

Integrating Sex-Gender for Informative Clinical Trials: Points to Consider

Overview

Integrating sex-gender considerations into clinical trials facilitates analysis of biological and social variables and gender-sensitive methodologies that support scientific rigor, promote informative discovery, and lead to clinical relevance. The best practices outlined below are designed to inform BMGF's Design, Analyze, Communicate (DAC) approach to capacity building for foundation-funded clinical trials.

Defining Sex and Gender

"Sex" and "gender" have been used interchangeably in the literature, leading to some blurring of meaning. Analytical distinctions typically assign "sex" to biological differences between males and females, whereas "gender" refers to economic, social and cultural attributes and opportunities associated with being male or female in a particular social setting at a particular time.

Best practices for sex-gender considerations in clinical trials

1. Collecting and Reporting Data

Collecting and reporting on sex-gender data provides transparency, allowing for critical assessment of published results, as well as enhancing reproducibility and contributing to meta-analyses. Disaggregation by sex reduces potential for waste in research since if sex-gender data is not disaggregated repetition of studies may be required.

- a. At a minimum, reporting conventions should reflect linguistic and analytical accuracy: Avoid setting males as the standard in language, overgeneralizing where sex specificity may be relevant, or pathologizing normal female biology (e.g., menopause, pregnancy).
- b. Reporting of available data should be accurately rendered, including disaggregation by sex. Even if not including sex differentiation hypotheses in study plans, disaggregation of data by sex is usually desirable.
- c. Even where statistical power is not sufficient for sex-differentiated inferences, clinically meaningful sex differences for primary effectiveness and safety endpoints, and secondary endpoints should be reported, although care should be taken to characterize the data accurately.

2. Investigation of sex-gender factors in studied disease or treatment

Gather all available evidence of sex-gender dimensions in the condition studied including from real world data sources, previous studies, the scientific literature, or disease science. *Have you determined:*

- a. How sex-gender should be represented in the sample? Are there age differences or differences in hormonal profiles in presentation or effect size?
- b. What dose/dosing regimens should be tested by sex? Sex differences in pharmacokinetics that can affect adverse drug reactions?
- c. What other confounders or co-variables might be impacted by sex-gender? Are there gendered social or behavioral factors that influence the condition or treatment, such as education, life stressors, tobacco/alcohol use, or physical activity?

NOTE: Researchers are likely to encounter significant gaps in the existing literature and real world data, given the historic lack of systematic reporting on sex. Current large data sets may have “sex” as a variable, but these should be used cautiously, due to insufficient contextualization, which may lead to clinically meaningless results that appear to be statistically significant.

3. Inclusion: Eligibility criteria should support representative sampling

a. Avoid inadvertent sample bias from inclusion/exclusion factors that skew by sex, such as size, age, or certain medical or social conditions.

b. Special populations

Efforts should be made to include women of child-bearing age, with the appropriate safeguards, as well as women who are pregnant or breast-feeding, or who become pregnant during the trial. These special populations require careful attention to risk-benefit assessments and informed consent, however, given heavy burden of disease, it may be both inaccurate and inequitable to exclude them where safety can be determined.

4. Sensitivity to gender aspects of recruitment, retention and adherence

Gender considerations are often important for efficient and relevant trial enrollment practices, and are critical for protecting women as research subjects.

a. Barriers to and motivations for women’s participation should be evaluated at the local level and addressed accordingly. These might include: access to childcare, family planning, or transportation; interference with work and/or family; financial costs; appropriate knowledge or family/community support.

b. Women should be empowered from the early trial stages in community outreach and in interactions with local authorities.

c. Clinical trials staff with sex-gender training are likely to display less conscious or unconscious bias in conducting trials.

5. Differentiation analyses of sex-gender that are hypotheses-driven

Early in clinical trial planning, investigators should determine whether the hypotheses prospectively built into the study should include testing sex-gender differentiation in treatment interaction or effect modification.

a. Where sex-based hypotheses are determined to be irrelevant or infeasible, there should be a well-explored rationale for not applying them—sex differentiation should not be overlooked or assumed away.

b. At the same time, making inferences about sex differences should be approached with rigorous methodology to guard against type I and type II errors. Post hoc analyses should be avoided or carefully labeled as such.

c. Resources required to sufficiently power studies to detect sex differences may not be warranted where differences are not likely to be clinically meaningful. Most analyses of sex differences will require a sample size that is up to four times a non-differentiated study. Bayesian statistical methodologies may help to reduce this requirement.

TOOLS

Baseline

- Stanford [Health & Medicine Checklist](#)
- [NIH Inclusion Checklist](#)
- CIHR: Key considerations for the appropriate [integration of sex as a biological variable](#)
- Nieuwenhoven (2010) Scientific Excellence in [Applying Sex- and Gender-Sensitive Methods](#) in Biomedical and Health Research
- Sex and Gender in Biomedical and Health Research: [Gender Awakening Tool](#)

More developed Roadmaps

- Franconi (2019) [Sex-Gender Variable](#): Methodological Recommendations for Increasing Scientific Value of Clinical Studies
- Rich-Edwards (2018) [Sex and Gender Differences Research Design](#) for Basic, Clinical, and Population Studies: Essentials for Investigators
- Day (2017) [Essential metrics](#) for assessing sex & gender integration in health research proposals involving human participants
- The [NIH](#) site includes a [curated list](#) of news and journal articles related to sex and gender in health research going back to 2013.

Regulatory guidance

- EMEA (2005) [Gender Considerations in Clinical Trials](#)
- FDA (2014) [Evaluation of Sex-Specific Data](#) in Medical Device Clinical Studies
- Health Canada (2013) Considerations for [Inclusion of Women in Clinical Trials and Analysis of Sex Differences](#)

Women as subjects in medical research: Resources

- [Women as Subjects of Research](#) (Stanford)
- NIH [Outreach Notebook](#), Section 4 on Recruitment and Retention of Women and Minorities
- Couderc-Petry (2020) [Inclusion of women susceptible to and becoming pregnant](#) in preregistration clinical trials in low- and middle-income countries: A proposal for neglected tropical diseases. (Includes an algorithm for inclusion decisions.)

Pregnancy and clinical trials

- FDA Draft Guidance (2018) [Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials](#)—Guidance for Industry
- FDA ORWH (2010) [Enrolling Pregnant Women in Clinical Research](#) and related PPT:
- Feibus and Goldkind (2010) Pregnant Women & Clinical Trials: Scientific, Regulatory, and Ethical Considerations [“Getting your brain around medicine use in pregnancy” [www.fda.gov](#) media download]

- FDA Draft Guidance (2004) [Pharmacokinetics in Pregnancy: Study Design, Data Analysis, and Impact on Dosing and Labeling](#)
- Pregnancy and vaccine development
 - Krubiner (2019) [Pregnant women & vaccines against emerging epidemic threats](#): Ethics guidance for preparedness, research, and response
 - Jones (2016) [Guidance for the collection of case report form variables to assess safety in clinical trials of vaccines in pregnancy](#)
 - Munoz (2013) [Research on vaccines during pregnancy: Protocol design and assessment of safety](#)
 - Sheffield (2013) [Research on vaccines during pregnancy: Reference values for vital signs and laboratory assessments](#)

Other works referenced

Bothwell (2017) [Adaptive design clinical trials](#): a review of the literature and ClinicalTrials.gov

Chukwunke (2012) [Enrolment and Retention of African Women in Biomedical Research: the Challenges](#)

Cirillo (2020) [Sex and gender differences and biases in artificial intelligence for biomedicine and healthcare](#)

Clayton (2017) [Applying the new SABV](#) (sex as a biological variable) policy to research and clinical care

Cutland (2015) [Lessons learnt from enrolment and follow up of pregnant women and their infants in clinical trials in South Africa](#)

Duke-Margolis Center for Health Policy (2016) [Biologic Variability to Drug Response: Sex Differences in Clinical Trials](#) (meeting summary)

Gomes (2017) [Protected to death](#): systematic exclusion of pregnant women from Ebola virus disease trials

Klap (2019) [Designing studies for sex and gender analyses](#)

Klein (2020), [The impact of sex and gender on immunotherapy outcomes](#)

Lobato (2014) [Impact of gender on the decision to participate in a clinical trial](#): a cross-sectional study

Mills (2006) [Enrolling Women into HIV Preventive Vaccine Trials: An Ethical Imperative but a Logistical Challenge](#)

Smith (2020) [Exclusion of Pregnant Women from Clinical Trials](#) during the Coronavirus Disease 2019 Pandemic: A Review of International Registries

Wallach (2016) [Sex based subgroup differences in randomized controlled trials: empirical evidence from Cochrane meta-analyses](#)

Zucker (2020) [Sex differences in pharmacokinetics predict adverse drug reactions in women](#)