SEX AND GENDER IN CLINICAL RESEARCH

TRAINING FOR INCLUSION

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History of sex and gender considerations in research.

Why consider sex differences?

Status of sex differences considerations in research here at Penn.

What is considered to be adequate justification?
WOMEN’S HEALTH RESEARCH TIMELINE

- Thalidomide Tragedy
  - US Congress passes the Kefauver-Harris Amendment to strengthen FDA Authority

- 1965
  - Pregnant Women Vulnerable research subjects
  - FDA Ban

- 1975
  - US PHS Task Force on Women’s Health
  - “research should focus on diseases specific or more common to women”
  - NIH Committee
  - Must provide Rationale if women are not included in research

- 1977
  - FDA REQUIRES 1977 BAN
  - CONGRESS MANDATES INCLUSION

- 1985
  - NIH OFFICE OF WOMEN’S HEALTH RESEARCH IS FORMED

- 1986
  - IOM REPORT: Attention on historical gender bias in research
  - FDA mandates that new drug applications provide safety data by sex

- 1990
  - IOM Report
  - “DOES SEX MATTER?”

- 1993
  - 1994
  - 1998
  - 2001
  - 2010
  - 2014
  - IOM Report
  - Highlights progress and continued deficiencies

SEX AS A BIOLOGICAL VARIABLE
WHY CONSIDER SEX DIFFERENCES?
SEX DIFFERENCES IN PREVALENCE OF COMMON DISORDERS
MEN AND WOMEN DIFFER IN RESPONSE TO PHARMACOLOGIC TREATMENTS

Low Dose Aspirin for the Primary Prevention of Myocardial Infarction: The number one killer of both males and females

- Physicians Health Study (circa 1989)
  - Over 20,000 male physicians
  - Decreased (44%) risk of myocardial infarction
  - Slight increased risk of stroke

- Women’s Health Study
  - 39,000 women followed on average for 10 years
  - NO effect on risk of myocardial infarction
  - Reduced risk of stroke

Ridker et al, JAMA, 2005;352:1293-1304,
Glynn et al., JAMA, 1994;154:2649-2657
FEMALE SEX IS A RISK FACTOR FOR ADVERSE EFFECTS OF MANY PHARMACOLOGIC AGENTS

- 10 prescription drugs removed from the US market between 1997 and 2001
  - 8 drugs were found to have greater adverse effects in women than men.

Zolpidem Story
- Approved in the 1990s for the short-term treatment of insomnia
- FDA enforced labeling changes in 2013
- Women may require a lower starting dose due to increased risk of early morning sedation.

- Lipitor- can cause Type II diabetes in women
- Accutane- fetal malformations
- Hip Replacement- 29% higher failure rate in women
Advertisements Targeted Women

Darvon and Darvocet
Opioid pain relief.
Serious cardiac toxicity
More than 2000 deaths over 18 years
Marketed for 55 years
1955-2010
“Really?”

Yes... desPLEX®

To prevent abortion, miscarriage and premature labor

recommended for routine prophylaxis in ALL pregnancies...
Including Females

Excluding Females
STATUS OF SEX DIFFERENCES RESEARCH AT PENN

REVIEW OF RECENT IRB PROTOCOLS FOR INCLUSION OF SEX/GENDER DIFFERENCES CONSIDERATION

University of Pennsylvania

HS-ERA
Human Subjects Electronic Research Application
Methods

- Vice Provost for Faculty, Anita Allen: Diversity Pilot Funding Program
- Emily Hartshorne Mudd Summer Research Fellowship
- Key Terms “Sex” and “Gender”
  - Reviewed all 240 for a 2nd time to add search for terms “male” “female”, ”men”, or “women
- Where were term(s) mentioned in the IRB protocol
- Review literature to determine strength of evidence supporting sex or gender differences in proposed area of investigation.
SOURCES OF FUNDING

- Pharmaceutical: 33%
- National Institutes of Health: 20%
- No Funding: 21%
- Penn Internal Grant or Funds: 5%
- Foundation: 5%
- Other Funding: 16%
STRENGTH OF LITERATURE INDICATING SEX DIFFERENCES

- 0: Literature does not suggest that there are sex differences.

- 1: Literature suggests that there may be sex differences, but studies are small, from only one lab, or not well controlled.

- 2: Literature suggests that there are sex differences in at least 1 aspect of the topic under investigation. Studies may be small but come from multiple research groups or have been replicated.

- 3: Literature suggests that there are sex differences in at least 2 aspects of the topic under investigation. Studies many be small but come from multiple research groups or have been replicated.

- 4: Literature suggests that there are sex differences in at least 2 aspects of the topic under investigation. Studies are large and from multiple groups.

- 100: There is no research that directly studies sex differences for this disorder or condition.
EVIDENCE FOR SEX DIFFERENCES

- No sex differences: 63%
- There may be sex differences: 26%
- Sex differences in at least two aspects: 14%
- Sex differences in at least two aspects, studies are large, from multiple groups: 18%
<table>
<thead>
<tr>
<th>RATIONAL FOR KEYWORD</th>
<th>Protocols studying topic with significant sex AND/OR gender differences</th>
<th>Protocols studying topic with no or little evidence of sex or gender differences, or have not been studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible impact on primary outcomes</td>
<td>3 (1.9)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Rationale for choosing particular study population</td>
<td>7 (4.5)</td>
<td>17 (20.2)</td>
</tr>
<tr>
<td>Inclusion/exclusion criteria, reason not specified</td>
<td>5 (3.2)</td>
<td>4 (4.8)</td>
</tr>
<tr>
<td>Inclusion/exclusion criteria, regarding pregnancy</td>
<td>72 (46.2)</td>
<td>29 (34.5)</td>
</tr>
<tr>
<td>Stating the population that will be studied</td>
<td>46 (29.5)</td>
<td>16 (19.0)</td>
</tr>
<tr>
<td>Data that will be collected or recorded, reason not specified</td>
<td>5 (3.2)</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Provides background</td>
<td>10 (6.4)</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (4.5)</td>
<td>5 (6.0)</td>
</tr>
</tbody>
</table>
In summary, the majority of studies protocols proposed at Penn focus on conditions for which the literature indicates an important sex or gender difference.

The majority of protocols do not mention terms related to sex or gender.

Less than 5% of protocols indicated that sex or gender would be considered in the data analysis.
WHAT IS ADEQUATE JUSTIFICATION?
IT DEPENDS

- Disorder, procedure or treatment in question is specific to one sex.
  - Uterine or ovarian cancer
  - Prostate cancer

- Prevalence of the disorder is significantly greater in one sex such that focusing solely on that sex is warranted at this stage.

- Regardless of the reason.. When investigators are proposing to study one sex, the NIH will expect an explanation.
How can the IRB help?
Considering Sex and Gender Differences in Clinical Research:
Our goal is to assist you in addressing the National Institute of Health mandate to consider sex as a biological variable (SABV) in clinical research. Please consider the following resources or contact Penn PROMOTES Research on Sex and Gender in Health for more information.

Penn PROMOTES Research on Sex and Gender in Health
https://www.med.upenn.edu/penn-promotes/


NIH Office of Research on Women’s Health
https://orwh.od.nih.gov/

Canadian Institutes of Health Research
http://www.cihr-irsc.gc.ca/e/8673.html
4.2 Exclusion Criteria

List of criteria that would exclude a subject from study enrollment.

For example:

- Prior diagnosis of prostate cancer
- Alcohol consumption greater than 12 drinks per week
- Participation in another clinical trial within 3 months of the current study
- Medications which may exclude a subject from the study

Suggesting a new 4.3 here

4.3. Will this study enroll both males and females?  □  Yes  □  No

________

If no, please provide a brief rationale for choosing to study only one sex.

4.3 Subject Recruitment
8.4 **Statistical Methods**

Summarize the overall statistical approach to the analysis of the study. The section should contain the key elements of the analysis plan, but should not be a reiteration of a detailed study analysis plan. Logistically it is easier if the full Statistical Analysis Plan is maintained as a “stand-alone” document that can undergo edits and versioning outside of the protocol and therefore each revision does not trigger an IRB re-review—AS LONG AS THE KEY ELEMENTS OF THE ANALYSIS PLAN DO NOT CHANGE.

Be clear on primary as well as any applicable secondary analyses. Examples of common analyses are included below. Please note all of these may not all be applicable to your study.

*Please include discussion of statistical plan to examine impact of sex on primary and/or secondary outcomes or reason such analyses are not warranted at this time.*
Given the prevalence of sex and gender issues in research being conducted at Penn and that we believe the best science should take these into consideration...

- Penn is missing many opportunities to improve the scientific quality of our research product.

- By adding a clear and rational focus on sex and/or gender in IRB protocols at the time of submission, pilot projects would lead to more competitive NIH application.
Penn PROMOTES Research on Sex and Gender in Health
https://www.med.upenn.edu/penn-promotes/

Bale TL, Epperson CN.

NIH Office of Research on Women’s Health
https://orwh.od.nih.gov/

Canadian Institutes of Health Research
http://www.cihr-irsc.gc.ca/e/8673.html
Reporting a sex difference in a dependent variable requires that the measurements for females and males be compared using a single statistical test that allows an assessment of the statistical significance of the sex variable.

For example, if one is testing the effect of a treatment (treatment vs. control) on males and females, an appropriate test would be a 2-way ANOVA, with factors of sex and treatment.

Concluding that a sex difference exists would be supported by a statistically significant main effect of sex, or a significant interaction of sex and treatment. It is usually not sufficient to show a significant treatment effect in one sex but not the other, using one statistical test for each sex.