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FDA/CDRH Webinar

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CDRH Final Guidance: Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies

Kathryn O’Callaghan
Assistant Director for Strategic Programs, CDRH

&

Katherine Kim, M.P.H.
BIMO Reviewer, Bioresearch Compliance Branch I
Center for Devices & Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
U.S. Food and Drug Administration

October 31, 2017
OUTLINE

• Background & Origins of the Guidance
• Scope & Objectives
• Terminology
• Key Recommendations by Section
BACKGROUND

• In 2012, Section 907 of the Food and Drug Administration Safety and Innovation Act directed the FDA to examine participation of diverse subgroups and corresponding data in medical product submissions, and availability of this information to the public.

• In 2014, the FDA issued an Action Plan to improve participation, quality and transparency of medical product performance in ARE subgroups.

• The Age, Race, and Ethnicity (ARE) Guidance was a commitment by CDRH under this Action Plan.

• The FDA sought input from experts, stakeholders and the public via numerous fora, including a 2015 Institute of Medicine workshop.

• Draft guidance was issued June 20, 2016, for public comment. Final guidance issued and went to effect on September 12, 2017.
Food and Drug Administration Safety & Innovation Act (FDASIA) Section 907

FDASIA 907 Report

- Reviewed 37 original Premarket approval (PMA) applications approved in 2011:
  - 46 pivotal clinical studies
- Demographic data variables:
  - Sex, Age, Race, Ethnicity
- Documents reviewed:
  - PMA applications submitted by industry
  - Final labeling (industry public info)
  - FDA internal review documentation
  - SSED: Summaries of Safety & Effectiveness Data (FDA public decision summaries)
Need for Improved Consistency in Analysis & Public Transparency

Sex
- 88% of PMAs analyzed
- 63% presented publicly

Age
- 70% of PMAs analyzed
- 57% presented publicly

Race & Ethnicity
- 27% of PMAs analyzed
- 16% presented publicly
Participation by Age Range

- Lack of consistency in the type of descriptive statistics on age reported in the PMAs.
- Age range was most commonly reported.
Participation by Race

For some indications, racial composition was consistent with disease prevalence.

For other indications, racial composition did not appear to represent disease prevalence in the U.S. population.

Abbreviations: NH = Native Hawaiian, OPI = Other Pacific Islander, AI = American Indian, AN = Alaska Native
Participation by Ethnicity

Figure 2-3: Ethnic Composition by Submission (CDRH)

Note: the y-axis for this graph only goes up to 40%.
ARE Guidance: Commitment Under FDASIA 907 Action Plan

- Participation
- Quality
- Transparency
WHY CONSIDER A-R-E SPECIFIC DIFFERENCES

• Differences in biology, environment and interactions between them which could affect health, disease, and response to medical devices.
  – Pediatric patients are more sensitive to ionizing radiation exposure

• Benefit-risk profile and other important aspects of device performance may differ across ARE subgroups.
  – Certain dermatology devices may have different considerations for use in a specific racial or ethnic population
  – Certain orthopedic devices may have different considerations for use in specific age subgroups
IMPORTANCE OF DIVERSE PARTICIPATION IN CLINICAL TRIALS

• Historical lack of diverse enrollment in clinical studies → lack of available data re: risks and benefits of medical device use in ARE subgroups.

• Clinical trials should aim to include diverse populations that reflect the intended population whenever possible and appropriate.

• Recognizing the practical challenges in doing so, the guidance includes recommendations for overcoming common barriers, to balance with least burdensome principles.
Guidance Objectives

• **Diverse Participation.** Encourage the collection and consideration during the study design stage of relevant ARE and associated covariates

• **Consistent Analysis.** Outline recommended analyses of study subgroup data with a framework for considering demographic data when interpreting overall study outcomes

• **Transparency.** Specify expectations for reporting ARE-specific information in summaries and labeling
Scope of the Guidance

- To **improve the quality, consistency, and transparency of data** regarding the device performance within ARE-specific subgroups

- Applies to **devices that include clinical information** in support of a marketing submission (510(k), De Novo request, PMA, HDE)

- Also applies to **post-approval study submission and postmarket surveillance studies**

- Extends the policy set forth in the Sex-Specific Guidance to include age, race, and ethnicity (ARE)
TERMINOLOGY

SEX

AGE

RACE

ETHNICITY
TERMINOLOGY: AGE

• Trial participants should be grouped into categories appropriate for the disease/condition
• Pediatric population is defined in device regulations as less than 22 years of age
• Geriatric or elderly population is not defined
TERMINOLOGY: RACE & ETHNICITY

• Participants self-report on 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.
  – Methodology should be defined in the study protocol

See FDA’s Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials
RACE & ETHNICITY TWO-QUESTION FORMAT

• **Question 1 (answer first):** Do you consider yourself Hispanic/Latino or not Hispanic Latino?

• **Question 2 (answer second):** Which of the following five racial designations best describes you? *More than one choice is acceptable:*
  – American Indian or Alaskan Native
  – Asian or Pacific Islander
  – Black
  – Hispanic
  – White

Per OMB Policy Directive 15
Enroll Diverse Patients: Section IV

Analyze & Interpret Study Data: Section V

Submit & Report ARE Data: Section VI
Recommendations Grouped By Stage of Development

- Study Design, Early Enrollment
- Premarket Submission Stage
- Postmarket Submission Stage
RECOMMENDATIONS BY SECTIONS

IV: Enrolling Diverse Patients

V: Analysis & Interpretation of Study Data

VI: Submit & Report ARE Data
Planning for Diverse Enrollment

• Ideally plan to enroll a representative proportion of ARE subgroups consistent with the intended use population of the device.*

• Consider:
  – Disease incidence or prevalence in subgroups
  – Diagnosis and treatment patterns in subgroups
  – Proportions of subgroups included in past studies for target indication
  – Clinically meaningful subgroup differences in safety, effectiveness, or overall benefit-risk profile

*See pg. 13 for Enrollment Resources
To Enhance Diverse Enrollment

• Include investigational sites with access to ARE subgroups
• Alternative communication strategies for study materials
• Consider broader enrollment criteria
• Investigate reasons for no or low inclusion of ARE subgroups
• Involve community providers and patient advocacy groups in recruitment
• Compensation for transportation costs
• Flexible scheduling and child care and elder care

*See pg. 13 for Enrollment Resources
To Enhance Retention

Sponsors

• Develop follow-up plan including proxy contact info and actions to take when patient misses a visit
• Closely monitor follow-up rates so problems can be addressed quickly
• Report accountability of participants in study report

Investigators

• Stress the importance of follow-up at time of informed consent and subsequent visits
• Reminder calls for upcoming visits
• Attempt to locate patients lost to follow-up
• Record reasons for patient withdrawals
• Maintain continued interest in patients with post-op and follow-up visit calls

*See pg. 19 for approaches to minimize loss-to-follow-up
RECOMMENDATIONS BY SECTIONS

IV: Enrolling Diverse Patients

V: Analysis & Interpretation of Study Data

VI: Submit & Report ARE Data
Statistical Recommendations – All Studies

- Statistical Analysis Plan (SAP) in the study protocol should:
  - Pre-specify assessment of heterogeneity across relevant demographic subgroups (may include interaction testing or other approaches)
  - Pre-specify reporting by demographic subgroup

*Refer to [FDA Guidance: Evaluation of Sex-Specific Data in Medical Device Clinical Studies](https://www.fda.gov) for additional statistical recommendations*
Subgroup Differences Anticipated?

- Consider proper study design, sufficient enrollment of subgroups to allow meaningful analysis, and potentially controlling for multiple comparisons
- May consider subgroup-specific objective performance criteria (OPC) or performance goal (PG)
- May consider powering for subgroup-specific claims
- May consider demographic subgroups as stratification variables in randomization process when appropriate

*Refer to FDA Guidance: Evaluation of Sex-Specific Data in Medical Device Clinical Studies for additional statistical recommendations*
Recommendations for Demographic Subgroup-Specific Statistical Design

**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**

**CONTINUE**

All Clinical Studies

**CONTINUE**

One-Arm Study

**YES**

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**

Comparative Study***

**YES**

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.

Randomized Controlled Trial (RCT)

**YES**

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**

- Reporting 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.

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*For ongoing studies, provide descriptive statistics. For new studies, provide statistical inferences
**Applicable when subgroup differences are anticipated
***A comparative study may include a non-randomized controlled trial (concurrent control, historical control) or a randomized controlled trial (RCT)
Recommendations for Demographic Subgroup-Specific Statistical Analysis for One-Arm Studies

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 difference between demographic subgroups?

NO → Data may be combined across subgroups.**

YES → Is there a significant difference between demographic subgroups that is clinically meaningful and statistically significant?

NO → Data may be combined across subgroups.**

YES → RECOMMENDATIONS

- Discuss how clinically meaningful differences across subgroups may contribute to differences in benefit-risk profile in certain subpopulations.
- Data may not be combined across subgroups.** Additional data may be needed pre- or postmarket to support marketing submission. Discussion 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 combining data across subgroups, if applicable.

Note: In some cases, the subgroup-specific difference can be 1) statistically significant but not clinically meaningful or 2) clinically meaningful but not statistically significant. In these cases, discussion with FDA is advised.
Recommendations for Demographic Subgroup-Specific Statistical Analysis for Comparative Studies

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

RECOMMENDATIONS

Data may be combined across subgroups**

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

NO

Data may be combined across subgroups**

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

Is interaction effect clinically meaningful and statistically significant?

NO

YES

*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 combining data across subgroups, if applicable.
Note: In some cases, the subgroup-specific difference can be 1) statistically significant but not clinically meaningful or 2) clinically meaningful but not statistically significant. In these cases, discussion with FDA is advised.
RECOMMENDATIONS FOR ANALYZING SUBGROUP DATA

• FDA submissions should include analysis of the following for clinically meaningful ARE-specific differences:
  – Primary effectiveness endpoints
  – Primary safety endpoints
  – Key secondary endpoints

• Regardless of the potentially limited statistical power of these subgroup analyses
OTHER CONSIDERATIONS OF SUBGROUP ANALYSIS

• 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 can sometimes be explained by other covariates

• Hypotheses for exploratory analyses should be consistent with the literature (natural history, subgroups, known pathophysiology).
INTERPRETATION OF ARE SPECIFIC DATA

• Clinically meaningful and/or statistically significant differences observed? Discuss with FDA.

• Describe how these contribute to overall benefit-risk profile in certain subpopulations.

• Limitations with small data sets or larger studies with underrepresentation of diverse subgroups → Discuss with FDA.
RECOMMENDATIONS BY SECTIONS

IV: Enrolling Diverse Patients

V: Analysis & Interpretation of Study Data

VI: Submit & Report ARE Data
RECOMMENDATIONS FOR SUBMITTING & REPORTING SUBGROUP DATA

Submit

The term “submit” refers to information submitted to the FDA for analysis.

Report

The term “report” refers to information that should be included in publicly available documents (i.e., labeling, FDA review summaries).
## RECOMMENDATIONS FOR SUBMITTING & REPORTING SUBGROUP DATA

<table>
<thead>
<tr>
<th>Submit to FDA</th>
<th>Publicly Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment demographics for ARE subgroups</td>
<td></td>
</tr>
<tr>
<td>Differences in relevant baseline characteristics &amp; co-morbidities</td>
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</tr>
<tr>
<td>Any disproportionate loss to follow-up</td>
<td></td>
</tr>
<tr>
<td>Outcome differences</td>
<td>Clinically meaningful and statistically significant outcome differences</td>
</tr>
<tr>
<td>Discuss generalizability of results when enrollment is substantially different than prevalence</td>
<td>How such differences affect overall benefit-risk profile for certain subgroups</td>
</tr>
<tr>
<td>Results of <em>pre-specified</em> subgroup analyses to support subgroup-specific labeling</td>
<td></td>
</tr>
</tbody>
</table>
Sample Reporting Format – Race

<table>
<thead>
<tr>
<th>Race</th>
<th>Hazard Ratio (95% CI)</th>
<th>Sample Size (n=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>2.57 (2.09 – 3.16)</td>
<td>2569</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>2.20 (0.59 – 8.19)</td>
<td>27</td>
</tr>
<tr>
<td>Asian</td>
<td>3.18 (1.43 – 7.10)</td>
<td>144</td>
</tr>
<tr>
<td>Black or African American</td>
<td>3.67 (2.22 – 6.05)</td>
<td>378</td>
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<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>1.68 (0.28 – 10.07)</td>
<td>10</td>
</tr>
<tr>
<td>White</td>
<td>2.69 (2.17 – 3.34)</td>
<td>2010</td>
</tr>
</tbody>
</table>
START

ENROLLMENT DEMOGRAPHICS

OUTCOME INFORMATION

Is overall treatment effect statistically significant and clinically meaningful?*

NO

Analysis raises questions about data to support marketing application.

YES

Is there a clinically meaningful subgroup difference?

NO

RECOMMENDATIONS

Submit and publically 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.

YES

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

NO

RECOMMENDATIONS

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

YES

Were the subgroup analyses pre-specified?

NO

Summarize the findings descriptively.*

NO

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

YES

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

NO

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, SSED).
Questions?

For general questions, please contact the Division of Industry and Consumer Education:  DICE@fda.hhs.gov

For questions related to the guidance document:  CDRHPatientDiversity@fda.hhs.gov

Slide Presentation, Transcript and Webinar Recording will be available at:
http://www.fda.gov/training/cdrhlearn

Under the Heading: How to Study and Market Your Device; Subheading: Clinical Studies/Investigational Device Exemption (IDE)

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