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Addressing the critical role of gender identity and sex in the planning, analysis, and conduct of clinical trials

#MindfulSex&Gender in Clinical Research

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In the clinical research history, the main protagonist has always been the white non-Hispanic men, leaving the secondary roles to underrepresented populations regarding age, sex, gender and ethnicity. This is a problem as many of the clinical research results are generalized to all the population without considering differences in each population's biological and psychosocial factors.

In the medical literature, the terms "sex" and "gender" have been used interchangeably. However, each term represents a different dimension of the human being. Sex is defined as the genetic and biological characteristics that differentiate men and women (Vargas-Trujillo et al., 2007). Whereas gender refers to the roles, expectations, values, attitudes and norms (Vargas-Trujillo et al., 2007) "that people relate to or that societies generally attribute to them" (Franconi et al., 2019). To note, gender identity is independent of sexual orientation and dependent on culture. (Rich-Edwards et al., 2018)

The sex differences have been widely explored throughout the years. (Ngun et al., 2011) (Shansky et al., 2020) (Mosca et al., 2011). For instance, women have a higher life expectancy, increase polypharmacy consumption (Wastesson et al., 2011), and a 2-fold increased risk of presenting adverse drug events (Tharpe et al., 2011), due to genetics and pharmacokinetics when compared to men. Premenopausal women have a lower incidence of coronary artery disease – due to estrogen protection – than their male counterparts; however, the incidence equals in the postmenopausal stage. (Wake et al., 2009) (Shufelt et al., 2018) Also, pain is another biological domain associated with sex differences. For example, Gasparin et al. (2020) has shown that women seem to have a more responsive descending inhibitory pain system (Gasparin et al., 2020). On the other hand, gender minorities, such as transgender or gender-nonconforming, have an increased prevalence of depression and anxiety than non-gender minorities (cis-gender female and male). (Reisner et al., 2016) These are only a few examples of how sex-gender differences may influence all aspects of diseases and treatment. (Miller et al., 2014) (Atiq et al., 2021)

Many governmental entities – like the National Institutes of Health (NIH) – across the world have issued policies regarding the inclusion of women in all phases of research. (Raz et al., 2012) However, the compliance to these policies remains controversial, as some authors insist there is still a sex-gender underrepresentation (Santos-Casado et al., 2019) whilst others deny it. (Labots et al., 2018) A relevant question would be: what should be considered representation? Will this percentage be enough to detect a statistical difference between the sexes?

In clinical research, "gender" is an essential but commonly forgotten variable. It is a determinant of health, influencing the physical and social environments of individuals, the access to healthcare systems, and other resources that affects health. (Rich-Edwards et al., 2018). Pelletier et al. showed that individuals with higher feminine scores (more feminine characteristics) had an increased risk of diabetes, hypertension, family history of cardiovascular disease, and depression and anxiety levels (Pelletier et al., 2015). Moreover, Vogel et al. assessed the differences in smoking characteristics depending on

sexual orientation and gender identity, and they found that transgender individuals smoked more cigarettes per day than cisgender and non-binary individuals (Vogel et al., 2019). The authors hypothesized that this increased consumption might be related to transgenders-specific stressors (Vogel et al., 2019), which would need further study. However, without clinical research targeting this population, these assumptions remain unproven.

Recommendation for future studies

Planning Stage

Future researchers must be mindful of all the challenges regarding this topic, addressing them accordingly (**Figure 1**). First, researchers should decide which term (sex, gender or both) suits the study's objective better. Second, search the literature for evidence of sex-gender differences that may influence the research questions. When evaluating the existing evidence, "consider [the] likelihood of false-positives (especially in context of multiple testing) and false-negatives (especially where statistical power is low)". (Rich-Edwards et al., 2018) Third, provide adequate people skills and basic terminology training to the research staff. Friendliness from the research team has proven to be a facilitator for participation in clinical research (Cardenas-Rojas et al., 2021) and the use of inclusive language may provide a safe, non-judgmental, culturally responsive health care environment (Goldhammer et al., 2021)

Research Design

Based on the scientific evidence in your field of research, select your inclusion and exclusion criteria. Be mindful of the possibility that the reproductive stage and cycle, the environmental factors, the use of exogenous hormones (e.g., contraceptives, hormonal therapy), and its way of administration may impact your results, therefore, collecting these data should be planned.

If the study's objective is to assess a true sex-gender difference, be aware that large sample sizes will be needed, as the increased power is required to detect differences and strength of associations. (Rich-Edwards et al., 2018) Rich-Edwards et al. suggest calculating, separately, the sample sizes needed to detect main effects in men and women and then add them. Considering the sex differences in disease prevalence, expected magnitude of effect sizes, and frequencies of certain exposures. (Rich-Edwards et al., 2018) If a large sample size is not feasible, there are other strategies that could be used, such as stratified randomization by sex-gender or, in the cases of sex, state a priori the use of this variable as a cofactor for the analysis plan.

Recruitment & Adherence

Discuss the feasibility of adding incentives to this part of the population for recruitment and adherence across your team. Due to the gender role associated with women, they are more prone to balance work, child or

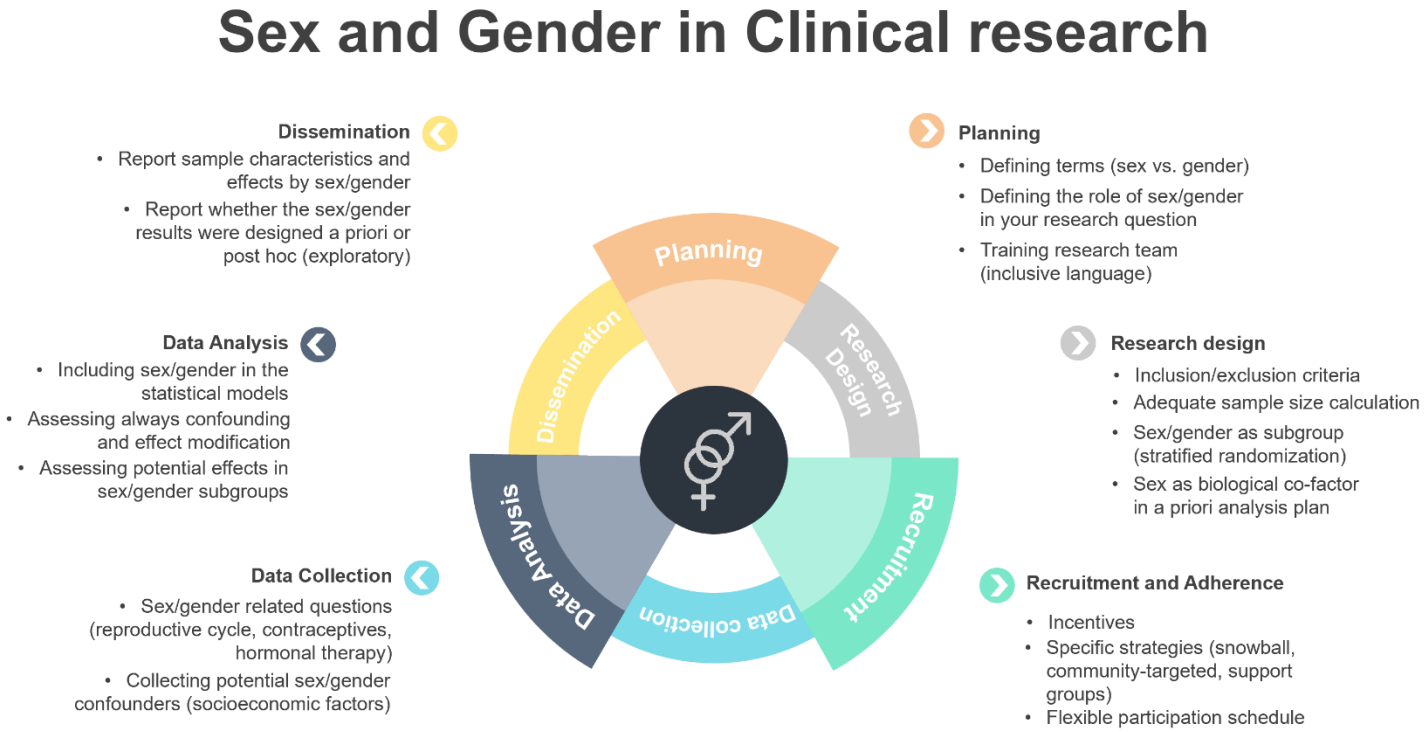

Figure 1. Strategies for integrating sex and gender into clinical research.

elderly care and household tasks, leaving little time to participate in clinical research. It may be easier to recruit a young white male than a woman with young children. Also, the availability of a flexible participation schedule may increase the enrollment and adherence of the research study. (Cardenas-Rojas et al., 2021)

The recruitment of gender vulnerable and often marginalized populations (Roberts et al., 2014) is challenging. Therefore, consider the use of snowball, community-target strategies and reach out to communities or support groups that are conformed by these populations.

Data Collection & Data Analysis

Be mindful of how the reproductive cycle, use of exogenous hormones (contraceptives, hormonal therapy), environmental and socioeconomic factors may impact results and collect this data. When analyzing the results, include the sex-gender variable in the statical models, assessing for confounders and its effect modification. If sex-gender categories were not defined a priori, subgroup analysis could assess the differences.

Dissemination

Report the sample characteristics – if possible, in the manuscript, if not as supplementary material – and the effects by sex-gender no matter the statistical significance. This information can be useful for future hypotheses or meta-analyses of the topic. Nonetheless, if the study's primary objective was not the sex-gender difference, always state the exploratory nature of these calculations and the risk of an underpowered sample size to detect true differences. Moreover, always interpret the sex and gender results considering the biological plausibility and social context. (Rich-Edwards et al. 2018)

In the end, when planning future clinical trials, it is important to give equally spotlight to several different characters, guaranteeing a truly representative sample on the research topic, not only emphasizing the importance of minorities role but also minding every step of the study design's process so the findings can be as significant and accurate as possible.

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