Division of Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2019-N-3804: Center for Devices and Radiological Health (CDRH) Health of Women Strategic Plan

Dear Sir or Madam:

The Advanced Medical Technology Association (“AdvaMed”) is pleased to provide comments on the Food and Drug Administration’s (FDA’s or “Agency”) Center for Devices and Radiological Health’s (CDRH) Health of Women Strategic Plan.

The Advanced Medical Technology Association (AdvaMed) is the world’s largest trade association representing medical device and diagnostics manufacturers. AdvaMed's member companies produce the innovations that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed has more than 400 member companies, ranging from the largest to the smallest medical technology innovators and manufacturers. AdvaMed advocates for a legal, regulatory and economic environment that advances global health care by assuring worldwide patient access to the benefits of medical technology. The Association promotes policies that foster the highest ethical standards, rapid product approvals, appropriate reimbursement, and access to international markets.

AdvaMed has general and specific comments below.

General Comments

AdvaMed strongly supports ensuring that devices are safe and effective for all patients and supports inclusion of sex-based clinical trial data analyses and inclusion of women in clinical trials based on prevalence of disease. It should be noted however, that trial sponsors, do not have direct access to patients and must rely on health care providers to appropriately identify diseases in women and refer them to clinical trials. We provide an example of this situation in the section below entitled “Gender Bias in Cardiovascular Device Trials.”
Gender Bias in Cardiovascular Device Trials

In response to continued concerns and challenges in recruiting women to cardiovascular trials, AdvaMed has undertaken a multi-year initiative. This included reaching out to leading women cardiologists to begin a dialogue and obtain their insights and recommendations and creating a working group to help develop targeted recommendations.

In our research on this topic, AdvaMed has learned that gender bias in the cardiovascular disease space is persistent and pernicious. One example is demonstrated in a study conducted by researchers in Canada in which clinical scenarios in patients with acute coronary syndromes were presented to physicians using a web-based computerized survey instrument. Results showed the physicians rated men as more likely to benefit from a cardiac catheterization than women and this effect persisted even in a low-risk group. Low-risk men were perceived to benefit more than low-risk women.\(^1\) Although these beliefs are unfounded and stem from long held stereotypes, in many cases the beliefs are so ingrained that they become unconscious acts. Physicians also refer women to trials less often than they do men\(^2\) and women receive cardiovascular diagnostic tests less often than men.\(^3, 4\) Of even greater concern is that physicians fared worst in identifying the significant incidence of heart disease in women. Only 8% of primary care physicians, 13% of gynecologists, and a startling 17% of cardiologists were aware of heart disease as a greater cause of mortality in women than men.\(^5\) Further, in a recent study evaluating the current classification schemes for acute myocardial infarction (AMI) in young women, approximately 1 in 8 young women with AMI were not classified by the Universal Definition of MI.\(^6\)

As part of the AdvaMed cardiovascular device trials initiative, an article was recently published in *JACC: Cardiovascular Interventions* entitled “Sex Disparities in Cardiovascular Device Evaluations: Strategies for Recruitment and Retention of Female Patients in Clinical Device Trials.”\(^7\) Among other important conclusions, the article states that:


\(^7\) M. Imran Ghare, BS; Jaya Chandrasekhar, MBBS; Roxana Mehran, MD; Vivian Ng, MD; Cindy Grines, MD; Alexandra Lansky, MD. Sex Disparities in Cardiovascular Device
Women tend to have more risk-averse behavior than men in making decisions, a difference that is amplified under stress. Inherent in clinical trials, the process of randomization, and the fear of adverse health effects from trial participation amplify risk-averse behavior and negatively influence their willingness to enroll.

Per the article:

Fundamental differences in the approach to communication related to decision making may further contribute to sex disparities in trial participation. Women are more likely to report that their decisions are influenced by friends, family, or researchers, and they are also more likely to make decisions on the basis of general altruistic consideration. Although patient autonomy is paramount, informed decision making for women will often include a greater network of trusted individuals, including family and friends.

The article also noted that “as primary caregivers, women are particularly vulnerable to study burden, and the impact of follow-up requirements on sex bias continues to be challenging in CV trials.”

For these and related reasons, AdvaMed is continuing to work collaboratively with leading women cardiovascular clinicians, leading cardiovascular societies and patient groups focused on women’s health and women’s heart health to initiate a coordinated education campaign entitled “Take Her Heart to Health” as recommended in the JACC article. The campaign targets health care providers and patients to improve awareness of heart disease in women including sex-specific symptoms and the importance of including women and other demographic subgroups in cardiovascular trials. Materials from the Take Her Heart to Health campaign can be accessed on AdvaMed’s website at: https://www.advamed.org/advamed-women-cardio-campaign.

Lastly, based on our dialogue with leading cardiovascular clinicians, AdvaMed has communicated our support in comments to FDA and elsewhere for identifying alternative clinical trial follow-up requirements that encourage participation of women and other demographic subgroups such as: requiring fewer follow-up visits, allowing phone follow up or home visits by nurse trial coordinators (in lieu of in-person visits by patients/subjects); allowing for on-line follow up options; permitting the patient’s/subject’s primary care provider to perform some of the follow-up requirements and to reimburse for such, to provide transportation reimbursement, and allow for weekend hours for required follow-up visits. We were pleased to see many of these concepts referenced in FDA’s recently issued draft guidance, entitled “Patient Engagement in the Design and Conduct of Medical Device Clinical Investigations.”

Evaluations: Strategies for Recruitment and Retention of Female Patients in Clinical Device Trials. JACC: Cardiovascular Interventions 2019. 12(3) 301-308.
AdvaMed Survey on Barriers to and Best Practices to Recruiting Diverse Clinical Trial Populations

In a January 6, 2016 Federal Register Notice on the Food and Drug Administration Safety and Innovation Act Section 907 Public Meeting: Progress on Collection, Analysis and Availability of Demographic Subgroup Analysis, FDA asked a number of questions on the recruitment and retention of demographic subgroups. In response, AdvaMed conducted a survey of its members to gather information and data on the questions posed by FDA concerning barriers to and best practices to recruiting diverse clinical trial populations. AdvaMed received 38 responses across 20 different device categories including among others: cardiovascular devices (50%), in vitro diagnostic devices (37%), diabetes (23%), and endo/peripheral vascular devices (16%). The FDA questions and the related survey responses are included below.

What approaches have been successful in addressing key barriers to recruiting diverse clinical trial populations? What have you learned about best practices for recruiting a broad representation of subjects for clinical trials? Which practices have been successful and why? Which have not and why?

We asked our member companies to share strategies and best practices – based on past successes and failures – that have worked to recruit diverse demographic subgroups to their clinical trials. Responses included the following: emphasizing the need to recruit demographic subpopulations with investigators (47.4%); communication with investigators on enrollment status (42.1%); relying on medical care providers (31.6%); use of clinic flyers (21.1%); partnering with patient advocacy groups (18.4%); advertisements (15.8%); use of live speakers/presentations (7.9%) and posting on ClinicalTrials.gov and use of social media (2.6% each). Some indicated that no recruitment strategies were needed (23.7%).

We also asked our members what barriers or impediments they encountered in recruiting or retaining diverse demographic subgroups to their trials. Barriers included the following: subject time or other commitment needed for trial participation (55.6%); risk aversion by potential subjects to participation in investigational trials (38.9%); cultural differences (30.6%); lack of subject interest (30.6%); subject objection to protocol-driven requirements (e.g., pregnancy testing where pregnancy is an exclusion criteria, drug testing, CT/MRI/X-ray scans, etc.) (27.8%); regulations or FDA protocol requirements

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8 Please note device companies may be active in more than one device category and there may be overlap between device categories.

9 Not all device clinical trials may require gender or other demographic subgroup diversity because the device itself is targeting one particular sex (e.g., gynecologic or obstetrical devices), there are no relevant anatomical differences due to sex, race or ethnicity (e.g., contact lenses) or there are no scientific reasons or scientific evidence to indicate there will be differences due to sex, race or ethnicity.
(such as requirement for in-person follow up) (27.8%); time and effort required by an investigator to obtain informed consent for the target demographic subgroup (27.8%); language differences (16.7%) and other (13.9%).

We asked those who selected “subject time or other commitment needed for trial participation” to provide further details. They responded that the following reasons were barriers to trial participation: the requirement for follow-up visits (e.g., lost time from work or child care related issues) (95.7%); distance too far to travel (i.e., to the travel site) (65.2%) and difficulty in returning to the investigational site (82.6%).

**What are your key limitations to conducting meaningful data analysis of underrepresented groups?**

Based on survey responses, the biggest limitation to conducting meaningful data analysis on underrepresented groups in medical device clinical trials are the challenges to obtaining statistically meaningful samples sizes (100%). The reasons or causes of being unable to obtain statistically meaningful sample sizes include the following: an inability to recruit sufficient numbers of patients in the targeted demographic subgroup (85.7%); under-diagnosis of the disease state in the target demographic subgroups (42.9%); lack of access to health care by the target demographic subgroup (42.9%); investigative sites not being co-located in areas with a high concentration of the target demographic subgroup (57.1%) and differences in patient care pathways hinder recruitment of target demographic subgroups (e.g., community health care centers vs. academic medical centers).

**What communication strategies have you successfully used that were also sensitive to the needs of underrepresented populations?**

We asked our member companies to share best practices for communication or other strategies – based on past successes and failures – that have worked to retain diverse demographic subgroups in clinical trials. They shared the following responses: reimbursement for participation (56.8%); reimbursement of transportation (51.4%); providing child care (8.1%); providing newsletters or similar written updates of clinical trial progress (8.1%); issuing social media updates (5.4%); investigator training on trust and cultural competencies (2.7%); providing investigator tools (e.g., call-scripts for patient follow-up, letter or email templates) (27.0%); extra or ongoing patient coaching on consent or risks and benefits of the trial (10.8%); extra or ongoing patient coaching on insurance vs. study coverage (8.1%); and no retention strategies are used (29.7%) or needed (13.5%).

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10 Not all device clinical trials may require gender or other demographic subgroup diversity because the device itself is targeting one particular sex (e.g., gynecologic or obstetrical devices), there are no relevant anatomical differences due to sex, race or ethnicity (e.g., contact lenses) or there are no scientific reasons or scientific evidence to indicate there will be differences due to sex, race or ethnicity.
What are potential methods FDA should consider using to effectively communicate meaningful information on demographic analyses to a diverse public? What are some of the actual or potential unintended consequences of data transparency you have encountered related to reporting demographic subgroup analysis?

Given the smaller number of patients that are typically required for medical device trials and the challenges that can occur in recruiting statistically meaningful sample sizes, the device industry is concerned that whatever communication methods FDA uses, strong care must be taken that the information cannot be misinterpreted (i.e., that it is different from labeling or is not clinically relevant). AdvaMed provided comments on January 23, 2015 in response to FDA Docket No: FDA-2014-N-1818 on FDA’s plan to share demographic data on an FDA website in which we expressed our concerns about possible approaches (see attached). Based on our concerns, we believe the best methods to effectively communicate demographic subgroup analyses to the public are to better publicize the existence of 510(k) Summaries and Summaries of Safety and Effectiveness for PMAs which already exist on FDA’s website, to partner with patient advocacy groups and to use ClinicalTrials.gov.

As noted above, a key finding of AdvaMed’s survey was that a leading barrier to recruitment of diverse subgroups is the patient/subject time or commitment needed for trial participation (96%) and patient/subject difficulty returning to the investigational site (83%). Improving demographic subgroup participation in trials necessitates exploring new methods to known barriers to participation. Although this initiative was focused on improving participation of women in cardiovascular trials, we believe many of the recommendations can be leveraged to help recruit and retain diverse demographic subgroups to medical device clinical trials.

Specific Comments

**Gender Data Collection:** We support the strategic plan’s focus on sex and gender and the fact it has taken into consideration transgender individuals and other gender minorities in the scope of the plan. However, to ensure least burdensome approaches to clinical trial requirements, before FDA begins proposing collection of gender data points for products, greater guidance is needed on what data points are important to collect and why. Collection of gender data points feels quasi-qualitative. We understand that it may add context to the data set, and but it seems different than capturing sex as a data point. For example, is collection of gender relevant when a study is distinguishing sex-based differences and diagnostic characteristics in blood samples?

**Need for Scientifically Valid References:** On page 9, the strategic plan makes two key statements: “Genes on sex chromosomes are responsible for sex determination, sexual differentiation, and the orchestration of developmental programs that produce male and female anatomy and physiology” and “Our understanding of one’s gender is highly influenced by our experiences, environment, and societal views of ourselves and others,
as well as our socially-defined gender ‘roles.’” Both of these statements reference footnote 15 which links to a U.S. FDA Conference in 2018: “Scientific Conference: Opioid and Nicotine Use, Dependence, and Recovery: Influences of Sex and Gender”. This may not be the correct link. These are important tenets of the Health of Women Strategic Plan and it would be helpful to have several scientifically valid references for these statements.

**Wording Around Gendered:** on page 9, it states “Every cell is sexed and every person is gendered.” We recommend changing “every person is gendered” to “most people identify as a specific gender.” The “every” statement may not be appropriate.

Based on a Google search, it seems not everyone considers themselves gendered. For example, there are agendered individuals (see https://en.m.wikipedia.org/wiki/Non-binary_gender). Additionally, this broad statement is linked to Footnote 14 which does not seem to provide scientific references. Again, given that this statement is a key premise of the Health of Women Strategic Plan, it would be helpful to link directly to several scientifically valid references.

**Editorial Suggestion:** on page 18, we suggest revising the first sentence in the first paragraph to say, “To achieve these strategies, we intend to employ both internal and external strategies to engage our customers.”

In closing, we greatly appreciate the opportunity to provide input on the CDRH Health of Women Strategic Plan. Please don’t hesitate to contact me if I can help answer any questions.

Sincerely,

/s/

Tara Federici
Vice President
Technology and Regulatory Affairs