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Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Preface

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Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

The purpose of this guidance is to outline the FDA's expectations and provide recommendations for the evaluation and reporting of age, race and ethnicity data in medical device clinical studies. The primary intent of these recommendations is to improve the quality, consistency and transparency of data regarding the performance of medical devices within specific age, race, and ethnic groups. Proper evaluation and reporting of this data can benefit patients, clinicians, researchers, regulators and others. Additionally, it is important that clinical trials include diverse populations that reflect the intended use population. In general, to achieve an unbiased estimate of treatment effect in the general population, sponsors should develop a strategy to enroll diverse populations including representative proportions of relevant age, race, and ethnicity subgroups, which are consistent with the intended use population of the device. This draft guidance includes recommendations and considerations to assist sponsors in developing such a strategy.

When finalized, this guidance will extend the policy set forth in the FDA's *Evaluation of Sex-Specific Data in Medical Device Clinical Studies* Guidance[1] to additional demographic subgroups of age, race, and ethnicity. FDA intends to integrate the final content into one final guidance document. When finalized, this guidance will also extend and complement FDA's

[1] See FDA's guidance *Evaluation of Sex-Specific Data in Medical Device Clinical Studies* (August 22, 2014) http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm283707.pdf.

Collection of Race and Ethnicity Data in Clinical Trials Guidance, which, for collecting and reporting race and ethnicity information in clinical trials, recommended the use of the standardized approach developed by the Office of Management and Budget (OMB).[2]

The specific objectives of this guidance are to:

1) 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, etc.), for devices for which safety, effectiveness (probable benefit, for HDEs), or benefit-risk profile is expected to vary across these groups;
2) outline recommended analyses of study subgroup data, with a framework for considering demographic data when interpreting overall study outcomes; and
3) specify FDA's expectations for reporting age, race, and ethnicity-specific information in summaries and labeling for approved or cleared medical devices.

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Scope

This guidance is intended for devices that include clinical information in support of a marketing submission, whether a premarket notification (510(k)), premarket approval (PMA) application, evaluation of Automatic Class III Designation (*de novo* request), or humanitarian device exemption (HDE) application. The recommendations contained herein also apply to post-approval study submissions and postmarket surveillance studies, where noted.

Age, race, and ethnicity are not the only demographic variables that may affect device performance. While this guidance focuses on the impact of age, race, and ethnicity, some of the recommendations may also be used to promote study enrollment and data analysis adequately accounting for other demographic variables, such as sex[3] and geographic location (e.g., rural). Other patient characteristics such as emotional, physical, sensory, and cognitive capabilities can often be important variables when evaluating medical device safety and effectiveness (or probable benefit for HDEs); however, these will not be addressed within this guidance. For further information related to these user considerations please see the *Design Considerations for Devices Intended for Home Use Guidance* document[4].

[2] See FDA's guidance *Collection of Race and Ethnicity Data in Clinical Trials* (September, 2005) http://www.fda.gov/RegulatoryInformation/Guidances/ucm126340.htm.

[3] See footnote 1.

[4] See FDA's guidance *Design Considerations for Devices Intended for Home Use* (November 24, 2014) http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm331681.pdf.

The impact of demographic variables on device safety, effectiveness (probable benefit, for HDEs), or benefit-risk profile may apply more to certain types of products or diseases than others. For example, certain dermatology devices may have different considerations for use in a specific race or ethnic population. Similarly, certain orthopedic devices may have different considerations for use in specific age groups. Studies of devices intended only for certain groups (e.g., pediatrics) would not be expected to address the potential differences in outcome for groups outside the intended use population. Additionally, some *in vitro* diagnostic (IVD) device clinical studies are conducted on de-identified leftover specimens, so it may not be possible to obtain demographic information, such as age, race or ethnicity. As a result, evaluation of age, race, and ethnicity data would not be possible in these cases. In general, when clinically relevant differences in treatment effect are anticipated across age, race, or ethnic groups, these effects should be considered in the study design and appropriately reported in the device labeling.

FDA recommends the use of this guidance document as a supplement to other FDA guidance where applicable, in particular, any relevant device-specific guidance, as well as FDA's *Collection of Race and Ethnicity Data in Clinical Trials* guidance.[5] Consultation with the FDA primary reviewing Division or Branch is advised.[6]

III. Background

Certain elements described in this guidance have been emphasized in Agency regulations and/or policy in the past. Over recent decades the Agency's views, as well as those of the medical community in general, have evolved regarding age, race, and ethnicity in clinical studies.

Prior to developing the policy set forth in this guidance, FDA publicly sought input from a variety of experts and stakeholders regarding the study and evaluation of age, race, and ethnicity in clinical studies for medical devices. On April 9, 2015, the Institute of Medicine convened a public workshop of various government agencies, physician professional societies, and patient advocacy groups participated in a public workshop to discuss strategies for ensuring diversity, inclusion, and meaningful participation in clinical trials.[7] This guidance document reflects the recommendations generated in this and other public fora. It is intended to provide guidance on the design, conduct, and reporting of clinical studies to improve age, race, and ethnicity information about the safety and effectiveness (or probable benefit for HDEs) of approved and cleared new medical devices.

[5] See footnote 2.

[6] See FDA's guidance *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff* (February 18, 2014) http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf.

[7] Institute of Medicine Workshop: Strategies for Ensuring Diversity, Inclusion, and Meaningful Participation in Clinical Trials. April 9, 2015. Agenda and presentations available at http://iom.nationalacademies.org/Activities/SelectPops/HealthDisparities/2015-APR-09.aspx.

A. Section 907 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)

Section 907 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) directed the Agency to publish and provide to Congress a Report followed by an Action Plan outlining "recommendations for improving the completeness and quality of analyses of data on demographic subgroups [including sex, age, race, and ethnicity] in summaries of product safety and effectiveness data [or probable benefit for HDEs] and in labeling; on the inclusion of such data, or the lack of availability of such data, in labeling; and on improving the public availability of such data to patients, health care providers, and researchers." In that Action Plan, CDRH committed to develop this draft guidance, as an action to improve the completeness, quality, and public availability of demographic subgroup data from medical device clinical studies.[8]

B. Terminology

(1) Age

When evaluating age-specific data, clinical studies should plan to group subjects by age groups as appropriate for the disease condition. Standardizing age categories may not be appropriate for all devices; however, more discrete age groupings should be considered. For example, you may group older patients for analysis at 65-74 years old, and 75-84 years old, rather than simply older/younger than 65.

FDA does not define a specific age for the geriatric population due to the different considerations for the wide variety of medical devices and diagnostics. However, we recommend stratifying age based on relevant disease characteristics (e.g. 65-74, ≥75 years).

Device regulations define the pediatric population as any patient less than 22 years of age.[9] It should be noted that this may differ from the drug and biologic regulations but for purposes of this guidance, the definition of pediatric patient in 21 CFR 814.3(s) should be used. This population is further subdivided into

[8] See FDA's *Report on Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products* (August, 2013), FDA's *Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data* (August, 2014), and other related information including public feedback and FDA's current progress, at: http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/ucm389100.htm .

[9] 21 CFR 814.3(s) defines pediatric patients as patients who are 21 years of age or younger (that is, from birth through the twenty-first year of life, up to but not including the twenty-second birthday) at the time of the diagnosis or treatment. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=814.3.

several age groups as described in guidance or by developmental milestones as appropriate.[10]

(2) Race and Ethnicity

In accordance with FDA's guidance *Collection of Race and Ethnicity Data in Clinical Trials*[11], patients may self-identify in both an ethnic and racial category (e.g., Hispanic-White, Hispanic-Black). This guidance specified that "the Office of Management and Budget (OMB) stated that its race and ethnicity categories were not anthropologic or scientifically based designations, but instead were categories that described the sociocultural construct of our society. The Department of Health and Human Services (HHS) chose to adopt these standardized categories for its agencies that report statistics because the categories are relevant to assessing various health related data, including public health surveillance and research." FDA accepts applications containing clinical study data with ethnic and racial demographic data captured as one category or separately, although the generally preferred method is to collect ethnicity and race separately.

More granular race data may be important depending on the disease or condition (e.g., if the condition is substantially more prevalent or varied in course for Ashkenazi Jewish or Han Chinese). Additionally, FDA acknowledges that other ethnic and racial categories may be appropriate depending on the study population, e.g., in global studies involving sites and patients outside the United States (OUS). The categories and identification method should be defined in the study protocol.

Collection and pooling of data from OUS study sites may result in confounding issues of ethnicity and standard of care. OUS sites may not categorize race and ethnicity in the same manner as US sites or may define certain race or ethnicity groups differently than do US sites (e.g., "Caucasian" vs "white" in European vs US data). Additionally, the standard of care at OUS sites may not be equivalent. These differences may make it difficult to pool race and ethnicity subgroup data from OUS sites.

[10] See FDA's guidance *Premarket Assessment of Pediatric Medical Devices* (March 24 2014). This guidance subdivides the pediatric age group as follows:

- Newborn (neonate) – from birth to 1 month of age
- Infant – greater than 1 month to 2 years of age
- Child – greater than 2 to 12 years of age
- Adolescent – greater than 12 through 21 years of age

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089742.pdf.

[11] See footnote 2.

C. Why Consider Age, Race, and Ethnicity Differences

(1) Age

Consideration of different age populations, particularly pediatric and older patients, which are often underrepresented in clinical trials, can be important for proper characterization of a device's safety and effectiveness (or probable benefit for HDEs) in the patient population. In the 2013 FDASIA 907 Report[12], of the approved PMAs evaluated for the report, only 40% publicly reported an age based analysis of outcomes data. The amount of age information available was inconsistent and often not detailed enough to analyze device performance related to age. The manner in which the age descriptive statistics are presented (e.g., mean, median, standard deviation, distribution) in a submission may affect data interpretation. Proper study of device use in both older and pediatric populations is important when the device is likely to be used for these subgroups.

Older patients and pediatric patients often have co-morbidities, concomitant therapies, or development considerations that could interact with the investigational device effects and impact device performance. Older patients may have age-related covariates such as characteristics of bone density, metabolism, digestion, synovial fluid, etc. that could affect the performance of medical devices. Meanwhile, medical devices may have different positive or adverse effects, or otherwise impact the development of a pediatric patient, where it would have no effect on an adult. For example, the use of cochlear implants in certain pediatric subgroups may not be advisable due to the size of the implant, or may be inappropriate due to the stage of the neurological development of the child.[13] In the case of intraocular lenses used to treat vision loss, device use may also improve future visual development in a young child.[14] For these reasons, it is important to consistently consider the potential impact of age on device effects, and to plan studies and analyses accordingly.

FDA provides guidance on developing medical devices for pediatric population subgroups (e.g., neonates, infants, children, and adolescents).[13] FDA currently has several device-related initiatives underway that aim to address challenges in the pediatric subpopulation. In 2007, Congress enacted the Pediatric Medical Device Safety and Improvement Act (PMDSIA) as part of the Food and Drug

[12] See FDA Report: *Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products,* issued August 2013, required under FDASIA Section 907. http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/UCM365544.pdf.

[13] See footnote 10.

[14] Institute of Medicine (US) Committee on Clinical Research Involving Children; Field MJ, Behrman RE, editors. Ethical Conduct of Clinical Research Involving Children. Washington (DC): National Academies Press (US); 2004. 2, The Necessity and Challenges of Clinical Research Involving Children. Available from: http://www.ncbi.nlm.nih.gov/books/NBK25553/.

Administration Amendments Act (FDAAA)[15] which provides that FDA may extrapolate adult data when appropriate.

PMDSIA also requires certain medical device applications to include, if readily available, a description of any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure and the number of affected pediatric patients.[16] FDA issued a guidance document outlining the implementation of this provision.[17]

(2) Race and Ethnicity

While the U.S. population demographic is changing, diverse representation in clinical trials remains a challenge, and inconsistent analysis and reporting contributes to a persistent lack of publicly available data on device performance in diverse ethnic and racial groups. The 2013 FDASIA 907 Report showed a distinct lack of publicly reported race and ethnicity data for medical devices.[18] Only 27% of the studies reviewed contained a race or ethnicity subgroup analysis, and only 16% had public statements regarding a race or ethnicity analysis.

There are several devices where differences in effect were observed that were correlated with race and ethnicity. For example, differences in skin structure and physiology can affect response to dermatologic and topically applied products.[19] Mortality rates of patients on dialysis have been shown to differ across race and ethnicity groups.[20] FDA encourages sponsors to collect race and ethnicity data according to the recommendations in the 2005 Collection of Race and Ethnicity Guidance Document.[21]

D. Participation of Age, Race, and Ethnicity Subgroups in Clinical Trials

[15] See PMDSIA Public Law No. 110-85. Available at http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf.
[16] Consult Pediatric uses of devices (21 U.S.C. § 360e-1). Available at http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec360e-1.htm.
[17] See FDA's guidance *Providing Information about Pediatric Uses of Medical Devices* (May 1, 2014) http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM339465.pdf.
[18] See footnote 12.
[19] Taylor, Susan C. "Skin of color: biology, structure, function, and implications for dermatologic disease." *Journal of the American Academy of Dermatology* 46.2 (2002): S41-S62.
[20] Yan, Guofen, et al. "The relationship of age, race, and ethnicity with survival in dialysis patients." *Clinical Journal of the American Society of Nephrology* 8.6 (2013): 953-961.
[21] See footnote 2.

It is important that clinical trials include diverse populations that reflect the intended population, especially when clinically meaningful differences in safety, effectiveness, (probable benefit, for HDEs), or benefit-risk profile are expected across these groups. In general, to achieve an unbiased estimate of treatment effect in the general population, sponsors should develop a strategy to enroll diverse populations including relevant age, race, and ethnic groups.

Where possible, it is also important to enroll diverse populations throughout the enrolling sites, particularly in studies where surgical or operator skill may be of key importance. If patients enrolled at one site are predominantly of one demographic subgroup, it may be possible to incorrectly attribute differences in device performance or surgical skill to demographic subgroups; this should be considered when planning and analyzing trials.

In general, study protocols should include pre-specified statistical plans for addressing these and other issues outlined in this guidance. Unplanned subgroup analyses or those with inadequate sample size are generally not considered to be adequate to support statements in the labeling regarding the safety or effectiveness of the device. However, the overall benefit-risk profile of the device will be considered.

(1) Barriers to Enrollment

Recruiting participants to clinical studies who represent the range of age, race, and ethnic groups consistent with the intended use population of the device may present additional challenges. There are numerous suspected reasons for low minority participation and low participation of older and pediatric patients.[22] In 2009, FDA published a Report to Congress on identified barriers to enrollment in clinical drug trials and recommendations on how to address the disproportionately low enrollment of certain populations in clinical trials, especially those trials in which these populations are highly affected by or are likely to suffer worse outcomes from the disease being evaluated.[23] FDA believes much of this information is relevant to medical device clinical trials as well.

The following have been identified as potential barriers to enrollment:

- lack of understanding about main obstacles to participation of different age, race, and ethnic groups in clinical research;

[22] See footnote 7.

[23] Report to Congress: *Food and Drug Administration Amendments Act (FDAAA) of 2007, Public Law No. 110-85 Section 901 of the Federal Food, Drug, and Cosmetic Act: Direct-to-Consumer Advertising's Ability to Communicate to Subsets of the General Population; Barriers to the Participation of Population Subsets in Clinical Drug Trials* issued September 2009. http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/FDAAAImplementationChart/UCM214303.pdf.

- inclusion/exclusion criteria which unintentionally exclude different age, race, or ethnic groups (e.g., creatinine levels for African Americans)[24];
- lack of understanding about differences in disease etiology and pathophysiology may lead to under-diagnosis and under-referral of specific demographic subgroups;
- patient concerns related to treatment group, randomization, possible side effects, privacy, and historical mistrust of clinical trial ethics;
- language, cultural, and health literacy gaps between investigators and patients;
- investigator and sponsor avoidance of specific age, race, or ethnic groups of patients due to the perception that it is more difficult and potentially more expensive to recruit and maintain participation;
- pressure on investigators to quickly enroll patients regardless of demographic characteristics;
- perceived ethical concerns among investigators regarding enrollment of certain demographic groups in clinical trials;
- trial logistics (e.g., transportation, childcare) may disproportionately affect specific age, race and ethnic groups' ability to complete study follow-up visits;
- disproportionate drop out and lost-to-follow-up rates[25, 26]; and
- type or location of study sites may limit participation of specific age, race, or ethnic groups.

(2) Enrollment Resources

Where ongoing enrollment data demonstrate an underrepresentation of certain subgroups enrolling in the study, sponsors are encouraged to investigate the reason(s) for lack of enrollment and consider the approaches in Section IV to enhance enrollment. It may be informative to evaluate whether the demographic distribution varies at different key time points (e.g., at screening, after evaluation of study inclusion/exclusion criteria, after consent, and at various follow-up time points). Information regarding changes in demographic distribution at key time points in study screening, enrollment, and follow-up can provide insight into root causes of lower enrollment rates in these groups. This may help identify ways to substantially lower barriers to enrollment of age, race, and ethnicity subgroups

[24] Neal, Ryan C., et al. "Relationship of ethnic origin, gender, and age to blood creatine kinase levels." *The American journal of medicine* 122.1 (2009): 73-78.
[25] See footnote 7.
[26] Wendler, David, et al. "Are racial and ethnic minorities less willing to participate in health research?" *PLoS medicine* 3.2 (2006): 201.

that have been shown to improve enrollment rates and study retention rates in other subgroups of study participants, (e.g., flexibility in follow-up visit scheduling with consideration of child care or elder care services during appointments).[25] Changes to a study protocol and informed consent may be made based on demographic distribution information with appropriate notification to and approval from the IRB and FDA, where necessary.

Sponsors may also wish to consider resources developed by the National Institutes of Health ,[27, 28, 29, 30] discussion with academic and contract research organizations, and practices of high-enrolling clinical study sites, in determining practices best suited to achieve appropriate enrollment of demographic groups, and to provide investigator training about these techniques. Some specific examples of strategies to increase inclusion of diverse study populations are discussed in Section IV below.

IV. Recommendations for Achieving Appropriate Enrollment

Historically, many medical device clinical studies have not enrolled proportions of age, race, and ethnic subgroups that reflect the underlying disease distribution in the affected population. This can be problematic because the ability to detect differences in response to treatment is markedly diminished if there is no or limited clinical experience with the product in the subgroup of interest. This has contributed to a substantial lack of available data regarding the risks and benefits of medical device use in age, race, and ethnic subgroups. Thus, it is important that clinical trials include diverse populations that reflect the intended population whenever possible and appropriate.

In general, to achieve an unbiased estimate of treatment effect in the general population, sponsors should ideally plan to enroll representative proportions of age, race, and ethnicity subgroups, which 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 or affected population.

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[27] NIH Office of Research on Women's Health has a number of publications available which provide advice on inclusion criteria, an overview of key elements in recruitment and retention, and a number of practical applications for conducting human subjects research, including ethical considerations. http://orwh.od.nih.gov/research/inclusion/index.asp.

[28] The National Institute of Mental Health developed a resource document ("Points to Consider about Recruitment and Retention While Preparing a Clinical Research Study"), which outlines common issues that can impact clinical recruitment and retention, and strategies to address these issues. http://www.nimh.nih.gov/funding/grant-writing-and-application-process/recruitment-points-to-consider-6-1-05_34848.pdf.

[29] The National Cancer Institute developed an online resource designed for practicing professionals to support clinical trial accrual needs. The Web site is a repository for literature and other resources and serves as a 'community of practice' to encourage dialog and discussion. https://accrualnet.cancer.gov.

[30] The National Institute on Minority Health and Health Disparities is active in the area of minority recruitment to trials. http://nimhd.nih.gov .

In cases where known disease science or prior clinical study results suggest a clinically meaningful difference in benefits or risks in one or more age, racial, or ethnic subgroups, sponsors should aim to enroll sufficient numbers of that demographic subgroup(s) to support robust analysis (i.e., a sample size sufficient for age-, race-, or ethnic- specific claims outcomes).

To overcome some of the barriers to adequate representative enrollment, FDA recommends the following considerations as sponsors proceed with their device development plans.

A. Consideration of Potential Age, Race, and Ethnicity Differences

To understand potential age, race, and ethnicity differences that may be relevant to the clinical evaluation of your device, we recommend that, for the disease or condition your device is intended to treat or diagnose, you identify and consider:

- age, race, and ethnicity-specific prevalence, if known;
- age, race, and ethnicity-specific diagnosis and treatment patterns, if known;
- proportions of age, race, and ethnicity subgroups included in past studies for the target indication, if known; and
- any known clinically meaningful age, race, and ethnicity-specific differences in outcomes related to either safety or effectiveness (or probable benefit for HDEs).

If information demonstrating age, race, and ethnicity differences in these areas is available, you should include it in your study protocol and submission documents as described in the following sections. FDA recognizes that such information is limited in some device development programs (e.g., those based on testing of de-identified non-annotated specimens).

(1) IDE Study Design, Early Enrollment Stage

You should include the information described above as part of the risk analysis section of your investigational plan (see 21 CFR 812.25(c)). We also recommend that you summarize this information in your study protocol and investigator training materials to explain the importance of enrolling appropriate proportions of age, race, and ethnicity subgroups. For studies that are already enrolling under an approved (or conditionally approved) IDE, where there is inadequate enrollment of age, race, and ethnicity subgroups, you should discuss with FDA an appropriate path to communicate this new information to investigators and how to use it without introducing bias to the study.

(2) Premarket Submission Stage

You should include this information as part of your marketing application in sections containing results of clinical investigations. A summary of any known clinically meaningful age, race, and ethnicity differences in disease course, 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).

FDA staff should include this information in the PMA Summary of Safety and Effectiveness, HDE Summary of Safety and Probable Benefit, and *de novo* decision summaries, which will be made publicly available on FDA's website.

(3) Postmarket Submission Stage

You should include this information in interim reports and in the results section of your final report for any mandated postmarket study(ies). Where available background information or clinical study results suggest there are clinically meaningful age, race, and/or ethnicity differences in disease course, outcomes, or benefit-risk profile, you should also submit revised labeling to include this information.

B. Planning for Diverse Study Recruitment

The approaches described below are aimed at increasing enrollment of age, race, and ethnicity subgroups in your study, as appropriate, with a goal of participation consistent with the intended use population of the device. In general, when clinically meaningful differences in treatment effect are anticipated across age, race, or ethnic groups, these effects should be considered during study planning. Some of these methods may also be adapted to increase enrollment of other typically underrepresented groups. These methods should be considered in addition to factors highlighted in the FDA guidance on Design Considerations for Pivotal Clinical Investigations for Medical Devices.[31]

(1) IDE Study Design, Early Enrollment Stage

You should develop and describe your plan to prospectively include appropriate demographic subgroups in your study based on the contextual information provided in Section IV.A. (e.g., consistent with the intended use population, including age, race, and ethnic prevalence of the disease or condition which your

[31] See FDA's guidance *Design Considerations for Pivotal Clinical Investigations for Medical Devices* (November 7, 2013). http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf.

device is intended to treat or diagnose, if known). To enhance enrollment of relevant age, race, and ethnicity subgroups, the approaches described below may be considered, with appropriate caution to avoid introducing bias or jeopardizing data validity.

a. Include a wide variety of investigational sites where recruitment of age, race, and ethnicity subgroups can be more easily facilitated (e.g., community clinics, nursing homes, pediatric hospitals, minority healthcare provider groups, urban hospitals).

b. Consider alternative communication strategies for study recruitment, informed consent documents, and patient materials (e.g., community-based organizations, places of worship, patient reading materials available in multiple languages with cultural references, accommodations for the visual and hearing impaired).

c. If age, race, and ethnicity subgroups are expected to benefit or benefit differentially from your device but may not meet certain study enrollment criteria, consider revising the enrollment criteria, when appropriate, or consider enrolling registries or parallel cohorts for collecting data on device use in particular age, race, and ethnicity subgroups (e.g., a pediatric registry).

d. Consider including provisions to encourage diverse enrollment of relevant age, race, and ethnicity subgroups consistent with the intended use population.

e. Consider investigating reasons for under-enrollment or non-enrollment of age, race, and ethnicity subgroups or other key demographic groups (e.g., consider periodically evaluating screening logs for all patients who are screened but not ultimately enrolled in studies, to identify and address root cause barriers to diverse enrollment).[32]

f. Consider planning focused efforts to enroll age, race, and ethnicity subgroups under a continued access study based on prior information or information collected in a study.[33]

g. Consider factors that generally increase recruitment and retention such as community or local health care practitioner involvement in recruiting or referring patients, compensation for expenses (e.g., for transportation costs), and maintaining communication with research participants (e.g., send a newsletter to participants to maintain interest).

[32] See footnote 26.

[33] See FDA's *Guidance on IDE Policies and Procedures* (January 20, 1998) http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm.

h. Consider flexibility in follow-up visit scheduling with provision of child care or elder care services during appointments or to allow various opportunities that match subjects' schedules, which may include evenings and weekends.

i. For *in vitro* diagnostic tests and diagnostic devices, consider including samples from each age, race, and ethnic group at the cutoff selection and validation stages.

(2) Premarket Submission Stage

In your marketing submission you should discuss study results (related to safety and/or effectiveness, or probable benefit for HDEs) and describe how any known clinically meaningful age, race, and ethnicity differences across subgroups may contribute to differences in benefit-risk profile in certain subpopulations.

When determining whether additional data collection is needed to address a clinically important question before the device is marketed, consideration should be given to whether market approval/clearance is supported for the general population, with postmarket studies to gain further information regarding any observed age, race, or ethnicity subgroup differences, or whether existing results support market approval/clearance in a specific age, race, or ethnicity subgroup, but additional pre-market data collection would be needed to generalize effects to a broader intended use population.

If additional data is needed before the device is approved or cleared, FDA may recommend that you consider including provisions to encourage enrollment of diverse age, race, or ethnicity subgroups (e.g., modify enrollment criteria to study outcomes in a specific subpopulation). In such cases, we recommend you discuss with FDA strategies to limit introducing bias or jeopardizing data validity.

(3) Postmarket Submission Stage

We recommend you consider whether outstanding questions warrant postmarket evaluation in a specific age, race, or ethnic subgroup. For example, postmarket data collection may be warranted if premarket clinical studies reveal signals of potentially clinically meaningful outcome differences in age, race, or ethnic subgroups, or if there are known subgroup differences in the underlying disease or the response to concomitant treatment or therapies that may affect safety or effectiveness (or probable benefit for HDEs). In such instances, FDA may determine that additional study of a particular age, race, or ethnicity subgroup is warranted in the postmarket setting.

You should develop and describe your plan to collect postmarket data on appropriate demographic subgroups in any mandated postmarket study(ies) based on outstanding questions described above, and/or based on the contextual information provided per Section IV.A. (e.g., consistent with the intended use population, including age, race, or ethnic prevalence of the disease or condition which your device is intended to treat or diagnose, if known).

To enhance enrollment of age, race, or ethnicity subgroups, we recommend that you undertake the approaches specified in Section IV.B.1.

C. Considerations for Study Follow-up Visits

We also recommend that sponsors and clinical study investigators consider the approaches described below, which can help avoid or minimize loss-to-follow-up of subjects (regardless of age, race, or ethnicity subgroup). While proper study conduct and follow-up are concerns for all patients, regardless of age, race, or ethnicity, concerns about disproportionate dropout and loss to follow-up are potential barriers to diverse study representation of minorities and older patients. The following considerations are not regulatory requirements; rather they represent good clinical study principles that may improve diverse participation throughout the duration of the study. We encourage sponsors and clinical study investigators to consider these where appropriate.

Sponsors should consider:

a. Developing a follow-up plan that details follow-up goals, frequency of upcoming scheduled follow-up visits, proxy contact information, and number and type of contacts for patients missing a follow-up visit.
b. Demonstrating continued interest in the subjects (e.g., send newsletter to participants to maintain interest).
c. Monitoring follow-up rates closely so that follow-up problems can be identified and addressed as soon as possible.
d. Reporting subject accountability data as part of the study report.

Investigators should consider:

a. Participating in cultural competency training prior to study recruitment.
b. Counseling subjects about the importance of returning to follow-up during informed consent and follow-up visits.
c. Reminding subjects of upcoming scheduled follow-up visits.
d. Attempting to locate/return patients who miss scheduled clinic visits.
e. Obtaining proxy information to use when unable to contact a study subject.

f. Asking subjects who withdraw during the study to provide the reason for withdrawal and ask them whether the investigator may contact them once more at the end of the study follow-up to assess the experience with device.
g. Demonstrating interest in the participants (e.g., telephone follow-up after surgery, particularly if the device is implantable).

V. Considering Age, Race, and Ethnicity in Study Design, Analysis, and Interpretation of Study Results

Intrinsic and extrinsic biological differences across age, race, and ethnic groups (e.g. gonad development, skin texture, skin color, hormone levels, metabolism, degenerative disease, bone density, cell receptors, etc.) exist that may influence the safety and effectiveness (or probable benefit for HDEs) of a device. For example, ionizing radiation exposure to pediatric patients from medical imaging procedures is of particular concern because pediatric patients are more radiosensitive than adults (i.e., the cancer risk per unit dose of ionizing radiation is higher).[34] Additionally, age, race, and ethnicity may play a role in an individual's interaction with his/her environment, which in turn could affect an individual's health. For example, intermittent exposures to intense UV radiation (e.g., tanning beds) leading to sunburns, especially in childhood and teen years, increase the risk of melanoma.[35]

Due to the potential impact on safety and effectiveness (or probable benefit for HDEs), unless the investigational device is intended for use in only one age, race or ethnic group (e.g., neonatal devices), it is important that the variation in data across age, race, and ethnic groups be accounted for both in study design and analysis of results, as appropriate.

Other patient characteristics (e.g., body size, diet, bone density, Fitzpatrick Scale) that may be correlated with age, race, or ethnic differences might sometimes explain apparent differences in clinical outcomes. If differences between evaluated subgroups are observed, FDA recommends that a sponsor investigate potential explanation of the differences by other patient characteristics. This will help users identify characteristics that can inform decision making for individual use.

As discussed in Section III.B., demographic data can be collected and categorized in a variety of ways. Categorization scheme may impact analysis (e.g., depending on whether age is treated as a categorical or continuous variable).

[34] See FDA's website on *Pediatric X-Ray Imaging*, available at http://www.fda.gov/Radiation-EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/ucm298899.htm.
[35] See FDA's website on *Indoor Tanning: The Risks of Ultraviolet Rays*, available at http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm186687.htm.

A. Assessing Heterogeneity Across Age, Race, and Ethnic Demographic Subgroups

There may be substantial differences in device safety and effectiveness (or probable benefit for HDEs) across age, race and ethnic subgroups. Therefore, when differences in treatment effect or benefit-risk profile are anticipated across age, race, or ethnic groups, sponsors should investigate heterogeneity across these demographic subgroups of clinical interest, especially for primary safety and effectiveness endpoints (or probable benefit for HDEs). Heterogeneity here refers to variation in outcome across subgroups. Statistical hypothesis tests can be performed to detect heterogeneity, and methods of statistical inference for estimating its magnitude are also available.[36]

In some cases the test for treatment by subgroup interaction (or heterogeneity in general) may have adequate power to detect only a very large interaction (or heterogeneity), but may not detect a smaller yet potentially clinically meaningful interaction (or heterogeneity).[37] Such situations may arise when the number of patients in one or several of the age, race, or ethnic groups is very small. Alternatively, observed heterogeneity across specific subgroups could be attributable to variability associated with small sample sizes; interpretation of clinical meaningfulness may be premature in those cases. Additionally, sample sizes in subgroups may not be large enough to detect clinically meaningful differences in device safety or effectiveness (or probable benefit for HDEs). Consultation with FDA is recommended in these cases.

For additional discussion of statistical concepts for assessing heterogeneity, please see the Evaluation of Sex-Specific Data in Medical Device Clinical Studies Section V.A, hereafter referred to as the Sex-Specific Guidance.[38]

All following recommendations presented in this section are applicable to age, race, and ethnic subgroups.

(1) IDE Study Design, Early Enrollment Stage

- When appropriate, the Statistical Analysis Plan (SAP) in the study protocol should include pre-specified plans for addressing the issues described in the sections below.

- It is important that clinical trials include diverse populations that reflect the intended population. In general, to achieve an unbiased estimate of treatment

[36] As statistical tests, hypothesis test significance levels should be pre-specified in any investigational plan. Note, however, that the power of such tests may be unspecified. The investigational plan can apply to premarket or postmarket studies.
[37] Tests for treatment by subgroup interaction may lack a significant interaction based on an interaction p-value. If an interaction is detected, sponsors should evaluate which subgroups are the same or different.
[38] See footnote 1.

effect in the general population, sponsors should develop a strategy to enroll diverse populations including relevant age, race, and ethnic groups.

- If differences are anticipated, sponsors should make an effort to identify in advance any key covariates that might explain possible differences across subgroups, plan to collect data on these covariates, and pre-specify a modeling approach to investigate the extent to which these covariates can explain the observed differences.

- Sponsors should consider whether clinical outcome measurements will or could differ across age, race, or ethnicity subgroups. For example, keloid formation following wrinkle filler application may differ between pigmented and non-pigmented skin, a characteristic that varies with race and/or ethnic background. Clinical measurements and endpoints in such a trial may differ across self-reported race or ethnicity subgroups, and this information should be captured accordingly.

(2) Premarket Submission Stage

- In general, sponsors should submit descriptive statistics for outcomes of interest by demographic subgroup as detailed in Section C below. After overall effectiveness (or probable benefit for HDEs) and safety have been investigated, outcome analysis by age, race, and ethnicity for primary endpoints for both safety and effectiveness (or probable benefit for HDEs) should be conducted.

- When exploring age-, race-, or ethnicity-related differences during analysis of premarket study data, we recommend you 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, etc.).

- If any clinically meaningful differences are suspected, either based on pre-specified or exploratory *post hoc* analyses, sponsors should discuss with FDA to determine whether additional data are needed to address any remaining subgroup-specific questions of safety or effectiveness (or probable benefit for HDEs).

(3) Postmarket Submission Stage

- For any mandated postmarket study(ies) involving continuing data collection on PMA cohort patients for the evaluation of longer term performance, we

recommend that you conduct the analyses described in Section C below for all follow-up time points.

- For any mandated postmarket study(ies) involving newly enrolled patients, you should include the analyses described in Section C below as part of a pre-specified SAP in your protocol. Furthermore, if results from demographic subgroup analyses of premarket data suggest there may be a clinically meaningful difference in outcomes, you should consult with FDA to determine whether this should also be incorporated into the study design and hypothesis for your postmarket study.

- When exploring age-, race-, or ethnicity-related differences during analysis of data from any mandated postmarket study(ies), we recommend you 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, etc.).

B. Designing Studies: Recommendations for Subgroup Specific Statistical Elements

FDA recommends sponsors consider the subgroup-specific statistical elements described in detail in the Sex-Specific Guidance[39] Section V.B., which are applicable to the demographic subgroups outlined in this guidance. Please refer to Figure 1 in the Appendix for a summary of these recommendations. The following specific topics apply to clinical trials for subgroup specific outcome analyses:

(1) Recommendations When Subgroup Differences are Anticipated

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 1 error, and simultaneous pivotal and subgroup-specific trials if appropriate.[40]

(2) Recommendations for Pre-specifying Assessment of Heterogeneity

[39] See footnote 1.

[40] See FDA's guidance *Design Considerations for Pivotal Clinical Investigations for Medical Devices* (November 7, 2013) http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf.

It is important that the SAP include a strategy for assessing heterogeneity across relevant demographic subgroups, and FDA recommends such an assessment as an integral part of interpreting study results for every submission. In particular, the heterogeneity assessment can serve as the basis for poolability conditions for studies with pre-specified success criteria expressed in terms of data pooled across subgroups. Such poolability conditions bear some resemblance to those commonly used for determining whether data can appropriately be pooled for analysis across different clinical sites.[41]

Additionally, adaptive study design strategies to pre-specify subgroups of interest for interim analysis and potential population enrichment for success should be preplanned and specified in the SAP prior to the start of the study.

(3) Additional Design Recommendations for Comparative and One-arm Studies

Application of certain study design recommendations may prompt a different approach depending on whether studies are comparative or single arm. Please refer to the Sex-Specific Guidance Section[42] V.B., for details.

(4) Special Study Design Considerations for Diagnostic Devices

There are additional study design recommendations specifically for in vitro diagnostic assays, imaging devices, and diagnostic devices. For example, age may be a significant risk factor in the prediction of risk, and should be considered as a covariate in the prediction model in such cases when evaluating diagnostic devices for risk assessment.

C. Completed Studies: Recommendations for Analysis of Subgroup-Specific Data

Please refer to the Appendix for flowchart diagrams summarizing the following recommendations for completed one-arm and comparative studies in Figures 2 and 3, respectively. For detailed recommendations on the analysis in completed one-arm or comparative studies, please see the Sex-Specific Guidance Section V.C.[43]

[41] Poolability conditions may be specified as statistical hypothesis tests, which, for studies involving the comparison of two treatments, would typically be tests of treatment by subgroup interaction. The interaction tests should ideally be able to detect interaction of relevant magnitude measured on pertinent parameters with a reasonably high probability, and this goal should guide the choice of appropriate significance level.

[42] See footnote 1.

[43] See footnote 1.

In general, sponsors should submit descriptive statistics for enrolled patients, outcomes of interest, including the estimate of variance or standard deviation (as applicable), by age, race, and ethnic groups. At the primary follow-up time-point, regardless of the potentially limited statistical power of these specific subgroup analyses, data should be examined for clinically meaningful age-, race-, and ethnicity-specific differences in each of the following:

- primary effectiveness (or probable benefit for HDEs) endpoint(s);
- primary safety endpoint(s); and
- key secondary endpoints.

- It is important to carry out all analyses set forth in the SAP. FDA expects sponsors to plan for and conduct analyses to evaluate heterogeneity by demographic subgroups, including treatment by subgroup interaction when applicable, as described in previous sections.

- Unplanned subgroup analyses or those with inadequate sample size are generally not considered to be adequate to support statements in the labeling regarding the safety or effectiveness of the device. However, the overall benefit-risk profile of the device will be considered.

- After overall effectiveness (or probable benefit for HDEs) and safety have been investigated, the analysis of subgroups outcomes for primary endpoints for both safety and effectiveness (or probable benefit for HDEs) and in some cases for important secondary endpoints as well should be assessed.

- If no clinical meaningful or statistically significant difference is observed across subgroups, data may be poolable across subgroups.

- If there is evidence of heterogeneity, it is important to describe its nature and assess the clinical importance of the differences. In some cases, the effect could be statistically significant, but not clinically meaningful, or clinically meaningful but not statistically significant. In these cases, discussion with FDA is advised.

- If a clinically meaningful difference is observed across certain subgroups (e.g., age less than 65 years old, between 65 and 75 years old, and over 75 years old), it is also important to discuss whether the observed heterogeneity could be mainly explained by other covariates (e.g., bone density), which are highly correlated with that subgroup (e.g., age).

- If a difference remains clinically meaningful and/or statistically significant after consideration of covariates, data may not be poolable across subgroups. In this case, discussion with FDA is recommended. Sponsors should describe how any

clinically meaningful differences across subgroups may contribute to differences in benefit-risk profile in certain subpopulations.

D. Interpretation of Age, Race, and Ethnicity Specific Data

- 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. You should describe how any clinically meaningful differences across subgroups may contribute to differences in benefit-risk profile in certain subpopulations.

- If results of your analysis suggest that there is insufficient data to assess whether age, race, or ethnicity is associated with clinically meaningful differences in outcome, FDA may determine that clinical data from additional subjects in one or several of demographic subgroups may be needed pre- or postmarket to address potential age-, race-, or ethnic-specific questions related to safety or effectiveness (or probable benefit for HDEs) in any or all of those subgroups.

- Although expected to be rare, in cases where clinically meaningful differences among the age, race, or ethnic groups are observed in safety or effectiveness (or probable benefit for HDEs), FDA may request additional confirmatory studies, implement specific pre- or post-approval study conditions, and/or recommend modifications to the design of subsequent studies. FDA will consider such requests in the context of a benefit-risk framework. Sponsors should describe how any observed clinically meaningful differences across subgroups may affect overall benefit-risk profile in certain subpopulations.

- There are limitations to interpreting clinically meaningful differences in small data sets or in larger studies in which certain subgroups are underrepresented. Mean differences could exist among demographic subgroups due to small sample sizes, and interpretation about whether they are clinically meaningful may be premature in many cases. Alternatively, sample sizes may not be large enough to detect clinically meaningful differences in device safety or effectiveness (or probable benefit for HDEs). Consultation with FDA is recommended in these cases.

VI. Recommendations for Submitting Age, Race, and Ethnicity Data in Submissions to the Agency and Reporting in Public Documents

Confidential submissions to FDA contain detailed analyses of clinical study data, which may include a variety of age, race, and ethnic subgroup analyses. However, public documents, including labeling and FDA summaries of review (e.g., SSED) for medical devices approved or cleared in the past are inconsistent with regard to the degree of information reported on device performance in demographic subgroups. Although sponsors may be most interested in the generalizability of the findings, individual patients and their medical providers may benefit from more data regarding effectiveness (or probable benefit for HDEs) and potential adverse events associated with device use in a particular demographic subgroup. 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).

Please refer to Figure 4 in the Appendix for a flowchart summary of the below recommendations.

A. Enrollment Demographics, Baseline Characteristics & Co-Morbidities

The strength of the conclusions of your clinical study(ies) with respect to device performance in age, race, and ethnic subgroups is linked to the number of individuals in the age, race, and ethnic subgroups in your study(ies). FDA recommends that you submit and publically report the number and proportion of subjects by age, race, and ethnic groups who were treated or diagnosed with your device as part of a clinical study as follows:

- You should submit and publicly report study demographics in terms of proportion enrolled and completed by subgroup. You should discuss whether the proportions enrolled are consistent with the age, race, and ethnic prevalence of disease, if known. If proportions enrolled are substantially different than prevalence of disease by age, race, and ethnicity, if known, you should discuss generalizability of study findings to the demographic subgroups. For studies with multiple cohorts, you should submit and publicly report enrollment proportions for each age, race, and ethnic subgroup in each cohorts.

- If co-morbidities and/or other baseline characteristics are collected, you should analyze and submit these by demographic subgroup as well as overall.

- If loss to follow-up disproportionally affects a particular subgroup (e.g., greater loss of older patients compared to younger patients), you should provide a discussion of differences across subgroups at different time points for the overall study sample and for each study arm. Different patterns in missing data may introduce bias in the study conclusions.

When publicly reporting, you may adapt the example language below or use similar language that incorporates the contents described above. Conclusions should only be based on factual data and not be assumptions or inferences based on non-significant trends or ad hoc analyses.

Example Language:

African American women represented [%] of the total patients enrolled in the overall study. The prevalence of [uterine fibroids] among African American women in the U.S. is [%], according to [source]. Among subjects in the treatment group, m1/n1 (p1%) were African American women, and m2/n2 (p2%) of subjects in the control group were African-American women.

Pediatric patients were more likely to have [disease or diagnosis] compared to adults (p1% vs. p2%).

Additionally, we recommend that you include this type of information in any applicable tables and charts.

(1) IDE Study Design, Early Enrollment Stage

You should submit demographic information outlined above as part of your IDE annual progress reports.

(2) Premarket Submission Stage

You should submit baseline demographic information outlined above as part of your marketing application in sections containing results of clinical investigations, including the labeling. You should also report a summary of this information in your 510(k) Summary, which will be made publicly available on FDA's website upon approval or clearance.

FDA staff should include this information in the PMA Summary of Safety and Effectiveness, HDE Summary of Safety and Probable Benefit, and *de novo* decision summaries, which will be made publicly available on FDA's website.

(3) Postmarket Submission Stage

You should submit the demographic information outlined above in interim reports and in the final report for any mandated postmarket study(ies).

FDA staff should include this information in mandated studies summaries, which are made publicly available on FDA's website, when appropriate.

B. Age, Race, and Ethnicity Outcomes (Safety or Effectiveness, or Probable Benefit for HDEs)

Outcomes analyses by demographic subgroup should be reported in the labeling and review summaries, as outlined below. Covariates that might explain possible outcome differences by age, race, and ethnicity should be described.

- If outcome differences by age, race, and ethnicity are statistically significant and clinically meaningful, you should report the results of the outcome analyses. You should also describe how such differences across subgroups affect the benefit-risk profile in certain subpopulations, as applicable.

- If results of these analyses suggest an age, race, and/or ethnicity difference in an endpoint or event that is clinically meaningful, but not statistically significant, you should report the findings descriptively.

- If results of these analyses suggest no age, race, and/or ethnicity differences in outcomes, you should report which analyses were conducted and that no clinically meaningful differences were found to be relevant.

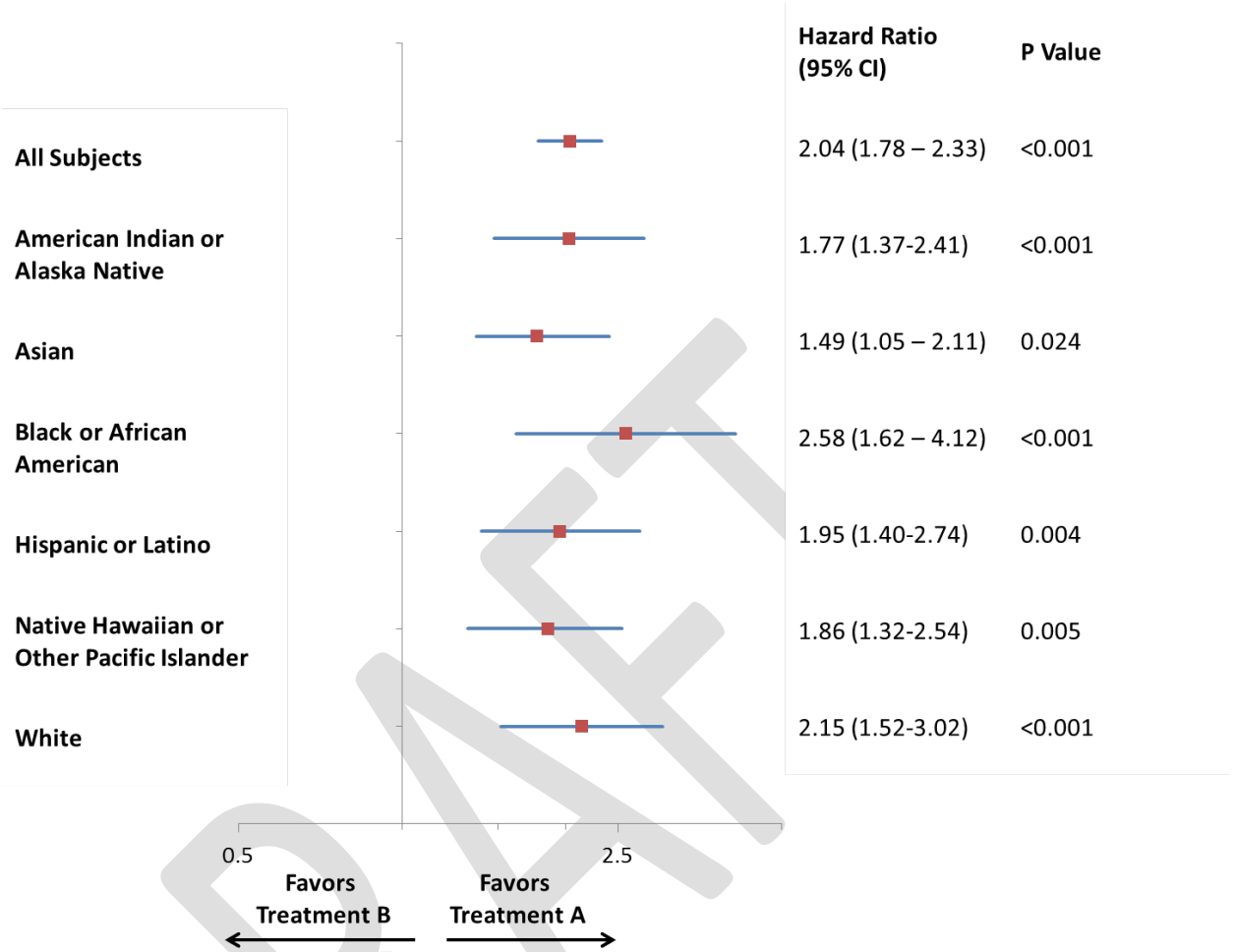
When publicly reporting, you may choose to adapt the example language and graph below, or you may use similar language, tables, and charts that incorporate the contents described above. The example below is one option. Alternatively, you may choose to illustrate performance separately by race and then by ethnicity, as the subgroups will be larger, improving the ability to ascertain subgroup effects.

It should also be noted that where there are many subgroups with small sample size, one may observe considerable variability in treatment effect due to random chance. Any such variability should be interpreted with caution.

Example Language & Graph:

The study data suggests a trend that patients of [age] years of age have a higher [study outcome] in comparison to younger patients, but these differences were not found statistically significant by [x] statistical analysis.

Tables or Forest plots showing outcomes by demographic subgroups are potential options for reporting outcomes.



Sample forest plot of hazard ratios by race and ethnicity subgroups[44]

(1) Premarket Submission Stage

When submitting or publicly reporting results of *pre-specified* age, race, and ethnicity subgroup analyses, we recommend the following:

- Clearly state which analyses were conducted.
- Specify statistical methods used to assess for heterogeneity of treatment differences by age, race, and ethnicity (as described above).
- You may include inferential statistics, including p-values and/or confidence intervals, if there is pre-specified statistical hypothesis testing for a subgroup with multiplicity adjustment. To provide appropriate

[44] Per FDA guidance (see footnote 2), FDA recommends the two-question format to collect data race and ethnicity. However, for readability purposes, the combined format is used in this example. In addition, this sample plot was generated for illustrative purposes and does not reflect actual clinical data.

context, describe prior scientific evidence suggesting that clinically meaningful differences by subgroup are expected, or describe statistical limitations of analyses.

Pre-specified analyses are recommended and preferred. When necessary, sponsors should consider the following when submitting or publicly reporting results of *post hoc* age, race, and ethnicity subgroup analyses:

- Clearly state that the analyses were unplanned.
- Clearly state which analyses were conducted.
- Specify statistical methods used to assess for heterogeneity of treatment differences by age, race, and ethnicity (as described above).
- Use descriptive statistics only (mean, standard deviation, etc.). When submitting results in confidential submissions to FDA, sponsors may include inferential statistics, with a disclaimer that these are from *post hoc* analyses. Post hoc analyses are generally not considered to be adequate to support statements in the labeling regarding the safety or effectiveness of the device. However, the overall benefit-risk profile of the device will be considered.

If clinically meaningful age, race, and ethnicity differences in safety or effectiveness (or probable benefit for HDEs) are observed, or if there are potential differences that might require follow-up studies, you should include in publicly reported labeling and review summaries a discussion on whether or how this affects the overall benefit-risk profile for different subgroups.

(2) Postmarket Submission Stage

When presenting results of age, race, and ethnicity subgroup analyses of any mandated postmarket study(ies), the recommendations above also apply.

If a clinically meaningful signal is detected in your final analysis, FDA may recommend changes to your approved labeling documents.

Appendix 1 – Decision Framework

We encourage the use of existing scientific data (e.g. recent previous studies, disease natural history studies) to determine whether there is a hypothesis for a clinically meaningful demographic subgroup-specific difference for your device. When there is a hypothesis for a clinically meaningful difference, the following decision trees provide a framework in deciding when various age-, race-, or ethnicity-specific statistical recommendations apply for different clinical study designs. Sponsors should also describe how any clinically meaningful differences across subgroups may contribute to differences in benefit-risk profile in certain subpopulations.

Figure 1: Recommendations for Demographic Subgroup-Specific Statistical Study Design

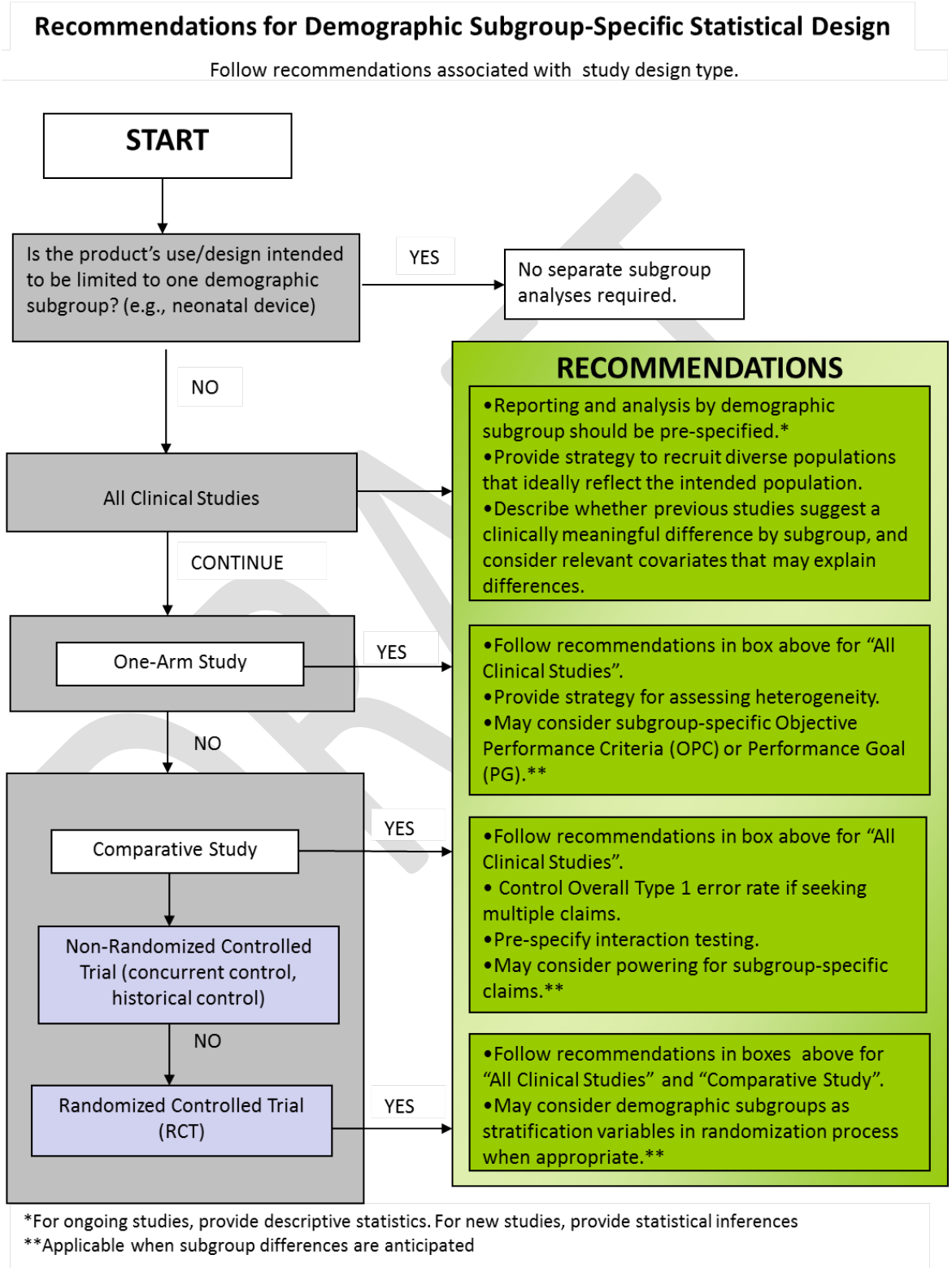
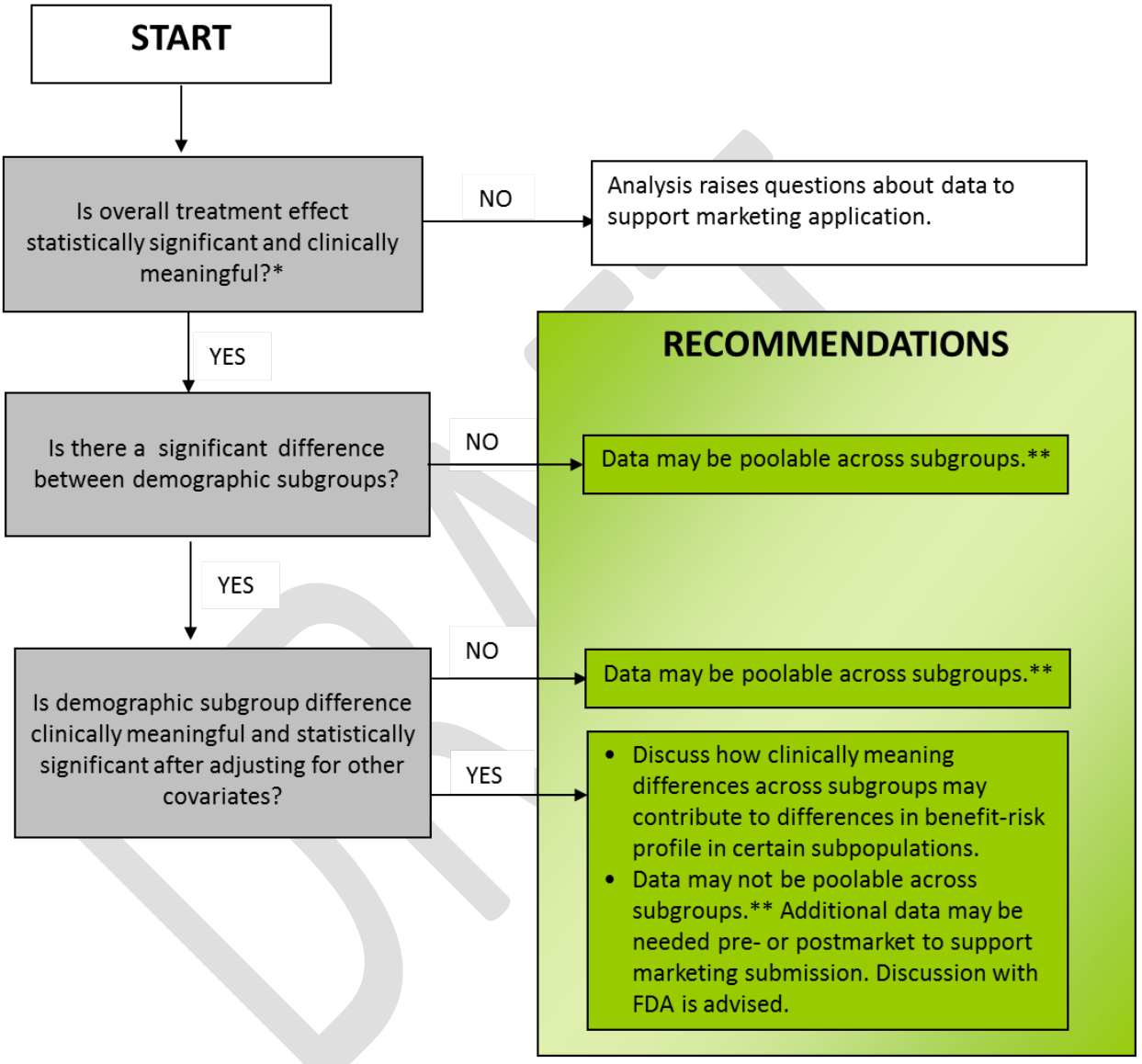


Figure 2: Recommendations for Demographic Subgroup-Specific Statistical Analysis for One-Arm Studies (Objective Performance Criterion, Performance Goal, Observational Study)

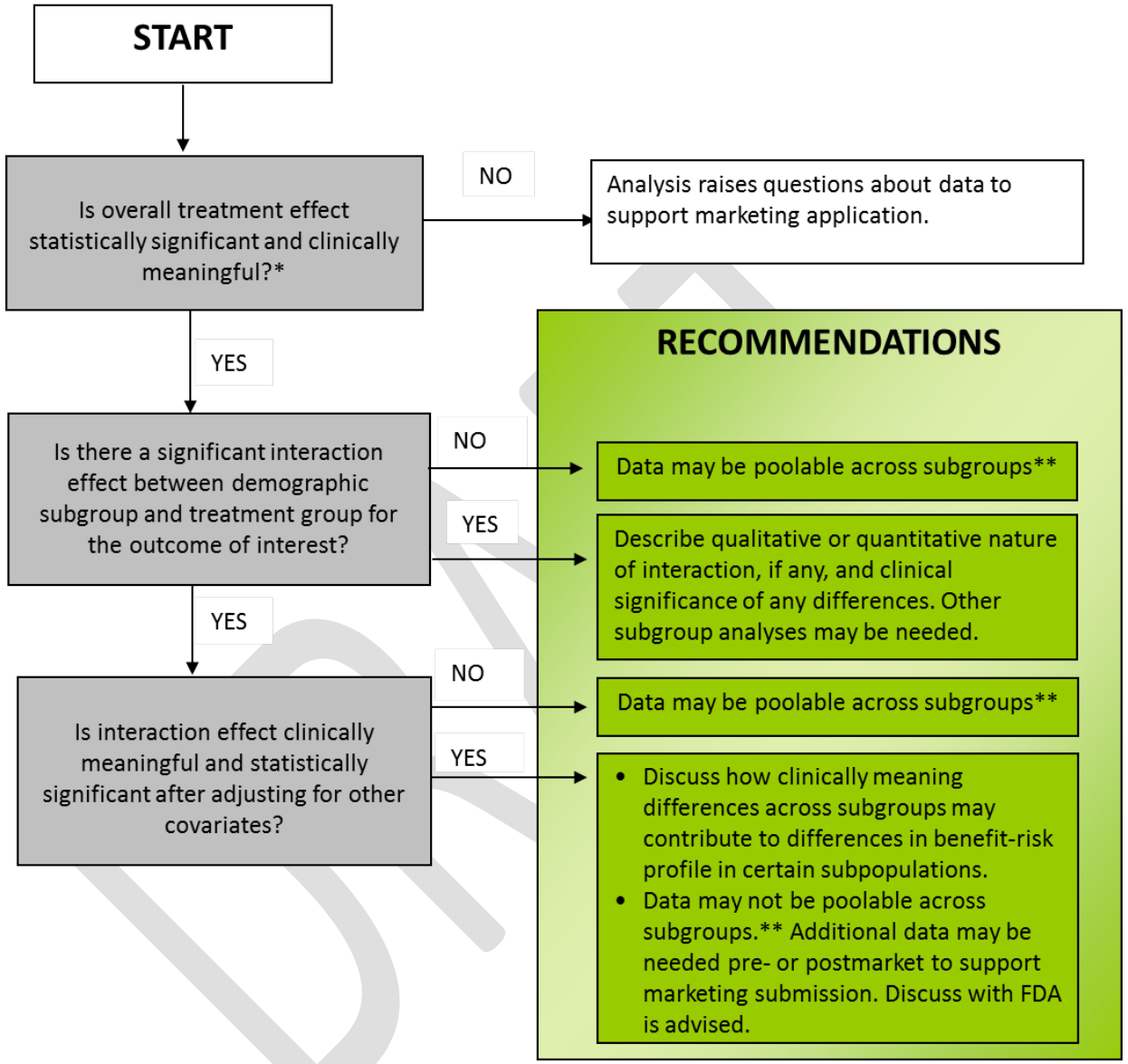


*Unplanned subgroup analyses are generally not considered to be adequate to support statements in the labeling regarding the safety or effectiveness of the device if overall treatment effect is not statistically significant and clinically meaningful.

**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.

Figure 3: Recommendations for Demographic Subgroup-Specific Statistical Analysis for Comparative Studies

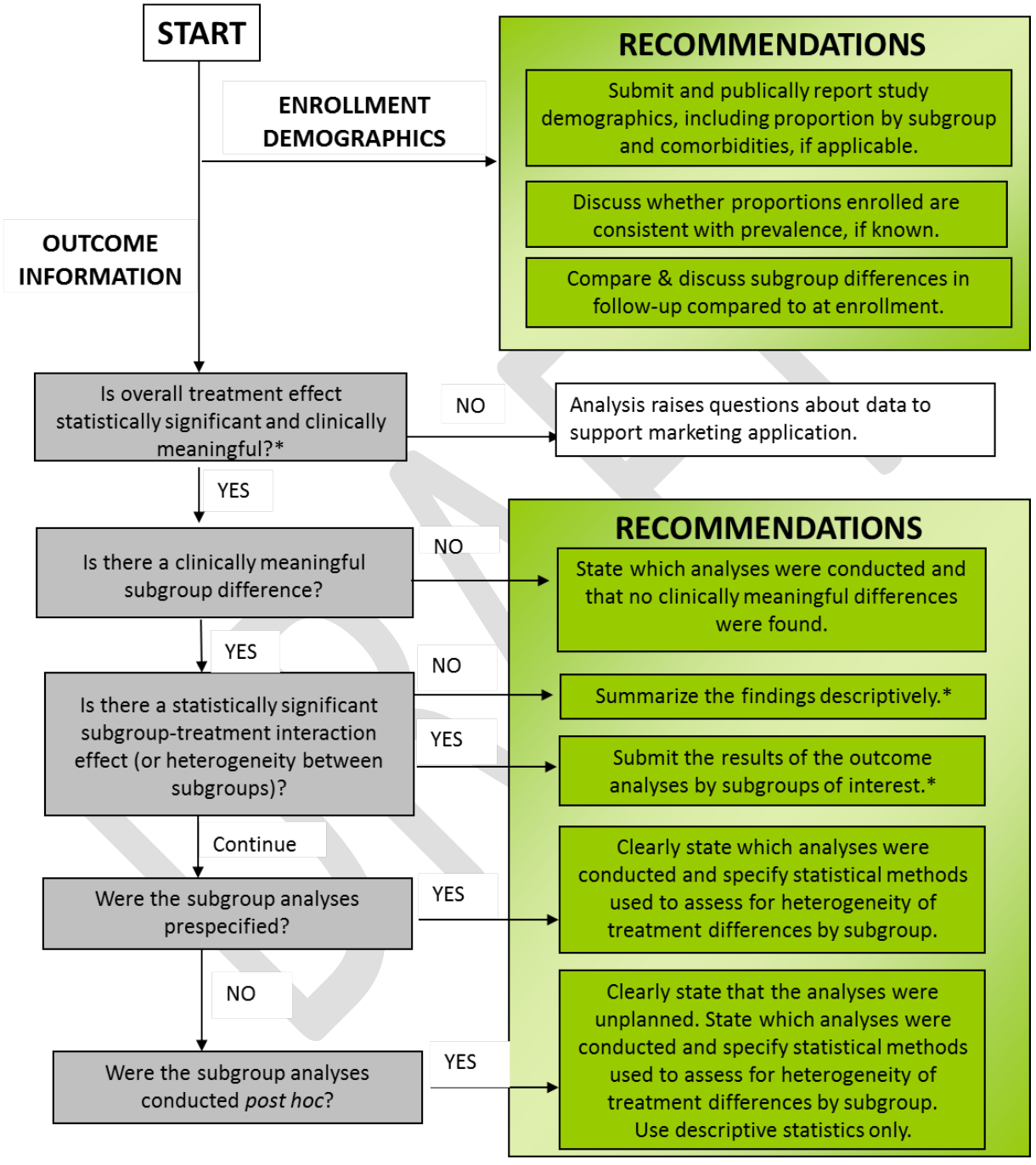


*Unplanned subgroup analyses are generally not considered to be adequate to support statements in the labeling regarding the safety or effectiveness of the device if overall treatment effect is not statistically significant and clinically meaningful.

**Provide justification for 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.

Figure 4: Recommendations for Submitting and Reporting Subgroup-Specific Participation and Outcome Information



* 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).