

**FDA Webinar- Evaluation and Reporting of Age, Race, and  
Ethnicity Data in Medical Device Clinical Studies**  
**Moderator: Irene Aihie**  
**October 31, 2017**  
**12:00 pm ET**

Operator: Welcome and thank you for standing by. At this time, all participants are in a listen-only mode until the question and answer session of today's conference. At that time, you may press Star 1 on your phone to ask a question.

I would like to inform all parties that today's conference is being recorded. If you have any objections, you may disconnect at this time.

I would now like to turn the conference over to Ms. Irene Aihie. Thank you. You may begin.

Irene Aihie: Hello and welcome to today's FDA webinar. I am Irene Aihie of CDRH's Office of Communication and Education. On September 12, 2017 the FDA issued the final guidance document, Evaluation and Reporting of Age, Race, and Ethnicity-Specific Data in Medical Device Clinical Studies. The data provides recommendations to improve the quality, consistency, and transparency of data on how medical devices perform in specific age, race, and ethnic groups. Proper evaluation and reporting of this data to benefit patients, physicians, researchers, and regulators.

Today, Katie O’Callaghan, Assistant Director of Strategic Programs in the Office of the Center Director, and Katherine Kim, a Consumer Safety Officer in the Office of Compliance here in CDRH will present an overview of the final guidance.

Following the presentation, we will open the lines for your questions related to information provided during the presentation.

Additionally, there are other subject matter experts here with us today to assist with the Q&A portion of our webinar. Now, I give you Katie.

Katie O’Callaghan: Hi. Good morning. This is Katie. I am from the Center Director’s Office here at CDRH and my group is responsible for: leading the Center’s efforts on patient engagement, patient preferences, patient reported outcomes; for increasing the impact of our regulatory science activities across the Center; for connecting our experts with experts outside of FDA, and we also play a key role in efforts around diversity in clinical trials.

I’ll provide a few remarks on the backgrounds and the origins of this guidance and then I will turn it over to Katherine Kim who served as the lead author for this guidance during the detail in my office.

So the origins of this guidance go back to the Food and Drug Administration Safety and Innovation Act or FDASIA, which was signed into law in 2012. In FDASIA there was a section 907, which directed the agency to examine the participation of diverse subgroups with respect to age, race, ethnicity, as well as sex and gender, and to evaluate the corresponding data the FDA was seeing in medical product submissions and whether this information was subsequently being made available to the public.

We evaluated our submissions and issued a report in 2013 which was made available to the public as well as to Congress and also an action plan in 2014. The action plan in 2014 provided a variety of recommendations and actions that the agency would take in order to improve the participation, quality, and transparency of medical product performance in age, race, and ethnicity subgroups. And this guidance was a commitment that we made under that plan.

In forming the recommendations in this guidance, we got input from experts and stakeholders as well as the public through a variety of public fora, including a workshop organized in 2015 by the Institute of Medicine. Draft guidance was issued in June of 2016 and we incorporated changes in response to public feedback we received and issued the final guidance which went into effect September 12, 2017.

In the report which was issued in 2013, we evaluated for CDRH 37 original premarket approval or PMA applications that had been approved in a prior year. This included 46 pivotal clinical studies. We looked for demographic variables on sex, age, race, and ethnicity subgroups.

And the documents we considered were the PMA applications submitted by industry as well as the publicly available final labeling, the publicly available summaries of safety and effectiveness data in which FDA provides an overview of the basis of our decision to approve as well as internal documentation provide by the review team.

What we found in fact there was a need for improved consistency in our analysis as well as in the information that's made available to the public.

For age groups, 70% of the PMAs which we evaluated included an analysis of this data and 57% presented some information in public documents regarding age groups. For race and ethnicity subgroups, these numbers were 27% analyzed and 16% presented publicly.

In terms of participation, the participation by age group varied depending on the indication. This information if you are interested in looking at some more detail can be found in the FDASIA 907 report which was issued in 2013 and is available on FDA's website. We observed a lack of consistency in the type of descriptive statistics on age that are reported in PMAs, but we did find that age range was most commonly reported.

Participation by race also varied by indication. In some cases, racial composition was consistent with disease prevalence, whereas in other cases it did not appear to match prevalence in the disease for the US population.

And participation by ethnicity varied as well.

In 2014 as directed by Congress, we issued an action plan which included 27 actions that the agency would take to address the gaps and issues that we found in the 2013 report. These actions fall into three broad categories -- participation, quality, and transparency.

So, why consider age, race, and ethnicity specific differences? There are differences in biology, environment and the interaction between these that could affect health, disease, and response to medical devices in different groups. For example, radiation emitting devices -- which are regulated by FDA -- we know that pediatric patients are more sensitive to ionizing radiation exposure.

FDA's decisions are made on the basis of an overall benefit-risk evaluation and we know that this benefit-risk profile, as well as other important aspects of device performance, can differ across age, race, and ethnic subgroups. Some examples listed here include dermatology devices and orthopedic devices, which may have different considerations in the different subgroups.

What about clinical trials? Why is diversity important? We know that there has been a historical lack of information in clinical studies about the risks and benefits of medical device use in these subgroups. And this is true not only for trials that are reviewed by FDA, but it's also been observed in academic research studies. Ideally, clinical trials should aim to include diverse populations which reflect the intended population of use whenever possible.

We also know that there's an abundance of research and recommendations about how to enhance diversity in clinical trials. This has been primarily organized and forwarded by groups like the National Institute of Health and other academic or community research parties.

So this guidance provides us an opportunity to raise awareness among the medical device industry and associated trial community about these recommendations. And with that, I will turn it over to Ms. Katherine Kim.

**Katherine Kim:** Thank you so much, Katie. Hello everyone. My name is Katherine Kim and I'll be talking about this particular guidance moving forward.

So the objective of this guidance is to provide recommendations to improve the quality, consistency, and transparency of data regarding the performance within medical devices within specific age, race, and ethnic groups. And for the purposes of simplicity, we've abbreviated age, race, and ethnicity to ARE

moving forward. FDA believes proper evaluation and reporting of this data can benefit patients, clinicians, researchers, regulators, and others.

This guidance also includes recommendations and considerations to assist sponsors in developing a strategy to enroll diverse populations that reflect intended use populations. So the purpose of the objective, there are three main ones -- by diverse participation, consistent analysis, and the transparency of reporting age, race, and ethnic specific information in summaries and labeling.

I'll be providing the scope of the guidance. And this is to improve the quality, consistency, and transparency of data regarding the device performance within age, race, ethnicity-specific subgroups. This applies to devices that include clinical information in support of a marketing submission, and that includes (510(k), De Novo request, PMAs, and HDEs. This also applies to post-approval study submissions and post-market surveillance studies.

As noted, the age, race, and ethnicity guidance builds upon the sex-specific final guidance and therefore extends the policy set for in that sex-specific guidance to include age, race, and ethnicity.

So next we'll go to the different types of terminology. There's a lot of subgroups and we want to define what they are.

When evaluating age-specific data, clinical studies should first plan to group age groups as appropriate for the disease condition. For device regulations, pediatric population is defined in device regulations as less than 22 years of age. Now, FDA does not define a specific age for the geriatric population due to different considerations for the wide variety of medical devices and diagnostics.

In accordance with FDA's guidance collection of race and ethnicity data in clinical trials, patients may self-identify in both an ethnic and racial category. The preferred method is a separate collection of two question formats. Other considerations noted that the disease or condition may warrant more granular race data and the categories may not be appropriate outside the US and the methodology should be clearly defined in the study protocol.

In the two-question format, this is what the two questions look like. Question one is answered first. Do you consider yourself Hispanic Latino or not Hispanic Latino? And question two -- which should be answered second -- is which of the following five racial designations best describes you? More than one choice is acceptable. And you have American Indian or Alaskan Native, Asian or Pacific Islander, Black, Hispanic, and White. And these are categories per OMB policy directive number 15.

Next, we'll get to the meat of the guidance. And they are categorized in three main sections. Section four talks about the enrollment of diverse patients. Section five talks about the analyze and interpreting the study data. And finally, section six talks about submitting and reporting age, race, and ethnicity data.

Each of the recommendations in each of the sections are grouped by different stages of development. The first stages are study design and early enrollment of clinical studies. The second stage is the premarket submission stage. And lastly, you have recommendations for a post-market submission stage. So we'll first tackle section four, enrollment of diverse patients.

Ideally the plan is to enroll a representative proportion of age, race, and ethnic subgroups consistent with the intended use population of the device. You can see page 13 for further enrollment resources.

Below are some of the key considerations -- disease incidence or prevalence in subgroups, diagnosis and treatment patterns in subgroups, proportions of subgroups included in past studies for target indication, and lastly clinically meaningful subgroup differences in safety, effectiveness, or overall benefit-risk profile.

Below are some considerations for enhancing diverse enrollment. Number one include investigational sites with access to age, race, and ethnic subgroups. Number two, alternative communication strategies for study materials. Three, consider broader enrollment criteria. Four, investigate reasons for no or low inclusion of age, race, and ethnic subgroups. Five, involve community providers and patient advocacy groups in recruitment. Six, compensation for transportation costs.

And lastly, flexible scheduling and child care and elder care. Again, see page 13 for enrollment resources. There are additional recommendations we have on there.

We also have recommendations to enhance retention. And these are categorized by what - considerations to sponsors to consider as well as what investigators should consider. So I'll kind of provide key points, key recommendations.

For the sponsors, recommend that they develop follow-up plan to include proxy contact information and actions to take when a patient misses a visit, closely monitor follow-up rates so problems can be addressed quickly, and report accountability of participants in the study report.



For investigators, stress the importance of follow-up at time of informed consent and subsequent visits, provide reminder calls for upcoming visits, attempt to locate patients lost to follow-up, record reasons for patient withdrawals, and finally, maintain continued interest in patients with post-op and follow-up visit calls. Page 19 also has additional approaches to minimize loss to follow-up.

We'll next go to section five, the analysis and interpretation of study data. These are the statistical recommendations that are included for all studies. The Statistical Analysis Plan -- also known as SAP -- in the study protocol should pre-specify assessment of heterogeneity across relevant demographic subgroups. And this may include interaction testing or other approaches. And SAP should also pre-specify reporting by demographic subgroups.

And a lot of this section refers to the FDA guidance evaluation of sex-specific data. So please refer to that for additional statistical recommendations.

When subgroup differences are anticipated, consider proper study design, sufficient enrollment of subgroups to allow meaningful analysis, and potentially controlling for multiple comparisons. You may also want to consider subgroup-specific objective performance criteria -- also known as OPC -- or performance goals -- PG.

You may also consider powering for subgroup-specific claims and may consider demographic subgroups as stratification variables in randomization process when appropriate.

Again, please see the sex-specific data guidance for additional statistical recommendations.

The chart in this figure depicts a series of decision trees that provide a framework in deciding when various age, race, or ethnicity specific statistical recommendations apply for different clinical study designs.

Now the FDA encourages the use of existing scientific data to determine whether there is a hypothesis for a clinically meaningful demographic group specific for your device. And this figure includes a flowchart summary of recommendations provided in section five.

And please refer back to these sections in the final guidance for a detailed explanation of these recommendations.

So this is again another flowchart identifying recommendations for demographic subgroup specific statistical analysis for one arm studies. And this is the flowchart summary for specific statistical analysis for comparative studies.

Furthermore, here are additional recommendations for analyzing subgroup data. Now FDA submissions should include analysis of the following for clinically meaningful age, race, ethnicity-specific differences: primary effectiveness endpoints, primary safety endpoints, and key secondary endpoints. Regardless of the potentially limited statistical power of these subgroup analyses, we recommend that you should provide them in your submission.

Other considerations of subgroup analysis -- there's an understanding that inadequate sample size and unplanned subgroup analyses are generally not considered adequate for statements in labeling. And sometimes effect can be statistically significant but not clinically meaningful and vice versa. We also understand that observed heterogeneity can sometimes be explained by other

covariates. And furthermore, hypothesis for exploratory analysis should be consistent with the literature, such as natural history, subgroups, and known pathophysiology.

Next we'll go to the interpretation of age, race, and ethnicity specific data. And the key question is are there clinically meaningful and/or statistically significant differences observed? If so, please discuss with FDA.

You should also describe how these contribute to overall benefit-risk profile in certain subpopulations. Finally, limitations with small data sets or larger studies with underrepresentation of diverse subgroups should be discussed with the FDA.

Lastly, we'll talk about section six, submitting and reporting of this data. And there's this I guess for definition purposes like to define submit as to refer to information submitted to FDA for analysis. And the term report refers to information that should be included in publicly available documents such as labeling or FDA review summaries.

Now, here are the recommendations for submitting and reporting subgroup data. And these are divided by both submitting to FDA and what should be publicly reported. And these are enrollment demographics for ARE subgroups should be for both submitting and reporting. But for submitting it's also important to note differences in relevant baseline characteristics and comorbidities, any disproportionate loss to follow-up, and outcome differences.

Now, when we're talking about outcome differences, should publicly report clinically meaningful and statistically significant outcome differences. When you submit to FDA, please discuss the generalizability of results when enrollment is substantially different than the prevalence.

And when you publicly report that, should explain how such differences can affect the overall benefit-risk profile for certain subgroups. And lastly, the results of pre-specified subgroup analysis to support subgroup-specific labeling should be both submitted to the FDA and publicly reported.

Tables or forest plots showing outcomes by demographic subgroups are potential options for reporting these outcomes. This is a sample plot generated for illustrative purposes and do not reflect actual clinical data.

And lastly, this is another flow chart summary for recommendations provided in section six. And please refer to this figure four in the appendix of the below summaries that we've covered.

Thank you so much and we'll take questions at this time.

Operator: Thank you. We will now begin the question and answer session. If you would like to ask a question, please press Star 1, unmute your phone, and record your name and company clearly. Your name and company are required to introduce your question. If you need to withdraw your question, press Star 2. Again, to ask a question, please press Star 1. It will take a few moments for questions to come through. Please stand by.

Katie O'Callaghan: While those of you on the phone are gathering your thoughts, one additional item I'd like to point out in regards to the scope of this guidance – as Katherine mentioned, PMAs, HDEs, as well as clinical data included in De Novo's and 510(k)s in the premarket domain are in-scope. Also in-scope are post-approval studies and post-market surveillance or 522 studies.

Some areas that would be out of scope for this guidance would include devices which are intended only for certain groups -- for instance, pediatrics. And also, we're aware of course that in vitro diagnostic device studies sometimes are conducted on de-identified leftover specimens. In those cases, it's often difficult to identify the demographic information for these specimens. And so in those cases, this guidance would not be expected to apply.

For companion diagnostics, this will oftentimes be a case-by-case determination. So we recommend that you contact the primary review division or branch to discuss.

Operator: All right. It sounds like we are ready for our first question. Our first question comes from (Melody Domurad) with Merit Medical. Your line is open.

(Melody Domurad): Good afternoon and thank you for this call. My question has to do with data from countries outside the US where it is considered not legal to ask for ethnic or racial information. We would like to include those countries in our studies but what do we do in that circumstance?

Katie O'Callaghan: Hi. Thank you, Melody for your question. We are certainly aware of that limitation. I would direct your attention to page nine in the guidance where we do address the recognition of special considerations for outside-of-the-US data that would be included.

I think a recommendation specifically to the case you bring up would be to simply make the FDA aware of that limitation and to which country it applies, but then to apply the recommendations of this guidance to the other patients in your dataset to the extent possible.

Does that address your question?

(Melody Domurad): It does. Thank you very much.

Katie O'Callaghan: Thank you.

Operator: Our next question is from (Tim Haring) with De Novo Pharmaceuticals. Your line is open.

(Tim Haring): Hi. Do you have clarification in the guidance about the differential definition of the age group for pediatric as compared to the guidance for pediatric waiver application?

Katie O'Callaghan: I do not believe this guidance, which was specific to CDRH, includes reference to the waiver guidance. It does include reference to the regulations in which the definition for pediatric for medical devices is included.

(Tim Haring): Thank you.

Katie O'Callaghan: You're welcome.

Operator: And again as a reminder to ask a question at this time, you can press Star 1 and record your name and your company name. Our next question comes from (Rob Nerr) with Zimmer Biomet. Your line is open.

(Rob Nerr): Hi. I was wondering how the ARE will affect randomization schemes or enrollment. So if you're halfway through the enrollment and you know you're not quite as balanced as you planned to be, should you adjust later on?

Katie O'Callaghan: In general, I'll say the guidance does include recommendations for things that you can do if you are already in study enrollment or have a completed study. But my recommendation to you would be to contact the review division and copy the patient diversity email address you see here on the screen to address your specific case.

Operator: Thank you. Our next question comes from (Elizabeth Orr) with Medtech Insight. Your line is open.

(Elizabeth Orr): Hi. Can you hear me?

Katie O'Callaghan: Yes.

(Elizabeth Orr): Okay, good. My question is say someone has attempted to enroll a diverse population, but hasn't been able to get the patients they would need for proper representation. At what point would FDA say that they sort of made a good faith effort and they can go ahead?

Katie O'Callaghan: That will depend on the specifics for the device and the condition and to what extent prior information indicates that age, race, or ethnic variables will have a bearing on outcome. So that would be a discussion that would be had with the review division.

(Elizabeth Orr): All right. Thank you.

Katie O'Callaghan: Thank you.

Operator: And again as a reminder to ask a question, please press Star 1 on your phone and record your name and company. Our next question comes from (Jane) with BBA. Your line is open.

(Jane): Hello. I have a quick question. I recently worked with one of the sponsors and when we told them that we need to collect the basic demographic information, including ethnicity and race, they were very hesitant to collect that information, saying that they don't want to label their patients. What do we do in that situation?

Katie O'Callaghan: So the recommendation in this guidance, as well as in the FDA guidance on Collection of race and ethnicity data, does recommend that patients self-report, which is a key principle in this area. If the company has further concerns or considerations that we could discuss, I would encourage you to contact the review division and copy the CDRH patient diversity email address listed here.

(Jane): Okay. Thank you.

Katie O'Callaghan: Thank you.

Operator: The next question comes from (Shomey) with Medtronic. Your line is open.

(Shomey): I know that it's a well-known example that drug treatment can affect differently in different race, like immunological responses. Did you know any well-known examples that different people race react differently to devices? Like scan or any other thing you can think about.

Katie O'Callaghan: Yes. Thank you for your question. The guidance does list a number of examples for each of the subgroups. There is a publicly available example where there were differences observed in particular race and ethnicity subgroups for devices used as dermal fillers, where differences in skin pigmentation were associated with differences in outcomes and in overall



benefit-risk profiles. And I would refer you to the guidance in the sections on each of the specific race and ethnicity and age subgroups for additional examples.

(Shomey): Okay. Thank you.

Katie O'Callaghan: Thank you.

Operator: The next question comes from (An Wen) with FD. Your line is open.

(An Wen): Yes. In regards to the 2005 guidance that was published is there any difference in reading this particular guidance?

Katie O'Callaghan: I believe you're referring to the FDA wide guidance on the collection of race and ethnicity data. That guidance was updated and is referred to in this guidance.

The agency-wide guidance primarily focuses on how that data should be collected and categorized in datasets and this guidance, which pertains to medical devices, also includes recommendations for how to analyze that data, how to report it to FDA, how to report it in publicly available documents as well as some recommendations about how to achieve diverse enrollment and retention. Does that address your question?

(An Wen): Yes.

Katie O'Callaghan: Thank you.

Operator: Our next question is from (Jane Feyl) with the Indiana Institute of Technology. Your line is open.

(Jane Feyl): Thank you. Hello everybody. I am a librarian at the Indiana Institute of Technology in Ft. Wayne, Indiana. This is my first semester of being embedded in our medical device classes. And I'd like advice on how I help our students locate and evaluate the studies and the complete reports and so forth. This is very new to me, so I appreciate any advice you all can give me, any hyperlinks. If you can email me I would most appreciate it. Thank you.

Katie O'Callaghan: (Jane), hi. Thank you for your comment. Are you able to see the slides that we're projecting at the moment?

(Jane Feyl): Yes, I am.

Katie O'Callaghan: I would recommend that you go there to the link for CDRH Learn. Do you see that? It's the third link on the slide. That includes the information from this webinar, but it also includes a wealth of information about regulatory background, expectations, slides from other webinars on other topics that may be of interest for your work.

(Jane Feyl): Well, thank you. I appreciate your help. Thank you.

Katie O'Callaghan: My pleasure. Thank you.

Operator: Thank you. And again as a reminder to ask a question, you can press Star 1 on your phone and record your name and company name. One moment please for any further questions. We're showing no further questions at this time. I would now like to turn the conference back over to Irene Aihie.

Katie O'Callaghan: One final comment from FDA. There are several points of intersection here with other activities in pediatrics. And so for those of you who may have

particular interest in that area, Dr. Vasum Peiris is our Chief Pediatric Medical Officer and leads those efforts.

And as was mentioned in some of the questions, there are some intersection points with other activities around race and ethnicity and FDA has an Office of Minority Health who leads those efforts as well. And with that I'll thank you all for your attention and I'll turn it back over to Irene.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions. Today's presentation and transcript will be made available on the CDRH Learn web page at [www.fda.gov/training/cdrhlearn](http://www.fda.gov/training/cdrhlearn) by Wednesday, November 8.

If you have additional questions about today's presentation, please use the contact information provided the end of the slide presentation.

As always, we appreciate your feedback. Following the conclusion of the webinar, please complete a short 13 question survey about your FDA CDRH webinar experience. The surveys will be found at [www.fda.gov/cdrhwebinar](http://www.fda.gov/cdrhwebinar) immediately following the conclusion of today's live webinar. Again, thank you for participating and this concludes today's webinar.

Operator: That does conclude today's conference. Thank you again for your participation. You may disconnect at this time.

END