What Women Want:
Taking Sex Differences Seriously in Clinical Trials

Understanding the Biology of Sex and Gender Differences, July 16-17, 2001, Washington, DC, USA

In clinical research, sex matters. What is more, sex-related data from clinical trials need not cost a fortune and might save a trial from failure. These were the take-home messages from the July 16 Scientific Advisory Meeting: Response to the Institute of Medicine Report, and July 17 workshop —Subgroup Analysis and Statistical Design for Clinical Trials— held by the Society for Women's Health Research in Washington, DC. The gatherings were held to follow up the report 'Exploring the Biological Contributions to Human Health: Does Sex Matter?' published in April by the Institute of Medicine (IOM).

Extensive research demonstrates that differences between male and female physiology extend far beyond the realm of reproduction (Table 1). At the Society, based in the capitol, it is gospel that taking sex into consideration in clinical trials will ultimately improve the health of women and men alike. Elsewhere though, this point of view has been slow to take hold. By promoting awareness of the IOM report, the Society hopes to move more researchers in its direction.

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"From womb to tomb"

The IOM is a nonprofit organization operating under the congressional charter granted to the National Academy of Sciences. The Society's conference on July 16—Scientific Advisory Meeting: Response to the Institute of Medicine Report—served to reinforce the conclusion of the IOM report's blue ribbon panel of basic and clinical researchers that sex counts in basic as well as clinical research.

The report evaluates the state of knowledge regarding sex-based biological differences, especially outside of reproduction and behavior where such differences are most expected. It concludes that the effects of reproductive hormones do not explain all the differences between male and female physiology. Understanding these differences should improve disease prevention, diagnosis and treatment. Therefore, "sex should be considered when designing and analyzing studies in all areas and at all levels of biomedical and health-related research." In fact, sex should be an experimental variable whenever possible, advises report editor Mary-Lou Pardue of the Massachusetts Institute of Technology: "…from womb to tomb." The report advocates research on sex differences and similarities for every human disease that affects both sexes.

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Clinical researchers should determine the occasions when men and women respond differently to drugs. A sex-based difference in response can exist for a variety of reasons. Factors that are sometimes important for drug safety and effectiveness are that women weigh less than men and have a larger percentage and distribution of body fat. There are also drug metabolism differences, so one would not necessarily expect the same dose to be suitable for both sexes. The report also advises that clinical researchers should find out whether data from female volunteers is affected by the menstrual cycle and hormone replacement therapy.

The consensus at the conference was that the IOM report validates the Society's position on sex difference research. It makes "...a case that women's health [research] isn't just about being nice to the ladies, of giving them their long overdue share," states Wanda Jones, Director of the Office on Women's Health at the US Department of Health and Human Services. "Women's health research has benefits for men as well."

"What we are asking is that researchers take seriously the possibility that there might be sex differences in whatever they are measuring. We want them to design studies to reveal those differences, and to report what they find," says Sherry Marts, Director of Scientific Programs at the Society. That is especially applicable for clinical trials, where the areas that should be examined for sex differences include pharmacokinetics, pharmacodynamics, safety and side-effects. In some cases, this would mean testing men and women with different drug doses during clinical trials.

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Table 1. The biology between the sexes.

Many studies find differences in men and women that may have a bearing on medical practice. Examples from the past 10 years:

- Women mount more aggressive immune responses to infections and are more likely to develop autoimmune diseases
- Nicotine replacement therapy is more effective in male smokers. The risk of developing lung cancer from smoking might be higher in women
- Women might be better protected than men against language impairment from a left-sided stroke. Men rely on the left side of the brain for language, while women use both sides
- Women will progress to AIDS with about half the viral load counts required for men
- Women are much more likely to develop life-threatening ventricular arrhythmia or torsades de pointes from a variety of drugs, including antihistamines, antibiotics, antimalarial drugs, cholesterol-lowering agents, and antiarrhythmia drugs
- Women's blood alcohol levels are higher than men's after consuming comparable amounts of alcohol. Women break down alcohol more slowly because they produce less gastric alcohol dehydrogenase. Ethanol has a more sedating effect in women
- Men synthesize serotonin at a rate 50 percent higher than women. This could partly explain why women are two to three times more likely to experience depression
- Ibuprofen is a more effective painkiller for men than women
- Pentazocine, acting at the kappa opioid receptor, provides more post-operative pain relief in women than men
- The sexes tend to have different heart attack symptoms. Chest pain is most common in men while women's symptoms can be subtler—abdominal pain, fatigue and nausea. Cardiovascular disease deaths are declining in men and increasing in women. Men have heart attacks nearly 10 years earlier than women, yet have a better 1-year post-attack survival rate than women
- A liver transplant is significantly less likely to be successful when the liver is donated by a woman

Source: Society for Women's Health Research.

Sex, money and power

The following day, July 17, the Society held a workshop about discovering differences between men and women participating in clinical trials, and how best to use that information. Historically, clinical trials have not been designed to detect sex differences.

Enrolling women in clinical trials is, for the most part, no longer a problem. A US Food and Drug Administration (FDA) survey of clinical trials between 1995 and 1999 showed that women made up half of all the participants in Phases II and III. Only in Phase I were women under-represented, constituting only 30% of those enrolled. Women can no longer be excluded from clinical trials of drugs for life-threatening diseases solely because

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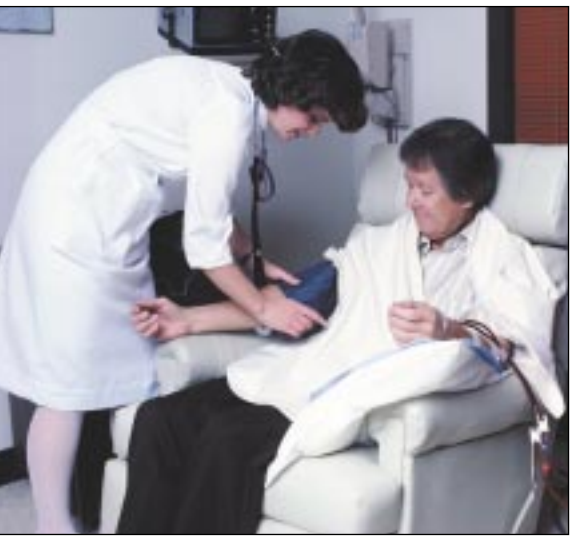

they might get pregnant. As of 1998, the FDA requires investigational new drugs (INDs) and new drug applications (NDAs) to present data by sex, race and age. However, there is no required reporting format, or level of participation and no requirement to demonstrate that differences are statistically significant—"You present your data as you have it," says Susan Wood, Director of the FDA Office on Women's Health.

There are often too few women enrolled in trials to determine whether sex differences are statistically significant. In statistician's jargon, these trials are 'under powered' for determining statistical significance. Inadequate power, in turn, creates a publication problem, says Wood. Journal editors often decline to publish data on sex differences if statistical significance has not been demonstrated, and frequently consider findings of no difference as not worth publishing.

Improving the chances of obtaining statistically significant data often simply requires the enrollment of more women. But obtaining this sex-specific data by increased enrollments implies that, "…clearly the costs would go up," says Michael Kafrissen, Vice President for Clinical Affairs at Ortho-McNeil Pharmaceutical in Raritan, NJ. Kafrissen worries that if these costs get too high, companies will cancel the development of a wide range of drugs, on the grounds that they would not make enough money to justify development costs. Drugs that might fit that category are those earning less than US$ 300–400 million a year, he says.

Mention of money brings the workshop to its theme—getting and using sex difference data without breaking the bank. "There are several ways to approach this [problem] that aren't the classical 'power the study to statistical significance' approach," says Marts. Carl Peck, the Director of the Center for Drug Development Science at Georgetown University in Washington, DC, and a former director of the FDA Center for Drug Evaluation and Research, agrees. Adequately powered trials for subgroup analysis of men and women could mean enormous cost increases in clinical trials. Peck advises that if women want drug companies to look for sex differences, they should offer companies cost-effective ways of doing it.

Peck's proposal: Sex data early and cheap

In Peck's opinion, companies resist the whole notion of different doses for men and women. 'One dose fits all' is what marketing managers want, so companies have little incentive to gather information supporting sex-tailored doses. "I am actually quite skeptical of the drug label that says there are no [sex] differences," he declares, "because I know how these data are obtained and analyzed, and because of the negotiations to go on between sponsors and the FDA."

Looking for sex differences should begin in Phase I but, according to Peck, drug companies tend to use only young men in the Phase I trials upon which Phases II and III are based. Often they delay using women in Phase I trials until Phases II and III are completed or well underway. But this delay has a drawback—if pharmacokinetic studies in Phase I indicate that men and women should receive different doses or that a drug is safer for one sex than the other, it is too late to use that knowledge in Phases II and III.

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The high point of the workshop was Peck's proposal of a low-cost way to obtain sex-related data in Phase I. "I suggest that we encourage an emphasis on men in the first part of Phase I trials where pharmacokinetics, metabolism and early safety pharmacodynamics data are gathered," he says. In a typical trial there might be 18 young men. The trial would then be extended to an identical study with one-third as many young women. What comes next is of key importance: Bayesian statistical methods are used to estimate female distributions of pharmacokinetics and pharmacodynamics, given the male distributions. "In other words, make the initial assumption that women are not different from men. Use the Bayesian method to evaluate the distributions for women given the men's [distributions], and see whether the analysis makes sense."

"If you determine that the female distributions are very different," Peck proposes, "for example, that [drug] clearance is three times faster in females than males, then you should intensively study women to understand these differences." Sex-specific information would then be used prospectively to design Phases II and III. Sex-tailored doses would only be utilized if a need for this was indicated by the Phase I trials. "On the other hand, if you find the distributions are similar, you proceed to Phase II under the assumption that there are not major differences." Peck recommends enrolling numbers of men and women in Phases II and III to reflect their proportions in the drug's target population.

There is an ethical concern about exposing women unnecessarily, because of the unknown affect of a drug on female germ cells. Peck believes it would be possible to closely monitor the handful of women in Phase I to make sure that they do not become pregnant, and to use blood level measurements to prevent overdoses. "I would feel more comfortable, if my daughter were enticed into a Phase II or III trial, that at least six young women had

been previously compared with 18 normal males in a Phase I trial," he summarizes, "because I know that even in those highly defined populations you are likely to find systemic differences if they exist."

If sex-related doses are important, it follows that ignoring them could jeopardize a trial. A case in point is tirilazad, a drug for stroke and spinal cord injury. According to Peck, after the drug failed in clinical trials, post-mortem analysis determined that the sponsor had set doses too low for both men and women. The dose was especially low for women, who cleared tirilazad so quickly that they effectively received only one-third as much as the men. Had tirilazad's early pharmacokinetic analysis been timely and correct, and had sex-tailored doses been used in the trials, Peck believes that the FDA might have approved it. Tirilazad was "a probable winner that became a preventable loser."

Investigators from outside drug companies will also carry out clinical research into sex-differences. Studies by academia and government will analyze published clinical data and FDA reports to identify differences between women and men. An example is an FDA project examining whether adverse drug reactions affect women more often than men. This study, directed by FDA Medical Officer Ana Szarfman, sifts through the FDA's Spontaneous Reporting System Database looking for correlations between sex and adverse drug reactions. With over 30 years of safety information on approved drugs and over two million records, the database serves as an early warning system for drugs that might cause unexpected trouble. However, the database is imperfect—for instance, selection-bias and under-reporting are potential problems. The challenge, says Szarfman, is to use statistical methods that overcome these flaws to identify consistent, nonrandom patterns of adverse events that are reported more often than expected. The statistical tools developed for the study could indicate opportunities for developing new drugs and someday aid the day-to-day safety monitoring of new products.

'One dose fits all' is what marketing managers want: consequently, companies resist the notion of sex-tailored doses and have little incentive to gather any information supporting this

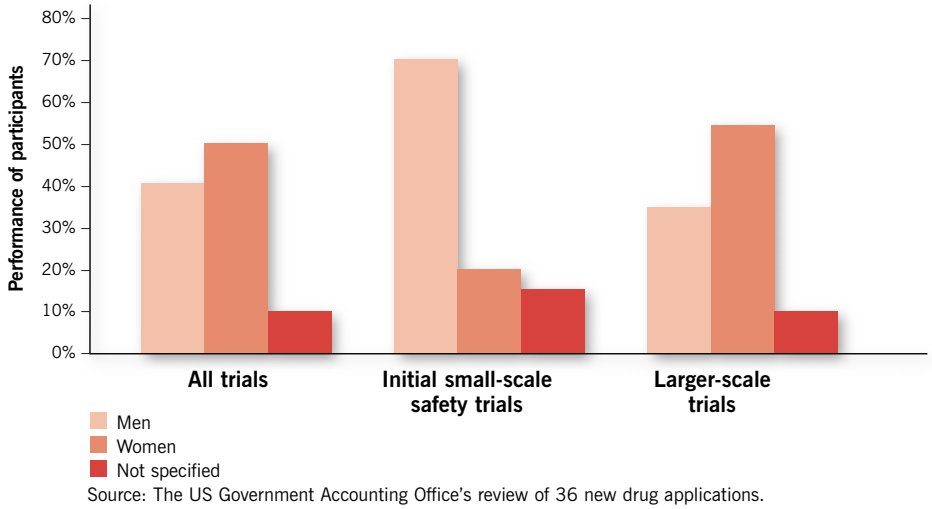
The FDA needs help

Improving the FDA's ability to notice sex-based differences is a move in the right direction, according to the US Government Accounting Office (GAO). A GAO report published in July 2001 concludes that the FDA has allowed drug sponsors to ignore its 1998 regulations for reporting sex-difference data. In a survey of NDA summary documents of drugs approved by the FDA between August 1999 and December 2000, the GAO found that 22% failed to provide separate efficacy data for men and women, and 17% omitted sex-based safety data (Fig. 1). The sponsors had the information, according to the GAO, but did not report it.

The GAO faults the FDA for not having a management system in place to track the inclusion of women in clinical trials and monitor compliance with regulations. The GAO also notes that FDA medical officers have not been required to discuss sex differences in their reviews. Consequently, the "FDA is unaware that many NDA submissions fail to meet requirements."

The GAO notes that the FDA is beginning to address these problems. But solutions will call for greater resources, says the Society's CEO, Phyllis Greenberger. She calls on Congress to increase FDA appropriations for a database to monitor the inclusion of women in all stages of medical research. Congress should also give the FDA more money for training, she believes. The FDA did a good job training medical officers about sex-based data after its 1993 guidelines were issued, says Greenberger, but had problems following through later as veterans departed and new medical officers came aboard. CR

Figure 1. Participants in clinical drug trials by sex.



Source: The US Government Accounting Office's review of 36 new drug applications.

Further information

The Institute of Medicine report, **Exploring the Biological Contributions to Human Health: Does Sex Matter?** is available from: National Academy Press. Tel: +1 800 624 6242. The full text of the report is available on the Web at: www.nap.edu/catalog/10028.html

The GAO report, **Women's Health: Women Sufficiently Represented in New Drug Testing, But FDA Oversight Needs Improvement**, published July 6, 2001, is available on the web at: www.access.gpo.gov/su_docs/aces/aces160.shtml
(Search for the report using its record number, GAO-01-754, enclosed within quotation marks)

www.womens-health.org
(The Society for Women's Health Research)