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

RE: Docket No. FDA–2016–D–0734: Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies; Draft Guidance for Industry and Food and Drug Administration Staff; Availability Docket

Dear Sir or Madam:

The Advanced Medical Technology Association (“AdvaMed”) is pleased to provide the following comments on the Food and Drug Administration’s (FDA’s) draft guidance entitled Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies.

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. Nearly 70 percent of our members have less than $30 million in sales annually. 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 U.S. and international markets.

AdvaMed has both general and specific comments (included in table form below).

**General**

As we have noted in previous AdvaMed comments on the Food and Drug Administration Safety and Innovation Act (FDASIA) Section 907 requirements, AdvaMed supports the collection, evaluation and reporting of demographic subgroup data by sex, age, race and ethnicity. In previous comments and public meetings on this topic, we have provided recommendations on best practices to improve and enhance recruitment and retention of diverse demographic subgroups.

We agree with previous analysis conducted by FDA in the *FDA Report on the Collection, Analysis and Availability of Demographic Subgroup data for FDA-Approved Medical Products* with respect to medical devices that:
Many Premarket Approval Applications (PMAs) ("nearly one quarter") include an additional pivotal study cohort "to obtain clinical experience in a specific subpopulation."

Demographic subgroups may vary by product area because a variety of factors may "influence the interpretation and clinical relevance of demographic information" including the intended population for use, the disease prevalence and the study sample size.

The unique nature of medical devices may mean that additional information on demographic subgroups may not "be contributory to FDA decision-making" (e.g., additional analyses by subpopulations may be unnecessary when the in vitro diagnostic test’s analyte detection and performance are highly accurate).\(^1\)

We concur with the principle included in the draft guidance that underscores the need to consider differences across age, race or ethnic groups when it is anticipated that there will be clinically meaningful differences in treatment effect. Without reasonable and scientifically-based rationales for subgroup analysis, medical device trials could become enormously large and expensive to conduct in order to power the trial for various demographic subgroups. Taken to extremes, this could limit patient access to innovative medical devices. To ensure that this principle is understood at the outset of the planning and development of the trial, we recommend that FDA include a brief discussion of this point early in the guidance (i.e., in the Scope section).

We would also note that in lieu of overly burdensome and costly large clinical trials, FDA has significant authority under device law to require post-approval studies as a condition of approval or clearance, or studies or registries under Sec. 522. Further, as suggested in FDA’s report, postmarket surveillance of approved or cleared medical devices enables FDA to monitor medical devices and other products in a broader population once the device is marketed.\(^2\) Any important demographic subgroup signals that are detected and require further study can be required under Sec. 522.

We would caution FDA on the implicit assumption that is contained in the guidance with respect to standard of care issues. FDA states that "collection and pooling of data from OUS sites may result in confounding issues of ethnicity and standard of care" (lines 294 -295) and "additionally, the standard of care at OUS sites may not be equivalent" (line 298). These statements assume that the standard of care within the U.S. is uniform which is debatable for many therapies.

FDA also states that "OUS sites may not categorize race and ethnicity in the same manner as U.S. sites or may define certain race or ethnicity groups differently than do U.S. sites (e.g., “Caucasian” vs “white” in European vs U.S. data)" (lines 294 – 298). We believe that

\(^1\) FDA Report on Collection, Analysis, and Availability of Demographic Subgroup Data for FDA Approved Medical Products, August 2013. p. 52-53.

\(^2\) Ibid. p. 60-61
differences in race and ethnicity can be controlled with the inclusion of clear definitions in
the protocol which would allow for pooling of U.S. and OUS race and ethnicity data.

As more and more studies are being conducted globally, it would also be helpful for FDA to
directly address in this guidance the conflict reflected between the FDA position on
collection of race and ethnicity data versus the position of the European Union and some
European countries. For example, The European Union and France and Portugal generally
prohibit collection of ethnicity and race data in clinical trials. Article 8 of the European Data
Privacy Directive 95/46/EC states: “The processing of special categories of data: Member
States shall prohibit the processing of personal data revealing racial or ethnic origin, political
opinions, religious or philosophical beliefs, trade-union membership, and the processing of
data concerning health or sex life.”3 France’s Data Protection Act No. 78-17 created the
French Data Protection Authority (Commission Nationale Informatique et Libertes (CNIL)).
Article 8 of this legislation states: “The collection and processing of personal data that
reveals, directly or indirectly, the racial and ethnic origins, the political, philosophical,
religious opinions or trade union affiliation of persons, or which concern their health or
sexual life, is prohibited.” Similarly, Portugal’s Act on the Protection of Personal data
includes a similar prohibition in Article 7.1: “The processing of sensitive data –The
processing of personal data revealing philosophical or political beliefs, political party or trade
union membership, religion, privacy and racial or ethnic origin, and the processing of data
concerning health or sex life, including genetic data, shall be prohibited.”

Specific Comments
AdvaMed’s specific comments on the draft guidance are presented below in tabular form.

In closing, thank you for the opportunity to comment on the draft guidance, *Evaluation and
Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies*. Please don’t
hesitate to contact me if you have any questions.

Sincerely,

/s/

Tara Federici
Vice President
Technology & Regulatory Affairs

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3 Sponsors may only request this information if the human subject has given explicit consent to processing of
the data except where the laws of a Member State provide that the prohibition against collection of this data
cannot be lifted by the subject’s consent.
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<td>1</td>
<td>121-128</td>
<td>Move Figures 3 and 4 to Appendix as that is where Figures 1 and 2 are found. The Table of Content does not include Figures 3 and 4.</td>
<td>If all figures are to be together they should be in the Appendix. If the intent was to have Figures 3 and 4 in the beginning of document then add them to the Table of Content.</td>
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| 2      | 514-517    | Strike and add the following:  
A summary of any known clinically meaningful age, race, and ethnicity differences in disease course, or outcomes, or benefit-risk profile should also be included in your 510(k) Summary and in your labeling (see Section VI below for more details).  
“Benefit-risk” terminology only applies to a subset of 510(k)s in which the technological characteristics of the candidate device differ from those of the predicate. As stated in section 513(i) of the FD&C Act, substantial equivalence may be obtained when a device has the same intended use and the same technological characteristics as the predicate device. In this circumstance, a benefit-risk analysis is not required. When a candidate device has the same intended use as the predicate device but different technological characteristics from the predicate device, it becomes necessary to evaluate whether or not these differences raise questions about the device safety and effectiveness. In carrying out this evaluation, the FDA may rely on a benefit-risk profile for the device. Section 513(a)(2) of the FD&C Act states that the FDA determines the "safety and effectiveness of a device" by "weighing the probable benefits to health from the use of the device against any probable risk of injury or illness from such use," among other relevant factors. As such, this risk-benefit analysis is only potentially required in situations where technological characteristics differ between the candidate and predicate device(s) and is therefore not applicable to all 510(k)s. Given this, we recommend that the reference to "benefit risk profile" be removed from this sentence. |
| 3      | 818        | Add the following:  
When differences in treatment effect are anticipated across age, race, or ethnic groups, it is important to consider proper clinical study design, sufficient enrollment of subgroups to allow meaningful analysis, controlling of Type I error, and simultaneous pivotal and subgroup-specific trials if appropriate and feasible.  
Differences in treatment effect may be anticipated, but prevalence may be low, making infeasible the enrollment of specific subgroups in the numbers required by this guidance. |
| 4      | 846-852    | Delete section V. B.4.                                                  | It is unclear why special study design considerations would only apply to diagnostic devices. The applicability of the example provided in this section to diagnostics is also unclear; age could be a significant risk factor in |
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| 5 | 888 | Add and strike the following:  
*If no clinically meaningful or statistically significant difference is observed across subgroups, data may be poolable across subgroups.* | This suggests that clinically non-meaningful differences that may be statistically significant can prevent data from being pooled. That's a challenge when large studies may yield significant p-values that have no clinical significance, especially when FDA employs a 15% significance level.  
Bullet 7 covers the situation where there is a clinically meaningful difference. |
| 6 | 910 | Add the following:  
*If any clinically meaningful demographic subgroup differences are found, either based on pre-specified or exploratory post hoc analyses, you should discuss with FDA whether additional data are needed to address any remaining subgroup-specific questions.* | Post-hoc analyses that are data dredging are problematic when not backed up by the disease process. |
| 7 | 930 | Section VI. Recommendations for Submitting Age, Race and Ethnicity Data in Submissions to the Agency and Reporting in Public Documents  
There are other guidance documents which discuss FDA expectations in terms of content such as Labeling, Post Approval Studies, etc. FDA should update or reference this guidance in the above mentioned guidances when this guidance is finalized. |  |
| 8 | 953 - 955 | Remove the following:  
*The term “submit” refers to information submitted to the FDA for analysis, whereas the term “report” refers to information that should be included in publicly available documents (i.e., labeling, FDA review summaries).*  
And  
Strike all references to “publicly report” in this section and change to include in product labeling, SSED or 510(k) Summary. | The struck sentence is confusing and implies that labeling, 510(k) Summaries and SSEDs are not submitted to FDA, when in fact they are.  
The term "publicly report" is confusing and implies that the company has some undefined obligation to report this information other than in the FDA labeling, SSED or 510(k) Summary. |
| 9 | P36 | Add the following to the third box on the left:  
To be consistent with the text of the guidance. In |  |
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<td>Flow chart</td>
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<td>Is there a significant difference between demographic subgroups <strong>that is clinically relevant</strong>?</td>
<td>addition, statistically significant differences due to a large sample size that are not clinically relevant should still be considered for poolability. Similar to the analog of qualitative and quantitative interactions in single arm studies. See also comment 5.</td>
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