Enrollment and Monitoring of Women in Post-Approval Studies for Medical Devices Mandated by the Food and Drug Administration

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Abstract

Background: Disease presentation, prevalence, and treatment effects vary by sex, thus it is important to ensure adequate participation of both sexes in medical device post-approval studies (PAS).

Methods: The goals of this study were to determine the participation rate of women in PAS mandated by the Food and Drug Administration (FDA) and if participation varied by clinical area. The study also evaluated the frequency in which enrollment by sex is reported by applicant reports and FDA reviews, as well as the frequency in which final study reports analyze whether outcomes differ by sex.

Results: Of 89 studies with enrollment completed, data on sex of participants were available in 93% of submitted reports, while data on enrollment by sex was evaluated and noted in 43% of FDA review memos. Study participation varied by clinical area, with female participation ranging from 32% in cardiovascular PAS to 90% in PAS for reconstructive devices. Of 53 completed studies, data on enrollment by sex was provided in 49 of the final reports. Of these 14% included a multivariate analysis that included sex as a covariate and 4% included a subgroup analysis for female participants.

Conclusions: Data on sex was not routinely assessed in FDA reviews. Based on these findings, FDA implemented new procedures to ensure participation by sex is evaluated in PAS reviews. FDA will continue working with applicants to develop PAS that enroll and retain proportions of women consistent with the sex-specific prevalence for the disease or condition the device is used to treat.

Introduction and Background

THE INCLUSION OF WOMEN in studies designed to evaluate medical device performance is crucial due to potential sex-related differences in device safety and effectiveness. Some medical devices may elicit different responses in women compared with men due to intrinsic factors (e.g., genetics, hormones, body size, sex-specific physiology), extrinsic factors (e.g., diet, sociocultural issues, environment) or interactions between these factors.^{1,2,3} Factors such as body size, age, or comorbidities may be responsible for differences in safety or effectiveness of some devices.^{4,5,6,7} Additionally, fluctuations associated with hormonal changes (e.g., onset of puberty, pregnancy, menopause, oral contraceptive or hormone replacement therapy use) may impact the clinical outcomes in women.

Several studies utilizing data from the American College of Cardiology–National Cardiovascular Data Registry have shown that women have almost twice the risk of adverse events

following cardiac catheterization.^{4,5,6} Alternatively, studies have suggested that women may derive a greater benefit from cardiac resynchronization therapy than their male counterparts.^{8,9}

Examples of differential response to treatments are not limited to cardiovascular devices. Differences between men and women with respect to conditions affecting the knee are well recognized.¹⁰ A meta-analysis of clinical studies published between 2000 and 2010 shows that sex has been shown to impact pain and function after total knee arthroplasty. Women have worse knee function and their reported pain is higher than men following the procedure.¹¹ Alternately, men may be at higher risk of revision surgery than women.^{11,12}

The Food and Drug Administration (FDA) has identified the importance of female participation in medical device trials and adequate representation of populations most likely to use a medical device. Accordingly, the FDA has conducted further evaluations and instituted policies to promote the participation of women in clinical trials. The 1994 Center for

Devices and Radiological Health (CDRH) Report on women's participation in clinical trials examined Pre-market Approval Applications (PMAs) that were not inherently sex-biased (i.e., obstetrics and gynecology, more often women; urology, more often men). In this report, data from publicly available summaries of safety and effectiveness data were reviewed for PMAs approved between 1985 and 1994. A weighted average of the number of female patients at different time periods of the PMA trial (enrollment, treatment, or completion) was calculated to estimate the level of women's participation in clinical trials for medical devices. Out of 55 PMAs included in the analysis, 5 had female enrollment between 45% and 49% and 24 had female enrollment over 50% (CDRH Report on Women's Participation in Clinical Trials Project, unpublished data).

A recent FDA report entitled *Collection, Analysis, and Availability of Demographic Subgroups for FDA-Approved Medical Products* was published in August 2013.¹³ An evaluation of 33 unique data sets for PMAs approved in 2011 showed that all PMA applications reported enrollment by sex. Representation of women varied by clinical area, with female enrollment of 18% for endovascular occlusion devices to approximately 90% for devices for facial wrinkle correction and fecal incontinence. Age range was reported in 29 (88%) of the PMA applications and race or ethnicity was reported in 23 (70%) applications. Of the 33 PMAs evaluated, 8 contained a second pivotal study cohort, which was designed to obtain clinical experience on a specific subpopulation. This included several cardiovascular PMAs that evaluated patients in the primary cohort and in patients with small blood vessels. FDA frequently considered demographic and subset analyses in PMA applications; 88% included a sex analysis, 70% included an age analysis, and 27% included a race or ethnicity analysis. Subgroup analyses were done more often than were presented in the device labeling or summaries of safety and effectiveness where 63%, 57%, and 16% including subgroup analyses on sex, age, and race or ethnicity, respectively.¹³

While these analyses were performed on PMAs, the corollary has not been performed to assess enrollment of women in post-approval studies (PAS), studies that are imposed as conditions of PMA approval to help ensure the continued safety and effectiveness of an approved device.^{14,15} A post-approval study required as condition of approval may be a clinical or nonclinical study, and is intended to gather specific information to address questions about the postmarket performance of, or experience with, an approved medical device.¹⁴ Since approximately 50% of PMAs and humanitarian device exemptions (HDEs) that were approved since 1995 have had one or more mandated PAS requirements¹⁶ and sex differences can impact the effectiveness and safety of medical device interventions, we conducted a study evaluating the participation of women in post-approval studies mandated by the FDA.

The goals of this study were to determine the overall participation rate of women in post-approval studies mandated by the FDA and evaluate if female participation varied by clinical area. Additional goals were to evaluate the frequency in which sex is (1) reported in interim or final study reports, (2) evaluated in FDA review of submitted reports, and (3) to determine if final reports submitted by the applicant

include evaluation of sex differences on safety and effectiveness outcomes.

Methods

Study design and data collection

This study was a retrospective evaluation of all clinical PAS required at the time of PMA or HDE approval. Medical devices approved with a PAS requirement were identified using the internal FDA submission tracking system. Eligible studies were those mandated by PAS required between September 1, 1991, and December 31, 2010, and had an applicant report submitted between January 1, 2005, and September 30, 2012. Data was abstracted from applicant reports, FDA reviewer assessments ("review memos") and applicant responses to FDA questions. For ongoing studies, the latest annual PAS report was used, while for completed studies, the final PAS report was used. Applicant submitted reports were available as an electronic file obtained from CDRH document storage system. FDA review memos were available in the Division of Epidemiology (DEPI) electronic document storage. Data on device intended population (male only, female only, both sexes), type of study performed, study progress (all patients enrolled, study pending, protocol pending, study on hold, or study terminated), and clinical area were abstracted from the reports.

From the eligible studies, information on the number of total enrollees, and the number of men and women enrolled in the study was recorded for studies where target enrollment was reached. Studies that included a summary of the study population stratified by sex or had sex listed in the demographic characteristic table were noted. From the final report, instances where sex was evaluated as a confounder or effect modifier of the final safety or effectiveness results were tabulated. The inclusion of either multivariate analyses and/or subgroup analyses was recorded. Follow-up data and responses to FDA inquiries for additional data and analyses were included in the evaluations.

From the FDA lead reviewer memo, information on the discussion or presentation of the enrollment of men and women in the study was tabulated. The frequency with which the FDA reviewer discussed or evaluated study enrollment by sex was recorded. Reviews were classified as either including or not including information assessing the sex of enrolled participants. Reports and review memos were reviewed independently by two reviewers (NH and EP) to ensure the accuracy of the data. Data were entered into an Microsoft Excel[®] spreadsheet. Data are presented as numbers and percentages.

Results

Data from 258 post-approval studies for 196 approved medical devices with a mandated PAS were reviewed. Of the 258 studies, 33 studies were excluded because they were for devices intended to treat only one sex (29 female only and 4 male only). There were a total of 225 studies required for devices used to treat a disease or condition that occurs in both men and women. Also excluded were 21 studies that did not evaluate human subjects (e.g., bench testing, fatigue testing, or enhanced surveillance systems). The 5 studies that included the same participants to fulfill two PAS requirements

FIG. 1. Status and design of post-approval studies as of September 30, 2012.

were counted once. Additionally, we excluded studies where the study protocol was under review, had not begun participant enrollment, or were terminated prior to completion or placed on hold (Fig. 1).

Data on sex of participants were available in 89 of the 96 applicant submitted reports where enrollment was completed (93% of studies). It was not possible to determine the representation by sex in the FDA review of 7 (7%) of the applicant submitted reports. Data on enrollment by sex was evaluated and noted in 43 (45%) FDA review memos.

Participation by sex

The 89 studies where enrollment was complete and sex was reported by the applicant comprised a total of 45,535 participants. These studies ranged in size from 4 to 6,412 participants, with average study size being 511 ± 874 . Overall, 18,643 (41%) of participants were women and 26,865

(59%) were men. Study participation varied by clinical area (Table 1). Female participation ranged from 32% in cardiovascular PAS to 92% in PAS for dental devices. Plastic and reconstructive, ophthalmic, renal and urologic, and orthopedic devices had greater than 50% female participation, while ear, nose and throat and neurologic devices had greater than 50% male participation. A further breakdown of cardiovascular PAS revealed that female participation varied by type of device. Women accounted for 15%, 32%, 36%, and 64% of participants in PAS for endovascular aortic grafts, coronary stents, implantable defibrillators and pacemakers, and occluders (septal or patent ductus), respectively.

Participation by clinical area and time

Overall, the evaluation of applicant submitted reports revealed 29 (33%) included 50% or more women, 60 (67%) enrolled less than 50% women, with 15 (17%) of these

TABLE 1. INCLUSION OF WOMEN IN POST-APPROVAL STUDIES FOR MEDICAL DEVICES

Clinical area	Number of studies	Number of completed studies	Total number of participants	Average study size N (range)	Female participants n (%)	Male participants n (%)
Cardiovascular	55	32	31,154	566 (4–3,620)	10,042 (32%)	21,107 (68%)
Dental	3	3	351	117 (78–145)	324 (92%)	27 (8%)
Diagnostic and general hospital	2	2	151	76 (69–82)	82 (54%)	69 (46%)
Ear, nose, and throat*	2	2	145	70 (70)	70 (48%)	70 (48%)
Neurologic*	4	1	1,201	300 (17–554)	512 (43%)	686 (57%)
Ophthalmic*	4	2	6,874	1,718 (30–6,412)	4,348 (63%)	2,524 (37%)
Orthopedic*	9	0	3,743	416 (70–1,316)	1,597 (43%)	2,139 (57%)
Plastic and reconstructive	7	5	1,768	253 (100–1,008)	1,592 (90%)	176 (10%)
Renal and urologic*	3	2	148	49 (31–62)	76 (51%)	67 (45%)
TOTAL*	89	49	45,535	511 (4–6,412)	18,643 (41%)	26,865 (59%)

*Data on sex missing for some participants.

FIG. 2. Female percent participation by clinical area.

studies enrolling less than 25% women. The number of studies that included 50% or more women varied by clinical area (Fig. 2). For the 55 cardiovascular PAS only 7 (13%) enrolled at least 50% women in the study. Additionally, in 14 (25%) of these PAS, female participation was 25% or less. While there was some variation in the percent of female participation in all clinical areas over time, there were no trends noted (Fig. 3). The clinical area with the lowest female participation, cardiovascular, also remained constant over time.

Final report assessment

Of the 53 completed studies, data on enrollment by sex was provided in 49 of the applicant submitted final reports. Cardiovascular PAS accounted for 32 of these 49 completed studies (Table 1). Of these 49 reports, 7 (14%) presented a multivariate analysis that included sex as a covariate and 2 (4%) showed a subgroup analysis for female participants. The 7 final reports that included a multivariate analysis were cardiovascular PAS, while subgroup analysis was included in one cardiovascular PAS and one PAS for a diagnostic device. One report included both a female subgroup and an adjusted

multivariate analysis. Of the 32 studies with a sample size of more than 100 participants, 6 (19%) included either a multivariate or subgroup analysis. Of the 17 studies with a sample size of more than 300 participants, 6 (35%) included either a multivariate or subgroup analysis. However, none of these studies were designed or powered to evaluate subgroup differences.

Conclusions and Discussion

Approximately 50% of PMAs and HDEs that were approved since 1991 have had one or more mandated PAS requirement.¹⁶ Of the PAS studies reviewed, we found that data on the sex of participants were available in over 90% of the reports submitted by the applicant. It is interesting to note that three clinical areas have less than 50% participation by women in the PAS: cardiovascular, orthopedic, and renal and urologic devices. Low participation by women in cardiovascular device studies has been previously noted.¹⁷ Participation has remained consistently between 30% and 37% in PAS for devices approved since 2001. Additionally, post-approval study enrollment is consistent with that seen in premarket cardiovascular trials (CDRH, unpublished data). In cardiovascular PAS, female participation varied by type of device. Variation in female enrollment was consistent with the prevalence of conditions the devices were intended to treat, with aortic aneurysms occurring more frequently in men¹⁸ and septal defects having a higher prevalence in women.¹⁹ A detailed analysis was not performed due to the limited number of PAS in each device group. In this analysis, it was not possible to determine if other factors, such as age, could partially explain enrollment differences. The PAS reports did not routinely provide data on participant age, nor is raw data for analysis usually submitted. Analysis that includes both sex and age is needed to further assess if enrollment of women is representative of cardiovascular disease prevalence.

The ophthalmic device studies showed a higher than 50% enrollment for women, which is likely associated with a number of the devices requiring a PAS being designed for older adults (e.g., intraocular lenses for aphakic patients). By

FIG. 3. Percent female participation by year of device approval.

the same token, the plastic and reconstructive device studies also had a higher level of enrollment by women. A number of research studies have shown that women are more likely to receive cosmetic procedures than men, although the procedures could be performed in both sexes.²⁰ The predominance of women in the dental PAS could be explained by the higher prevalence of certain dental conditions, such as temporomandibular joint and muscle disorder (TMJ) in women.²¹ TMJ devices were evaluated in the three dental PAS included in this evaluation.

The applicants conducting the post-approval studies evaluated have adequately tracked inclusion of women, with only seven reports not including this information. However, prior to this review, FDA did not consistently include an assessment of enrollment by sex in its reviews of PAS reports. Based on this analysis, templates used for the review of PAS reports were updated in October 2011 to include an assessment of enrollment by sex.

Data on age and race by sex was limited in the submitted reports and not routinely assessed in FDA reviews. Data on other demographic characteristics are needed as prevalence of disease varies by age, sex, and race. These factors are important in assessing if participation is representative of the intended population. Both the applicant and FDA should make additional efforts to ensure data on demographic characteristics are reported and assessed in a meaningful manner.

The FDA has recognized the under-enrollment of women in premarket studies and has responded by publishing the 2011 draft guidance, *Evaluation of Sex and Gender Differences in Medical Device Clinical Studies*.²² This guidance outlines CDRH's expectations regarding sex and gender-specific patient enrollment, data analysis, and reporting of study information. The specific objectives of this guidance are to encourage the consideration of the enrollment of women in clinical studies, to identify sex and gender-specific questions for further study, and encourage the consideration of sex and associated covariates during the trial design stage and in statistical analysis. Additionally, the guidance recommends sex-specific information in summaries and product labeling. These recommendations apply to PAS and post-market surveillance studies.

Additionally, sex should be included as a covariate in analyses when appropriate. For PAS protocols already approved by FDA, the analysis plan may not include these analyses by sex and inclusion of such analyses will be encouraged but not required. The sample size for PAS is determined by the number needed to test an overall safety or effectiveness hypothesis. FDA does not require that a PAS be powered to evaluate safety or effectiveness by sex, unless there is evidence that a sex difference may exist. However, there is a need to identify sex-specific questions for further study, and encourage the consideration of sex and associated covariates during the trial design stage and in statistical analysis during the design phase of a new PAS. Imbalanced participation by sex in clinical trials has resulted in an inequality in the understanding, diagnosis, and treatment of diseases between the sexes. Therefore, FDA will not only continue tracking, but will encourage the enrollment of women in clinical studies. Additionally, FDA will continue to update medical device labels with information on health and safety benefits and risks obtained during the conduct of PAS, including sex-specific information.

FDA will work with applicants to develop PAS that enroll and retain proportions of women that are consistent with the sex-specific prevalence for the disease or condition the device is used to treat. If there are sex-specific signals in the premarket studies or there are known sex differences that impact safety and effectiveness, the FDA may encourage targeting investigational sites where necessary subpopulation recruitment can be more easily facilitated. Tailored communication strategies, community involvement, and flexible follow-up schedules can also increase participation of women.²³ FDA will also continue to advocate for enrollment of women in both premarket and postmarket clinical trials. This includes participation in intra- and inter-agency workgroups and collaboration with external stakeholders to identify opportunities and barrier to women's participation in clinical research. FDA researchers will continue to conduct research on sex differences to provide insight on the differences in study outcomes and reported adverse events for medical devices.

Author Disclosure Statement

No competing financial interests exist.

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