U.S. FOOD & DRUG ADMINISTRATION

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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

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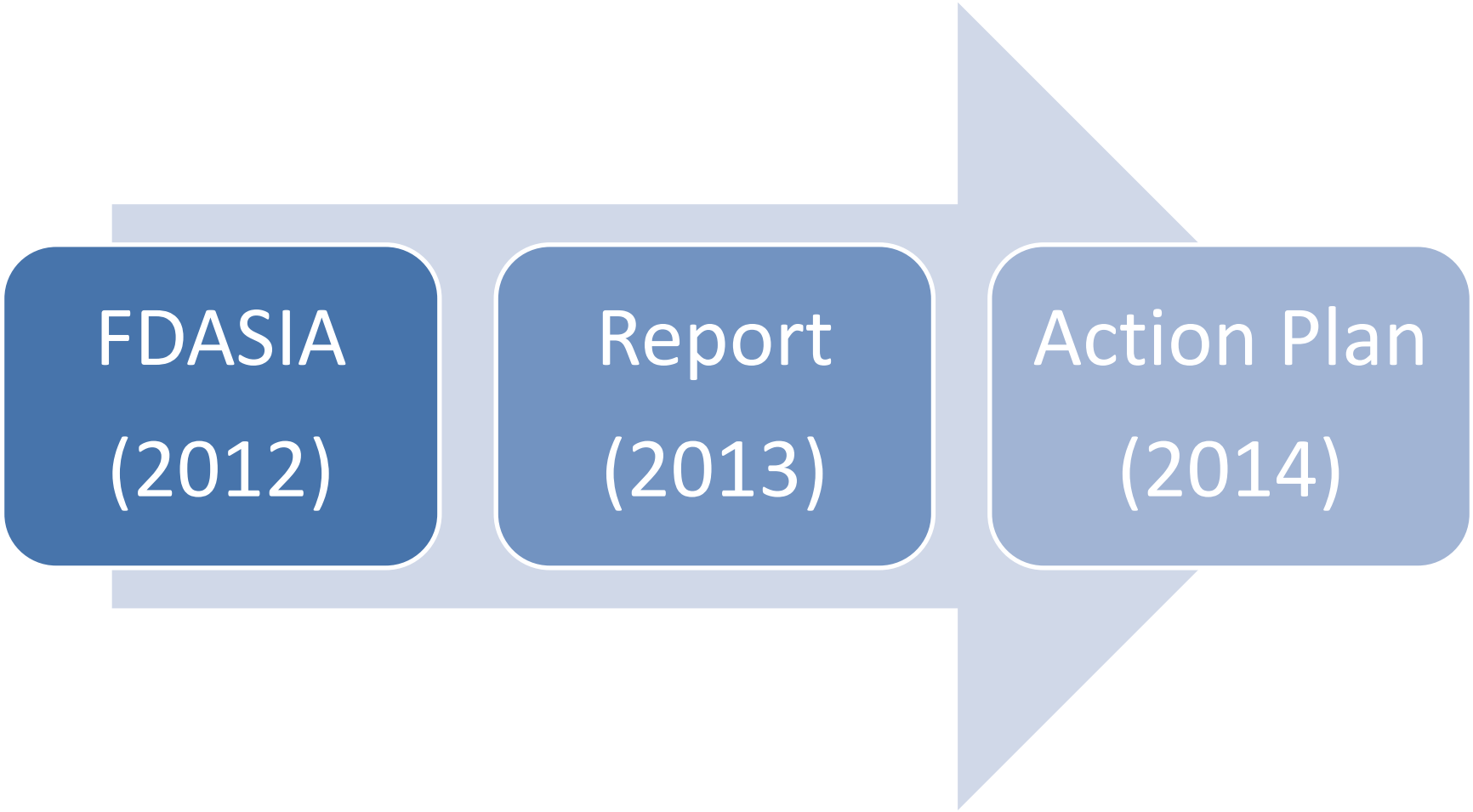
OUTLINE

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

BACKGROUND

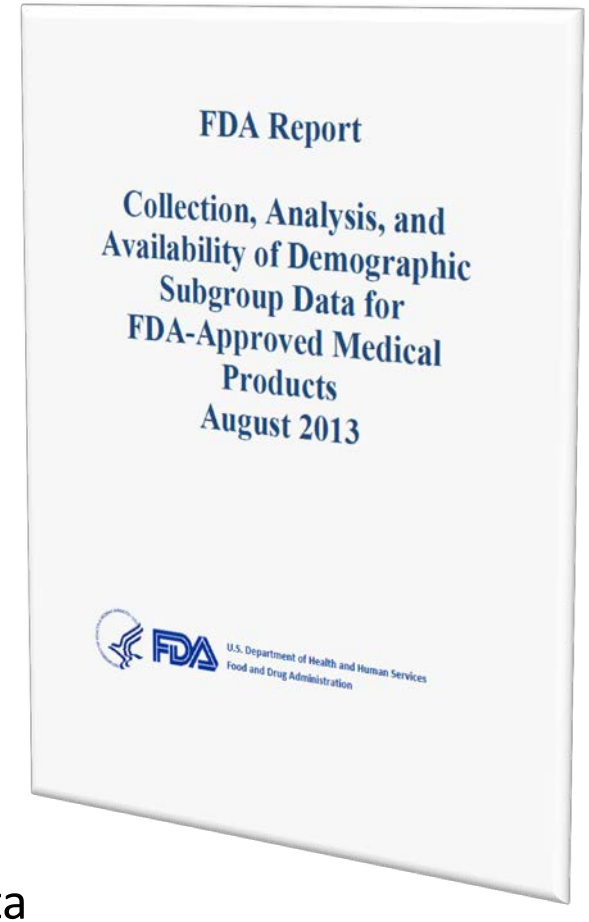
- In 2012, Section 907 of the Food and Drug Administration Safety and Innovation Act directed the FDA to examine participation of diverse subgroups and corresponding data in medical product submissions, and availability of this information to the public.
- In 2014, the FDA issued an Action Plan to improve 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- Draft guidance was issued June 20, 2016, for public comment.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)

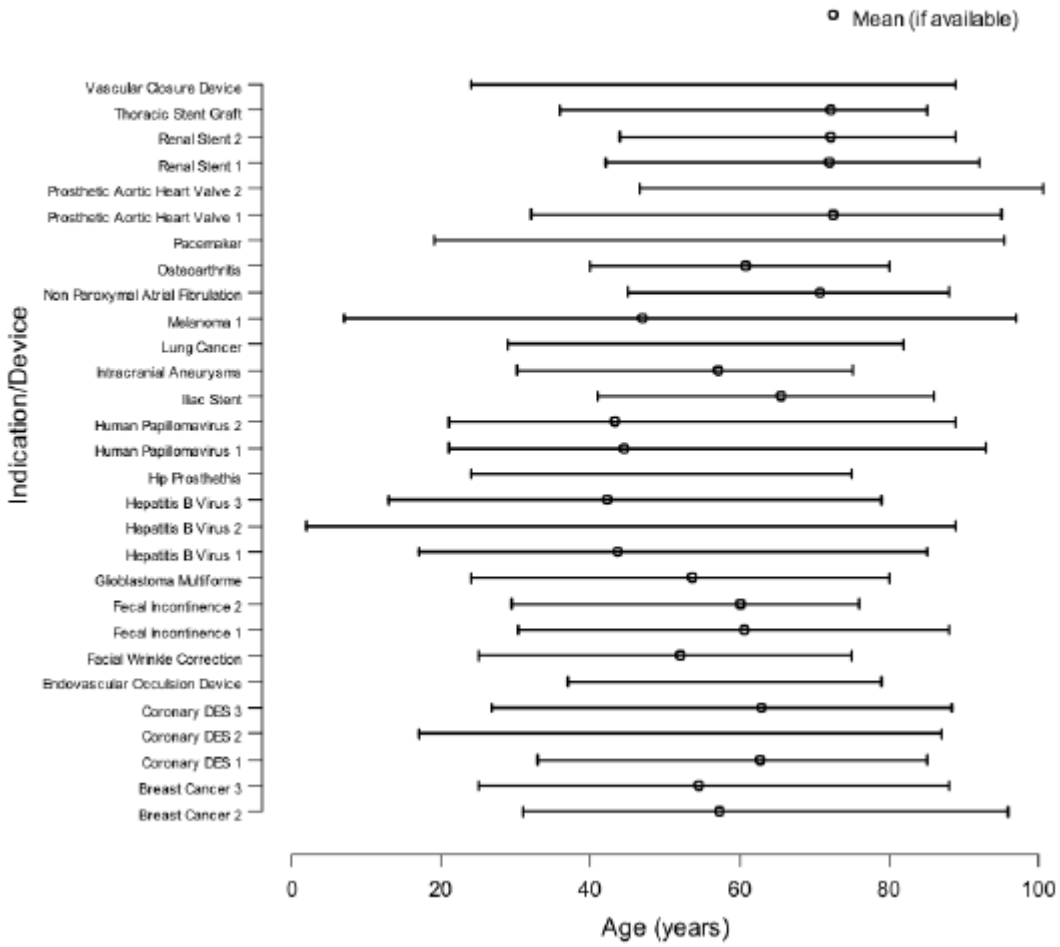


Need for Improved Consistency in Analysis & Public Transparency

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

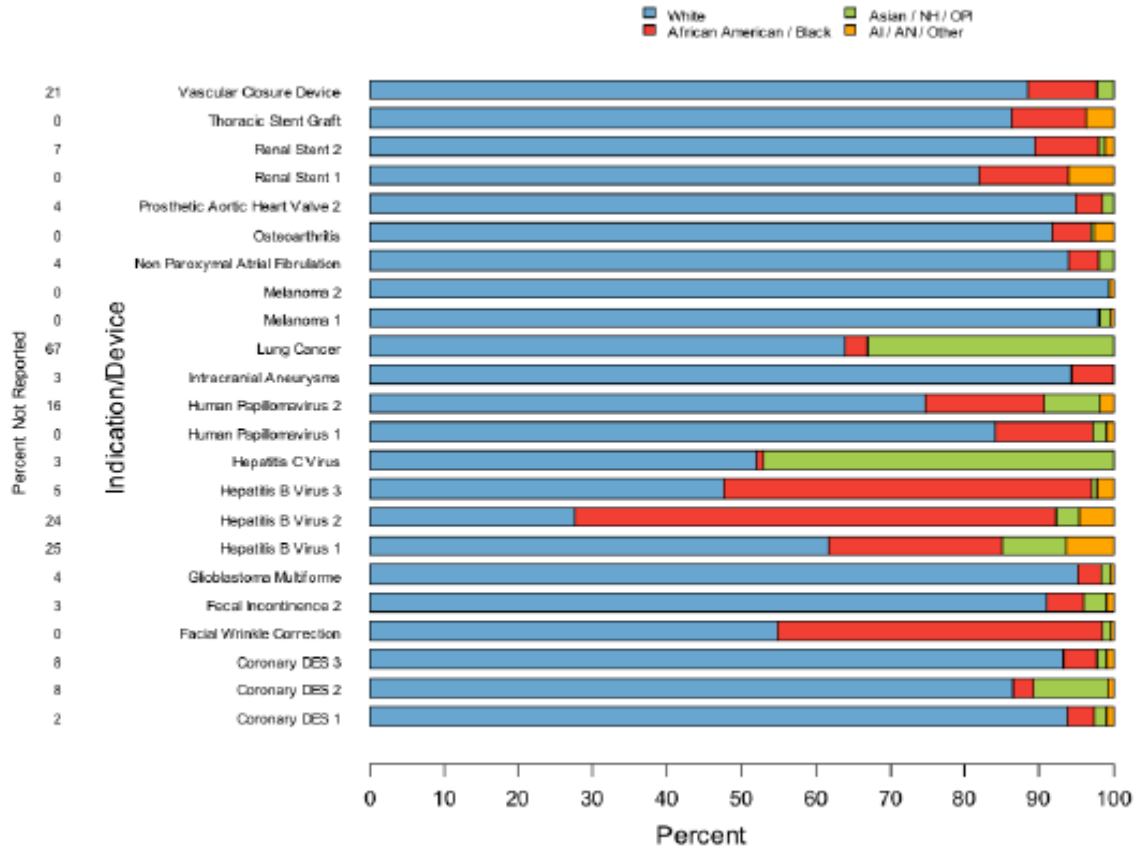
Figure 2-1: Age Range by Submission (CDRH)



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

Participation by Race

Figure 2-4: Race Composition by Submission (CDRH)

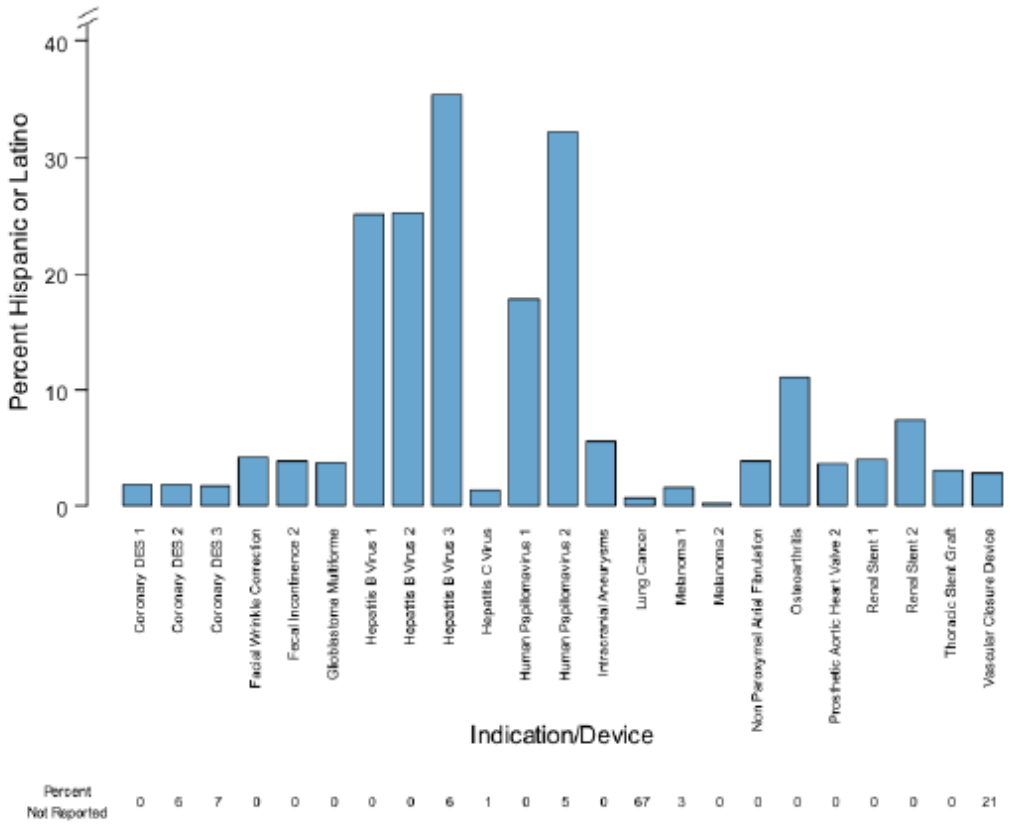


Abbreviations: NH = Native Hawaiian, OPI = Other Pacific Islander, AI = American Indian, AN =Alaska Native

- 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.

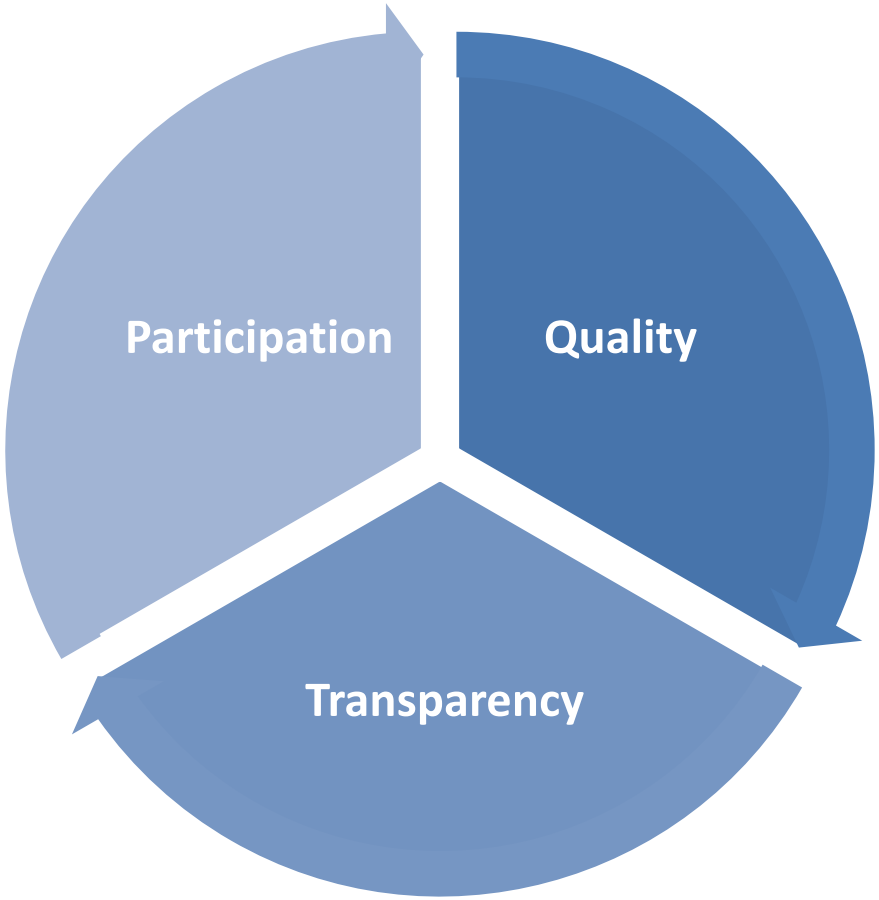
Participation by Ethnicity

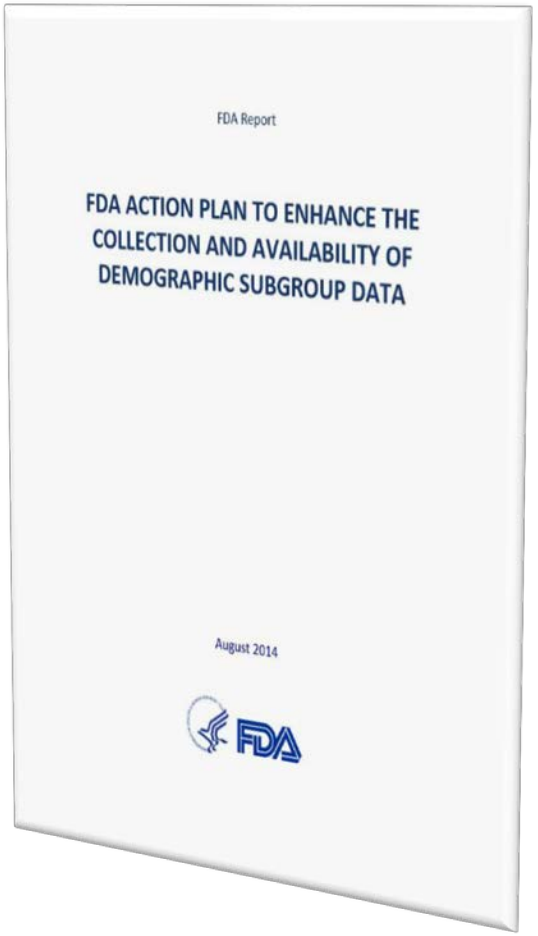
Figure 2-3: Ethnic Composition by Submission (CDRH)



Note: the y-axis for this graph only goes up to 40%.

ARE Guidance: Commitment Under FDASIA 907 Action Plan




FDA Report

FDA ACTION PLAN TO ENHANCE THE COLLECTION AND AVAILABILITY OF DEMOGRAPHIC SUBGROUP DATA

August 2014

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.

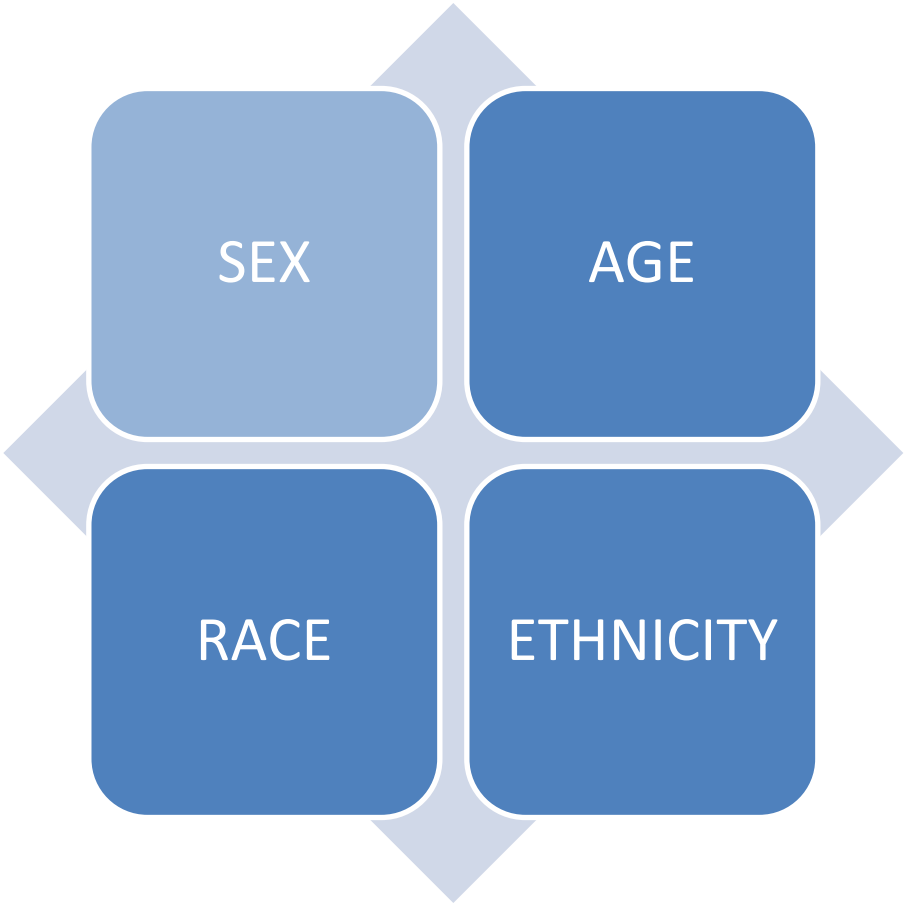
Guidance Objectives

- **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 submissions and postmarket surveillance studies**
- Extends the policy set forth in the Sex-Specific Guidance to include age, race, and ethnicity (ARE)

TERMINOLOGY



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:

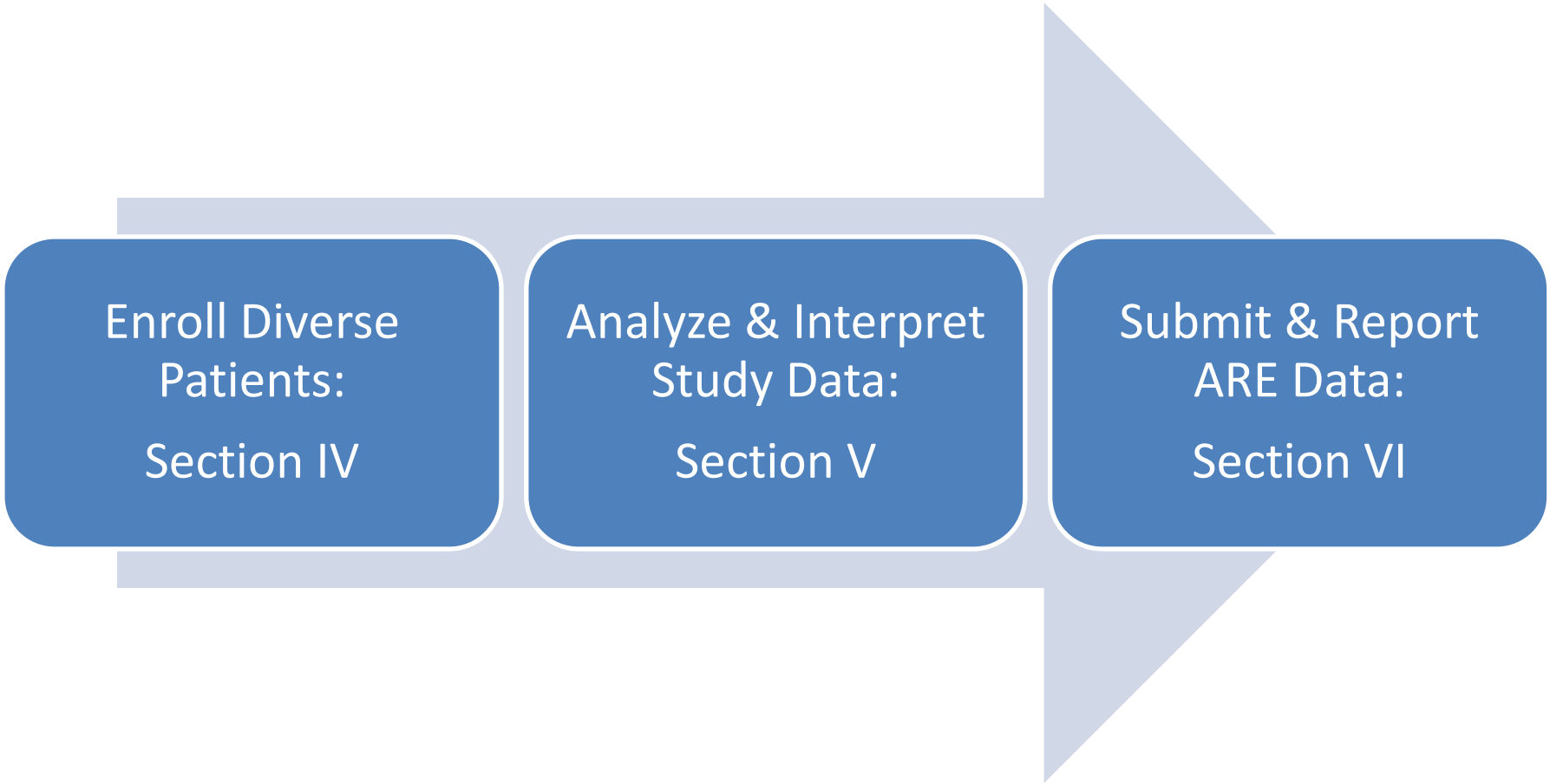
- Disease/condition may warrant more granular race data
- Categories may not be appropriate outside the U.S.
  - Methodology should be defined in the study protocol

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

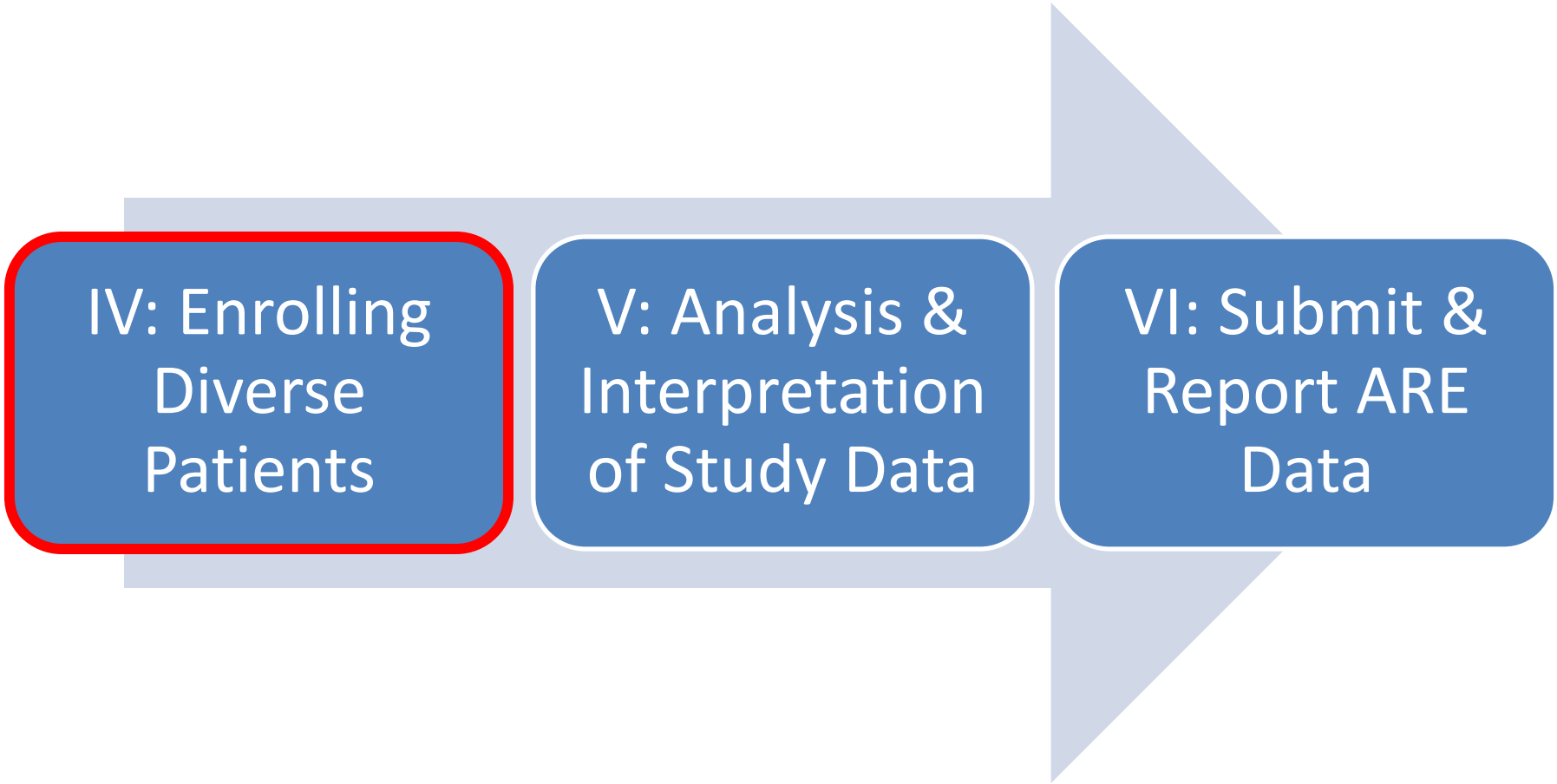
Per OMB Policy Directive 15


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



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

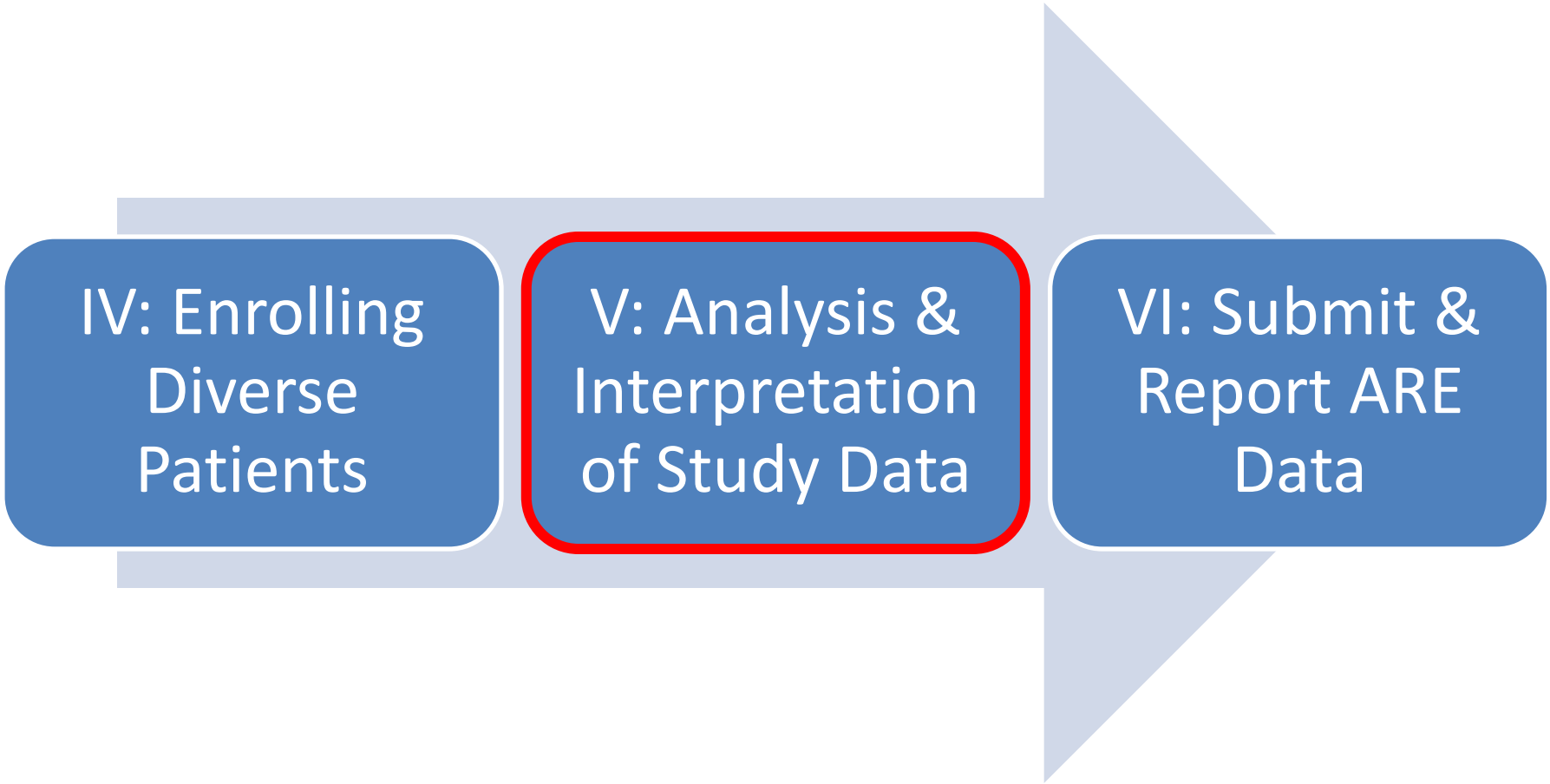
- Develop follow-up plan including proxy contact info and actions to take when patient misses a visit
- Closely monitor follow-up rates so problems can be addressed quickly
- Report accountability of participants in study report

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



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

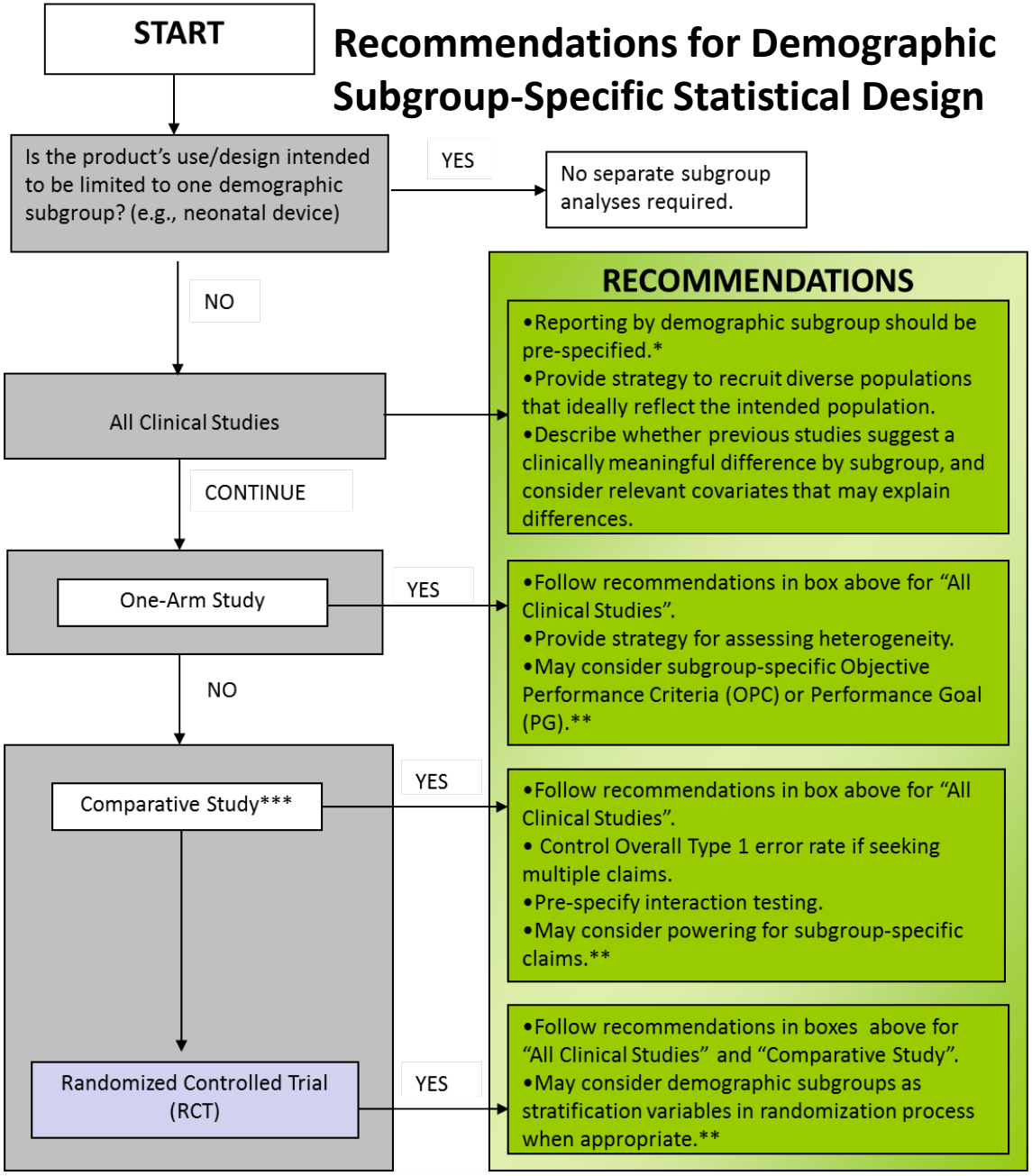
**Refer to FDA Guidance: Evaluation of Sex-Specific Data in Medical Device Clinical Studies for additional statistical recommendations*

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

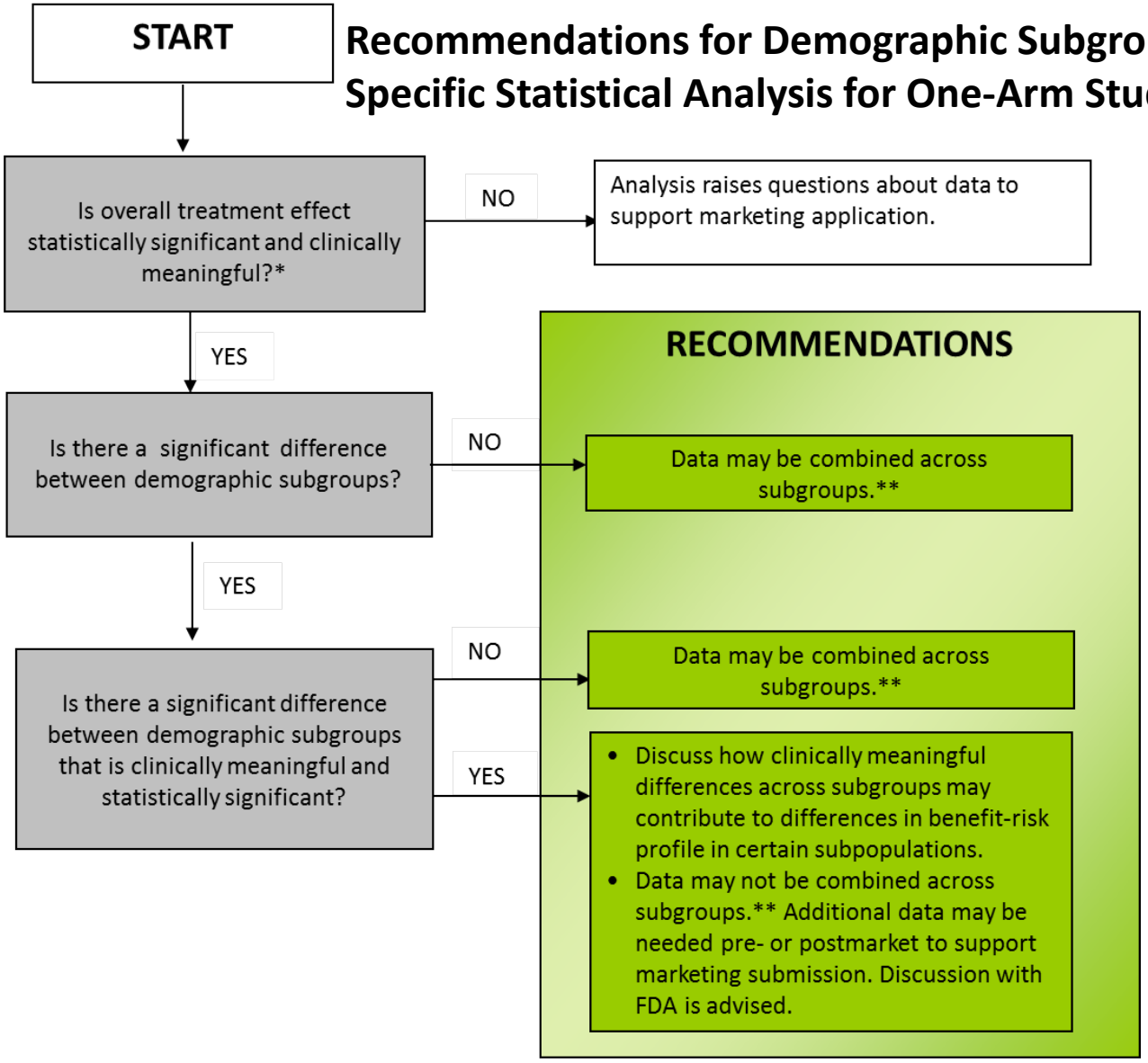
**Refer to FDA Guidance: Evaluation of Sex-Specific Data in Medical Device Clinical Studies for additional statistical recommendations*

Recommendations for Demographic Subgroup-Specific Statistical Design



*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

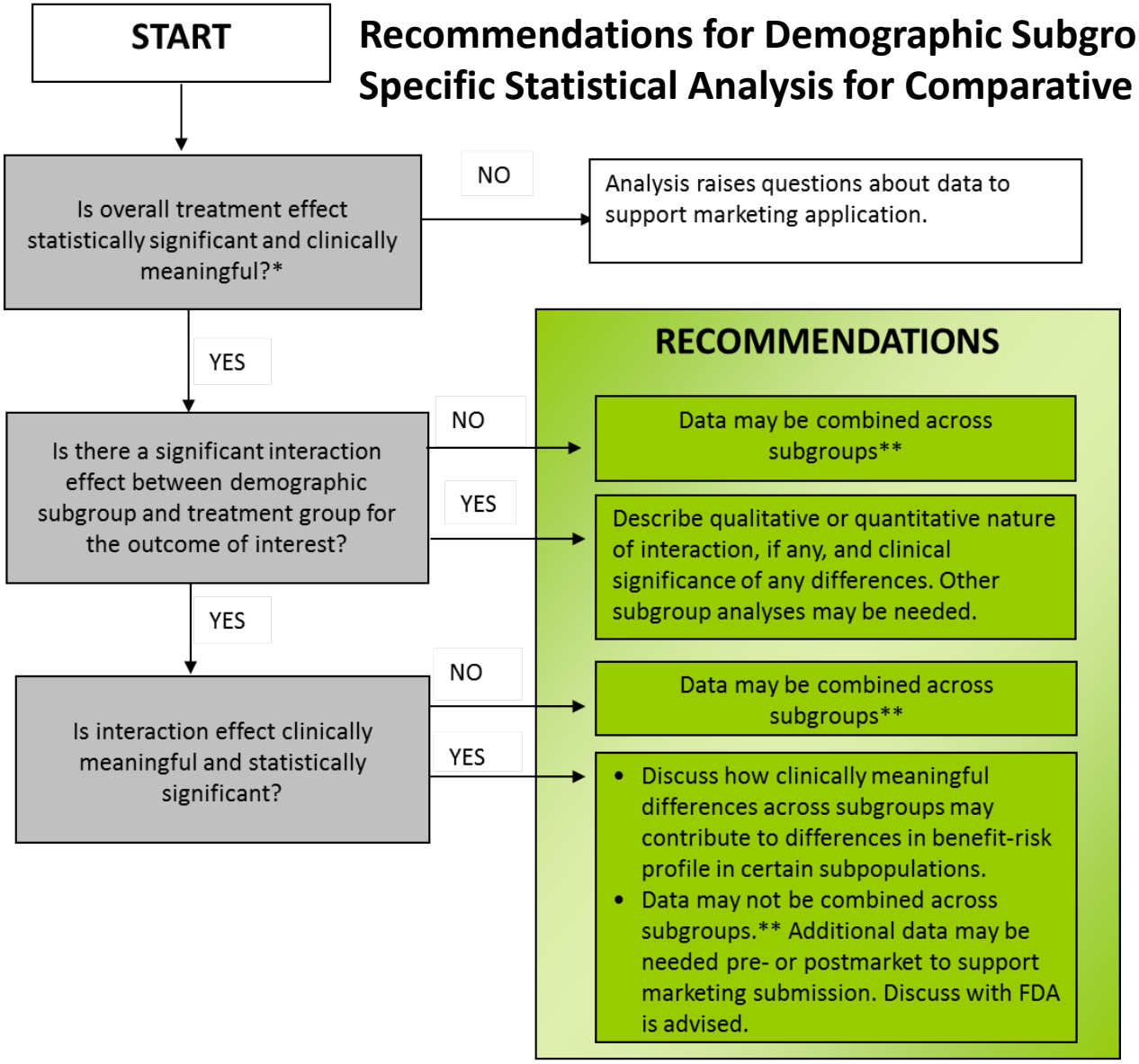


*Unplanned subgroup analyses are generally not considered to be adequate to support statements in the labeling regarding the safety or effectiveness of the device if overall treatment effect is not statistically significant and clinically meaningful.

**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



*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

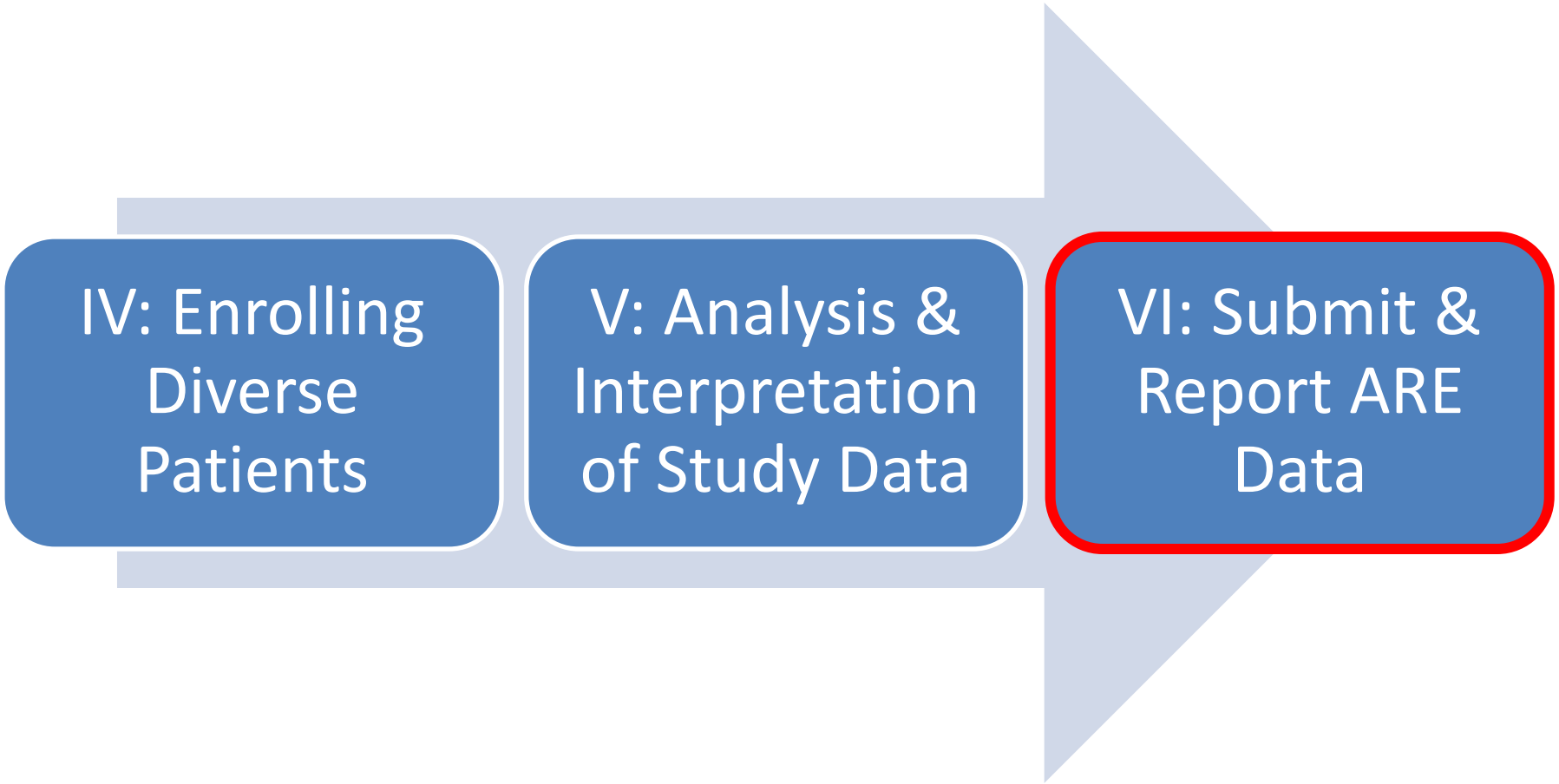
OTHER CONSIDERATIONS OF SUBGROUP ANALYSIS

- 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



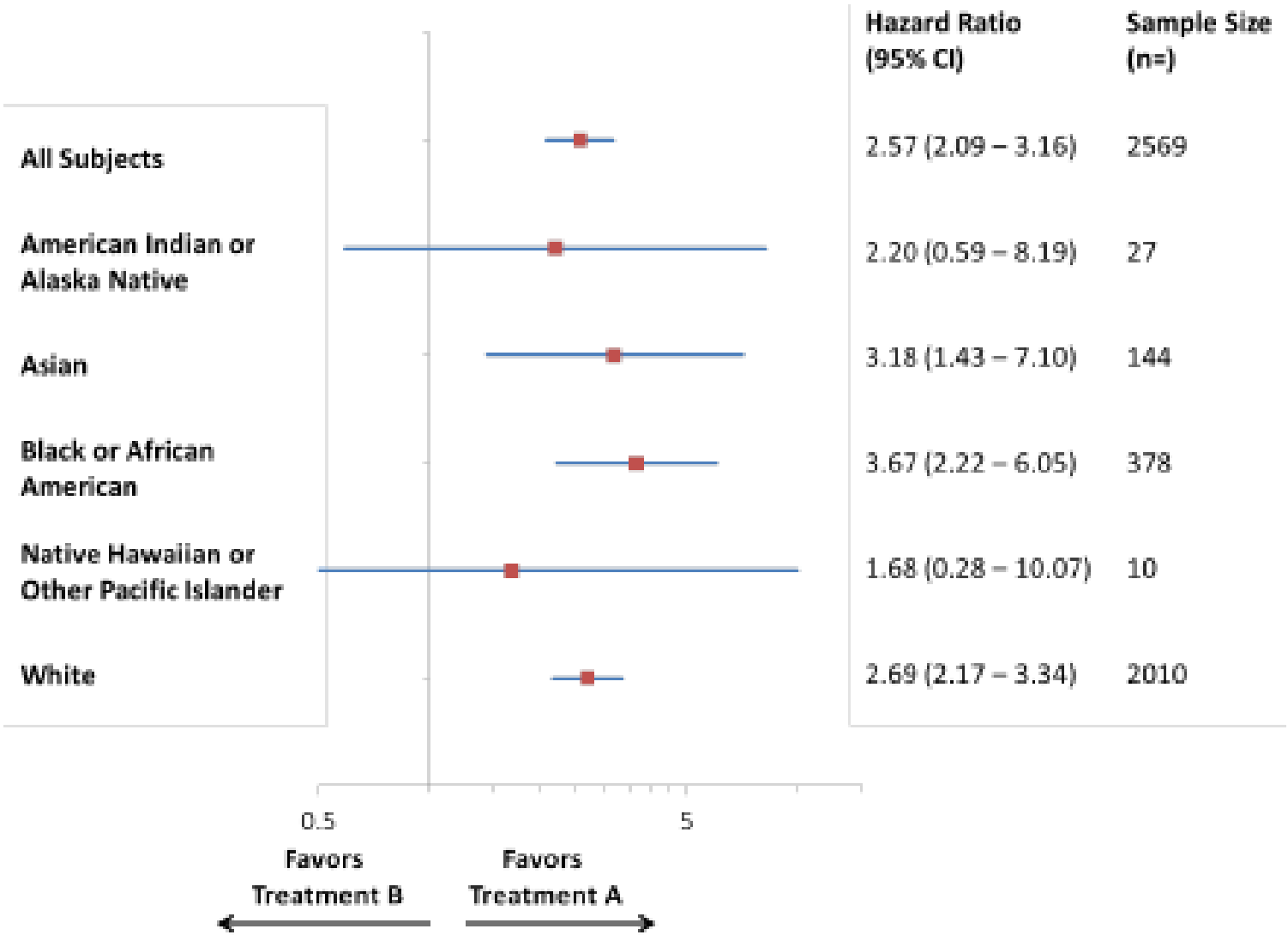
RECOMMENDATIONS FOR SUBMITTING & REPORTING SUBGROUP DATA

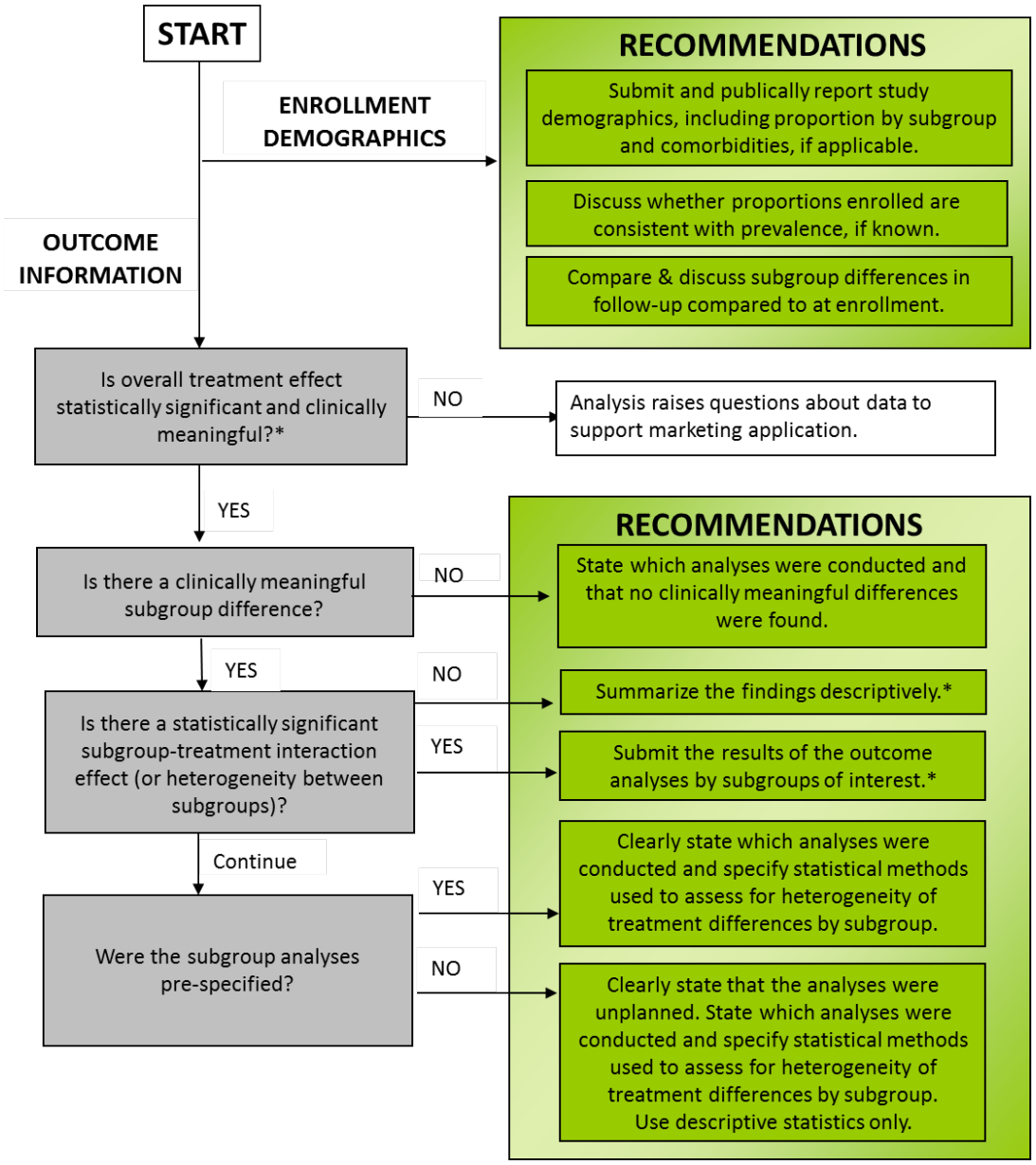
Submit	The term “submit” refers to information submitted to the FDA for analysis.
Report	The term “report” refers to information that should be included in publicly available documents (i.e., labeling, FDA review summaries).

RECOMMENDATIONS FOR SUBMITTING & REPORTING SUBGROUP DATA

Submit to FDA	Publicly Report
Enrollment demographics for ARE subgroups	
Differences in relevant baseline characteristics & co-morbidities	
Any disproportionate loss to follow-up	
Outcome differences	Clinically meaningful and statistically significant outcome differences
Discuss generalizability of results when enrollment is substantially different than prevalence	How such differences affect overall benefit-risk profile for certain subgroups
Results of *pre-specified* subgroup analyses to support subgroup-specific labeling	

Sample Reporting Format – Race





* 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 publically 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

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

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