-male population (i.e., sex and gender aligned) upon which most available scientific data are based. Additionally, those identifying or presenting as female are often less likely to be believed and/or correctly diagnosed and often have worse outcomes [4–8].

Recent examples of adverse consequences arising from failure to consider SABV include the Food and Drug Administration's (FDA) 2013 change in recommended dosing of zolpidem for biologic females vs males based on post-marketing reports of excessive daytime sedation in those of female sex [9]. These reports led to further investigation, demonstrating a longer half-life of zolpidem in biological females compared to males and subsequent recommendation to start females at a dose of 5mg instead of 10mg, which can be used for men. This finding has since been somewhat debunked [10] but nonetheless stresses the importance of considering SABV in the design of research studies to avoid such confusion.

Post-marketing studies have revealed that certain direct oral anticoagulants (DOACs), such as rivaroxaban, cause heavy menstrual bleeding in as many as 73% of menstruating individuals, with nearly twice as many requiring evaluation and/or intervention for vaginal bleeding compared to those on warfarin [11,12]. Heavy menstrual bleeding has strong negative impacts on quality of life [13]. However, this important discovery occurred years after DOACs entered clinical practice because menstruation, despite being a monthly event occurring in half the population, is not taken into account as a bleeding outcome in clinical trials of anticoagulants. Relatedly, women frequently continue to be excluded from phase 1 pharmacokinetic and pharmacodynamic studies regardless of potential for child-bearing, so early signals of harm may be missed [14–16].

RPTH has a longstanding commitment to diversity at all levels of involvement. From fostering a diverse editorial team, to carefully monitoring and encouraging equity in rates of female-identifying authors, to requiring reporting of race, ethnicity or a related surrogate marker in all clinical studies, [17] promoting inclusive publishing is a hallmark of what we do.

Following on our approach, we announce here that we will require authors to follow the Sex and Gender Equity in Research (SAGER) guidelines shown in Table [18]. Our goal is 100% compliance to the items in the table. We acknowledge that incorporation of these factors into research and protocols will take time, and that sex- and gender-based analyses will not be appropriate for all studies. However, we anticipate that, for most manuscripts, discussion of whether or not sex- and gender-based analyses are appropriate and/or included will be feasible. We wish to emphasize that manuscripts will not be rejected based on absence of these analysis. But we will ask that authors discuss whether or not such analyses would have been useful and acknowledge lack of such analyses as a limitation.

The SAGER guidelines were developed by the Gender Policy Committee of the European Association of Science Editors in 2012-

TABLE SAGER Guidelines Being Adopted by RPTH.

SAGER General Principles		
Use the terms *sex* and *gender* carefully to avoid confusion.		
Research should be designed and conducted in a way that can reveal sex-related differences in the results, even if not initially expected.		
When possible to differentiate by gender, research should be conducted similarly at this level of distinction.		
SAGER Principles by Manuscript Section		
Section	**SAGER Guidelines**	**RPTH Requirements**
Title/ Abstract	If only one sex or gender is included, the sex must be specified (inclusive of human participants, animals and cells, tissues or other materials derived from them)	As stated
Introduction	Report, where relevant, whether sex and/or gender differences were expected	Required for all studies including more than one sex or gender, even if analysis was not done.
Methods	Report how sex and gender were taken into account in study design, whether adequate representation of males and females was ensured, and justification for any exclusion of males or females.	As stated. Include how sex and gender were ascertained. If sex and gender were not taken into account in study design this should be stated explicitly.
Results	When appropriate, report data disagreggated by sex and gender. Report sex- and gender-based analyses regardless of outcome (positive or negative). This includes data on withdrawals and dropouts from clinical trials.	As stated. Such analysis is not appropriate when only one sex or gender is included. Otherwise, if these analyses are not done, it must be explained in the Methods and Discussion
Discussion/ Conclusions	Discuss potential implications of sex and gender on results. If sex and gender analysis was not conducted rationale must be given. Further implications of the lack of such analysis on results intterpretation should be discussed.	As stated, with the addition that lack of such analysis must be discussed as a limitation.

2015. The goal of these guidelines is to "encourage a more systematic approach to the reporting of sex and gender in research across disciplines" and they were created to address the overlooking of sex and gender differences in research design, study implementation, scientific reporting and science communication. These guidelines are recommended or required by many journals and have been referenced in our instructions at RPTH since the journal's inception.

While sex and gender are thought of mostly in relation to clinical studies it is important to consider the role of sex in fundamental science studies too. This includes but is not limited to sex of animals and of cells. While the NIH requires consideration of SABV only for studies of vertebrate animals and humans it is crucial to recognize that sex is genetically determined and applies on the cellular level as well. In 2014 an examination of studies utilizing human cell lines revealed that only 25% specified the sex of the cells [19]. At RPTH we would like to see sex reported on 100% of cell lines for which the information is available.

As with data on race, ethnicity or a surrogate, we consider it best practice to incorporate sex and gender into study analysis. Moving forward, for research involving human subjects and/or tissues, when feasible, authors should report data disaggregated by sex and gender. The methods section should include a discussion of how sex and/or gender information was defined (subject-reported or other). When appropriate, authors should report sex- and gender-based results regardless of outcome (positive or negative). This includes data on withdrawals and dropouts from clinical trials. If addressing these points is infeasible, authors should discuss how it might be a limitation. For fundamental science research, sex of cells and animals should also be reported, and results disaggregated by sex whenever possible, following the same principles as for human research.

RPTH remains committed to publishing the highest quality of research in thrombosis and hemostasis to move our field forward. This requires ensuring findings published are relevant to diverse patient groups or, if not, that the limitations of the research be addressed. At RPTH we have required and observed increasing inclusion of data on race, ethnicity and socioeconomic markers in clinical manuscripts and look forward to seeing increased consideration of SABV and gender in the future.

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