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FDA finalizes guidance on evaluation and reporting of age-, race-, and ethnicity-specific data in medical device clinical studies

October 4, 2017

On September 12, 2017, the U.S. Food and Drug Administration (FDA) released the final guidance that outlines the agency's expectations and recommendations for the evaluation and reporting of age-, race-, and ethnicity-specific data in medical device clinical studies. In recent years there has been increased emphasis by FDA on the need for clinical study populations to be broadly representative of the population in which medical products will be used. The final guidance is intended to help study sponsors develop a strategy for enrolling diverse study populations that will include representative proportions of relevant age, racial, and ethnic subgroups. Depending on the interpretation of the guidance by FDA review staff, the final document may significantly increase the importance of these data for sponsors not already analyzing this type of information. Given the concepts discussed in the final guidance, study sponsors will want to begin discussions with FDA regarding these topics early in the clinical study development process.

The draft (published on June 20, 2016) and final versions of the new guidance serve as part of a set of guidance documents discussing collection and analysis of data associated with race, ethnicity, sex, and other patient characteristics. Specifically, the final guidance follows the same principles set forth in the FDA's *Guidance on Evaluation of Sex-Specific Data in Medical Device Clinical Studies*, but expands the concepts to additional demographic subgroups. In addition, the final guidance also extends and complements FDA's *Guidance on Collection of Race and Ethnicity Data in Clinical Trials*, which recommended the use of a standardized approach for collection and reporting of these data developed by the Office of Management and Budget (OMB) pursuant to the Affordable Care Act.

As explained by the Agency, the overall purpose is to "improve the quality, consistency, and transparency of data regarding the performance of medical devices within specific age, racial, and ethnic groups." Specific recommendations are provided for three stated objectives of the guidance:

1. To encourage the collection and consideration during the study design stage of relevant age, race, ethnicity, and associated covariates (e.g., body size, biomarkers, bone density) for devices for which safety, effectiveness (or, for humanitarian device exemptions (HDEs), probable benefit), or benefit-risk profile is expected to vary across these groups;

2. to outline recommended analyses of study subgroup data, with a framework for considering demographic data when interpreting overall study outcomes; and

3. to specify FDA's expectations for reporting age-, race-, and ethnicity-specific information in summaries and labeling for approved or cleared medical devices.

We have provided a summary of the recommendation below, which is based on the phases of the study.

1. Study Design Phase

In the study design phase, FDA recommends that sponsors plan to enroll representative proportions of age-, race-, and ethnicity-specific subgroups that are consistent with the intended use population of the device, or justify in the investigational plan how the enrollment criteria will provide reasonable representation of the intended population. If existing knowledge suggests a clinically meaningful difference in benefits or risks for certain subgroups, such information should be provided in the study protocol and investigator training materials, and sponsors should aim to enroll sufficient numbers of that subgroup(s).

The guidance provides several suggestions for increasing diversity in investigational sites, including provisions to encourage diverse enrollment; using multiple study availability communication strategies and leveraging strategies that generally increase recruitment and retention such as utilizing community/local health care practitioners or compensation for expenses; and flexibility in follow-up visit scheduling. If enrollment in important subgroups is lagging, sponsors should investigate reasons for under-enrollment or non-enrollment and consider revising enrollment criteria or enrolling registries or parallel cohorts.

While this has been the Agency's general position for some time, it has not always been applied consistently across the Agency. Inclusion of these principles in the final guidance may increase review staff focus on the importance of representative data.

When designing clinical studies, FDA also recommends that sponsors investigate heterogeneity across the demographic subgroups of clinical interest, especially for primary safety and effectiveness endpoints. FDA recognizes, however, that the power of such test may be unspecified. When appropriate, pre-specified plans for assessing heterogeneity across relevant demographic subgroups should be included in the statistical analysis plan (SAP). In addition, the SAP should include adaptive study design strategies to pre-specify subgroups of interest for interim analysis and potential population enrichment for success where necessary.

2. Study Conduct and Analysis Phase

If any clinically meaningful differences are suspected during the conduct of the study, either based on pre-specified or exploratory analyses, sponsors should discuss with FDA to determine whether additional data are needed to address any remaining subgroup-specific questions of safety or effectiveness.

According to the guidance, subgroup-specific data should be collected and analyzed for clinically meaningful age-, race-, and ethnicity-specific differences in the primary and key secondary endpoints, regardless of the potentially limited statistical power of such subgroup analyses. The statistical methods may include inferential statistics, such as p-values and/or confidence intervals,

if there is pre-specified statistical plan to support subgroup-specific labeling; or descriptive statistics only (mean, standard deviation, etc.) for exploratory subgroup analyses.

If a clinically meaningful and/or statistically significant difference is observed, it is important to investigate further about the cause and discuss with FDA. If the analysis suggests that there is insufficient data to assess whether age, race, or ethnicity is associated with clinically meaningful differences in outcome, FDA may request clinical data from additional subjects in one or several of demographic subgroups. In addition, other patient characteristics (e.g., body size, diet, bone density, Fitzpatrick Scale Skin Type) may be correlated with age, racial, or ethnic differences and may sometimes explain apparent differences in clinical outcomes. FDA recommends that sponsors investigate these potential issues.

FDA also recommends the sponsors address the issue of confounding by using multivariable analyses adjusted for patient characteristics that may confound the relationship between the analyzed subgroup and study outcomes (e.g., body size, diabetes).

3. Study Report/Premarket Application Stage

FDA recommends that sponsors submit and publicly report (in 510(k) summaries, labeling, and other decision summaries) study demographics in terms of proportion enrolled and completed by subgroup, any co-morbidities and/or other baseline characteristics collected, and loss to follow-up that disproportionally affects a particular subgroup.

For age-, race-, and/or ethnicity-specific outcomes, FDA suggests using tables or Forest plots to report outcomes by demographic subgroups. Such information should be included in 510(k) summaries, labeling, and other publicly available decision summaries, as well as interim and final reports for mandated postmarket studies.

In addition, for the premarket submission, FDA recommends that sponsors clearly indicate what analyses have been conducted and describe the statistical methods used to assess heterogeneity of treatment differences by relevant subgroups.

At the end of the guidance, FDA offers four flowcharts to provide a framework for deciding when various age-, race-, or ethnicity-specific statistical recommendations apply for different clinical study designs.

Compared to the 2016 draft guidance, the final guidance includes a few minor changes, most of which are implemented to be consistent with other guidance documents. For example, instead of accepting ethnic and racial demographic data captured as one category or separately, the final guidance recommends capturing ethnic and racial data as distinct categories. In addition, the final guidance allows for combining U.S. and OUS race-and ethnicity-specific data if differences in race and ethnicity subgroup data are controlled with the inclusion of clear definitions in the protocol. Further, consistent with the recent guidance on the use of real-world evidence to support regulatory decision-making, FDA encourages using postmarket age-, race-, and/or ethnicity-specific data to modify labeling to support additional information regarding device safety or effectiveness and/or clarify how the device should be used.

While it remains to be seen to what extent the guidance will affect the burden on data collection and data analysis, sponsors should keep the considerations in mind when designing clinical studies, especially if existing knowledge suggests potential age-, race-, and ethnicity-specific differences in the intended population for the device.

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