CDRH’s Draft Guidance: Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies

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Overview

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• Background
• Terminology
• Subgroups in Clinical Trials
• Achieving Appropriate Enrollment
• Analysis of Subgroup Data
• FDA and Public Reporting of Subgroup Data
Objectives

• Encourage consideration during study design stage the collection of relevant demographics, (age, race, ethnicity), and other associated covariates (body size, biomarkers, bone density) for devices

• Outline analyses framework for demographic data and interpreting outcomes

• Specify FDA’s expectations for reporting demographics in summaries and labeling of medical devices
Background

Section 907, Food and Drug Administration Safety and Innovation Act of 2012

• Required a Report to Congress and the public on the inclusion of demographic subgroups in FDA applications

• Required an Action Plan to improve completeness and quality of data on demographic subgroups

• This Draft Guidance was a commitment by CDRH under the Action Plan!
Terminology: Age

- Subjects should be grouped as appropriate for the disease/condition
- Pediatric population is defined by CDRH as less than 22 years of age
- Geriatric population is not defined, but recommend stratifying age based on relevant disease characteristics
Terminology: Race & Ethnicity

FDA’s Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials

• Patient self-report of both race and ethnicity
• Preferred method is separate collection of race and ethnicity (i.e. two-question format)

Other considerations:
• Disease/condition may warrant more granular race data
• Categories may not be appropriate outside the U.S.
• In these instances, methodology should be defined in the study protocol
Participation of Subgroups in Clinical Trials

• It is important that clinical trials include diverse populations that reflect the intended population
• Including throughout the enrolling sites, where surgical or operator skill may be important
• Otherwise, differences in device performance or surgical skill may be incorrectly attributed to demographic subgroups
• Therefore, study protocols should include pre-specified statistical plans to address these issues
Consideration of Subgroup Differences

For potential age, race, and ethnicity differences relevant to the evaluation of the device for the disease/condition, consider

• Prevalence
• Diagnosis and treatment patterns
• Previous subgroup inclusion in past studies for target indication
• Any clinically meaningful subgroup differences in safety or effectiveness
Recommendations for Demographic Subgroup-Specific Statistical Design

Follow recommendations associated with study design type.

START

Is the product’s use/design intended to be limited to one demographic subgroup? (e.g., neonatal device)

YES → No separate subgroup analyses required.

NO → All Clinical Studies

CONTINUE

One-Arm Study

YES → RECOMMENDATIONS

- Reporting and analysis by demographic subgroup should be pre-specified.*
- Provide strategy to recruit diverse populations that ideally reflect the intended population.
- Describe whether previous studies suggest a clinically meaningful difference by subgroup, and consider relevant covariates that may explain differences.

NO → Comparative Study

YES → RECOMMENDATIONS

- Follow recommendations in box above for “All Clinical Studies”.
- Provide strategy for assessing heterogeneity.
- May consider subgroup-specific Objective Performance Criteria (OPC) or Performance Goal (PG).**

NO → Non-Randomized Controlled Trial (concurrent control, historical control)

YES → RECOMMENDATIONS

- Follow recommendations in box above for “All Clinical Studies”.
- Control Overall Type 1 error rate if seeking multiple claims.
- Pre-specify interaction testing.
- May consider powering for subgroup-specific claims.**

NO → Randomized Controlled Trial (RCT)

YES → RECOMMENDATIONS

- Follow recommendations in boxes above for “All Clinical Studies” and “Comparative Study”.
- May consider demographic subgroups as stratification variables in randomization process when appropriate.**

RECOMMENDATIONS

*For ongoing studies, provide descriptive statistics. For new studies, provide statistical inferences

**Applicable when subgroup differences are anticipated
Achieving Appropriate Enrollment

To enhance enrollment of relevant subgroups:

• Wide variety of investigational sites
• Alternate communication strategies
• Revise enrollment criteria
• Establish parallel cohorts or registries
• Investigate no or low inclusion of key demographic subgroups
• Involve community or local providers in recruitment
• Compensation for transportation costs
• Flexible scheduling and on-site child care and elder care
Investigator Tools & Techniques for Enrollment

• Cultural competency training
• Stress the importance of follow-up at time of informed consent and subsequent visits
• Reminder calls for upcoming visits
• Attempt to locate and return patients lost to follow-up
• Record reason for patient withdrawals
• Demonstrate patient interest with post-op and follow-up visit calls
Recommendations for Analysis of Subgroup Data

Data should be examined for clinically meaningful age, race, and ethnicity specific differences in:

• Primary effectiveness endpoints
• Primary safety endpoints
• Key secondary endpoints

Regardless of the potentially limited statistical power of these subgroup analyses!
Other Considerations of Subgroup Analyses

• Inadequate sample size and unplanned subgroup analyses are generally not considered adequate for statements in labeling
• Sometimes effect can be statistically significant but not clinically meaningful and vice versa
• Observed heterogeneity could be explained by other covariates
• Discussion with FDA is recommended if difference(s) remain clinically meaningful and/or statistically significant
Additional FDA Actions on Subgroup Analyses

- FDA may request additional subjects from one or more subgroups pre or post-market if data is insufficient to determine clinically meaningful differences.
- Or request additional confirmatory studies, implement specific pre or post-approval conditions, and/or subsequent study modifications where clinically meaningful subgroup differences are observed.
START

Is overall treatment effect statistically significant and clinically meaningful?*

NO
Analysis raises questions about data to support marketing application.

YES

Is there a significant interaction effect between demographic subgroup and treatment group for the outcome of interest?

NO

YES

Is interaction effect clinically meaningful and statistically significant after adjusting for other covariates?

NO

YES

RECOMMENDATIONS

Data may be poolable across subgroups**

NO

YES

Describe qualitative or quantitative nature of interaction, if any, and clinical significance of any differences. Other subgroup analyses may be needed.

NO

YES

- Discuss how clinically meaningful differences across subgroups may contribute to differences in benefit-risk profile in certain subpopulations.
- Data may not be poolable across subgroups.** Additional data may be needed pre- or postmarket to support marketing submission. Discuss with FDA is advised.

*Unplanned subgroup analyses are generally not considered to be adequate to support statements in the labeling regarding the safety or effectiveness of the device if overall treatment effect is not statistically significant and clinically meaningful.

**Provide justification for pooling data across subgroups, if applicable.

Note: In some cases, the subgroup-specific difference could be statistically significant but not clinically meaningful or clinically meaningful but not statistically significant. In these cases, discussion with FDA is advised.
Subgroup Data in Submissions to FDA and Public Reporting

Report the number and proportion of subjects by age, race, and ethnic groups treated/diagnosed with device:

• Proportion enrolled and completed
• Subgroup proportions consistent or not with prevalence
• Discuss generalizability of results when enrollment is substantially different than prevalence
• Co-morbidities and baseline characteristics for subgroups should be analyzed and submitted
• Discuss subgroups with disproportionate loss, by time points and study arm(s)
START

OUTCOME INFORMATION

ENROLLMENT DEMOGRAPHICS

Is overall treatment effect statistically significant and clinically meaningful?*

YES

Is there a clinically meaningful subgroup difference?

YES

Is there a statistically significant subgroup-treatment interaction effect (or heterogeneity between subgroups)?

YES

Were the subgroup analyses prespecified?

YES

Were the subgroup analyses conducted post hoc?

NO

NO

Analysis raises questions about data to support marketing application.

Continue

NO

NO

RECOMMENDATIONS

Submit and publicly report study demographics, including proportion by subgroup and comorbidities, if applicable.

Discuss whether proportions enrolled are consistent with prevalence, if known.

Compare & discuss subgroup differences in follow-up compared to at enrollment.

RECOMMENDATIONS

State which analyses were conducted and that no clinically meaningful differences were found.

Summarize the findings descriptively.*

Submit the results of the outcome analyses by subgroups of interest.*

Clearly state which analyses were conducted and specify statistical methods used to assess for heterogeneity of treatment differences by subgroup.

Clearly state that the analyses were unplanned. State which analyses were conducted and specify statistical methods used to assess for heterogeneity of treatment differences by subgroup. Use descriptive statistics only.

* Discuss how clinically meaning differences across subgroups may contribute to differences in benefit-risk profile in certain subpopulations.

Note: The term “submit” refers to information submitted to the FDA for analysis. The term “report” refers to information that should be included in publicly available documents (e.g., labeling, SSID).
Comments to the Docket

Stakeholders should submit comments on the draft guidance by September 19, 2016

- Federal eRulemaking Portal: http://www.regulations.gov. Comments are public and appear unchanged, including attachments

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
Comments & Questions
Thank you!

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