Webinar - Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions Final Guidance

Moderator: Irene Aihie
February 23, 2017
12:30 pm ET

Coordinator: Thank you for standing by and welcome to today's FDA webinar. For the duration of today's conference all participants' lines are in a listen-only mode until the question and answer session. At that time if you have a question press star one.

Today's call is being recorded. If you have any objections you may disconnect at this time. It is my pleasure to introduce Ms. Irene Aihie. Thank you ma'am you may begin.

Irene Aihie: Hello and welcome to today's FDA webinar. I am Irene Aihie of CDRH's Office of Communications and Education. On January 13, 2017 the FDA issued the final guidance for Investigation Device Exemption sponsors, sponsor investigators, including Food and Drug Administration staff.

This guidance document provides clarifying key factors to consider when accepting the benefits and risks of investigational device exemption submissions for (clinical) studies. The focus of today's webinar is to share information and answer questions about the final guidance document.

Today's presenter is (Karen Ulisney), policy analyst and the clinical (trials) program in the Office of Device Evaluation here in the Center for Devices and Radiological Health. Following the presentation we will open the line for your questions related to topics in the final guidance only. Additionally there are other center subject matter experts available to assist with the Q and A portion of our webinar.

Now, I give you (Karen).

(Karen Ulysmee): Thank you (Irene). Today I will be giving you an overview of the final guidance entitled "Factors to Consider When Making Benefit Risk Determinations for Medical Device Investigational Device Exemptions -- or IDEs -- Final Guidance".

Today's agenda includes providing highlights and scope of the final guidance, differences between the draft and final guidance, an overview of selected benefit risk guidance sections -- including regulatorystandards, and subject (protections) for IDEs -- the benefit risk framework applied to stages of device development, assessing benefits and risks for IDE applications, risk characterization and risk management -- and specifically highlight appendix A, the recommended general framework for benefit risk assessment.

We have provided ample time at the end of this short presentation for your questions specific to this guidance. The issuing of this guidance is part of CDRH's overarching mission which includes bringing high quality, safe, and effective devices to US patients first in the world. This contributes to FDA's ongoing efforts to improve patient access to new devices by strengthening and streamlining the clinical trials program.

It clarifies the principal factors that FDA considers when assessing the benefits and risks of medical devices and IDE submissions to improve transparency, predictability, and consistency of this process. The guidance does not propose to revise the sponsor requirements for providing a benefit risk analysis as part of an IDE application or the way FDA reviews IDE submissions.

The scope of this guidance includes factors that FDA considers when assessing the benefits and risks for diagnostic and therapeutic devicestudies that are regulated under 812 and these include IDEs for new devices, amendments and supplements to IDEs, and IDEs for new indications. The guidance is not intended to provide recommendations regarding device-specific data or study requirements.

The draft guidance originally published on June 18 2015. Careful consideration was given to the approximately 50 comments from industry professional, societies, and trade associations as we worked to finalize this guidance. Overall the feedback was supportive and encouraged the development of this guidance to provide a common framework and understanding between study sponsors and the FDA on what information informs the benefit risk assessment and transparency about the IDE decision process.

FDA made minor changes to the final guidance, which included clarification on terminology and modified language to align with our regulations and minor modifications to the text and the examples -- to clarify how study design considerations, the stage of device development, and incorporation of patient preference principles and tools can impact the benefit risk assessment.

The regulatory standards for IDEs, or the purpose of IDE regulations as set forth in the FDA Act and in regulations such as part 812, is to encourage the discovery and development of devices for human use and to maintain optimum freedom for scientific investigators in their pursuit of this purpose to the extent consistent with protection of public health and safety and within ethical standards.

Consistent with the regulations FDA will generally disapprove an IDE application if potential risks of the proposed study are not justified or if data provided are insufficient to adequately characterize the safety profile of the device. In this case human clinical investigation is not considered reasonable. Excerpts from the regulatory language on this slide - one second we're reversing. Excerpts from the regulatory language on this slide provide the citations that support this analysis.

The elements underscored in blue are specific to what is addressed in the benefit risk assessment. Continuing with the regulatory standards for IDEs, patient protection measures provided in the informed consent allows study participants to know what is expected of them in terms of participation as well as potential risks involved in the study before determining whether or not to participate.

Therefore a key principle of subject protections in the clinical investigation is the informed consent process. Sponsors are required to address benefit risk in the clinical study informed consent document, and two elements of the informed consent provided here specifically address the benefit risk considerations.

Also per the regulations the clinical investigation requires prior approval by an institutional review board or IRB before the study can begin.

FDA recognizes that in assessing risks and anticipated benefits the medical device total product lifecycle should be considered and the IDE application should be tailored to the stages of device development.

Device investigations during different stages of device development are associated with different types of risk and different levels of uncertainty. This graph shows uncertainty of device safety and performance at various stages of device development. Higher uncertainty exists with early feasibility studies or EFS studies because device design is typically not finalized. The study has a limited scope and duration, with typically a safety focus, and there are a smaller number of subjects and less non-clinical data for the study device.

Traditional feasibility studies have less uncertainty because the device design is near final or final and the aim is to capture preliminary safety and effectiveness data to inform the pivotal trial. There are typically fewer numbers of subjects than the pivotal trial and generally have more non-clinical or prior-clinical data.

Pivotal trials have an even lower degree of uncertainty at stages of device development. The device design may be finalized. You are collecting definitive evidence of safety and effectiveness data. Statistically justified number of subjects, clinical feasibility is established and all IDE non-clinical data are completed.

Post-market carries the least amount of uncertainty following device approval or clearance and the device is commercially available. An IDE may be necessary in some cases to expand the label. Later we'll talk about how the degree of uncertainties may be offset by certain risk control/risk mitigation measures which can help ensure appropriate patient protections in the investigational research settings.

Applying a benefit risk framework to IDE decision making is used as well for review of marketing submissions - for example, PMA or de novo and certain 510(k) substantial equivalence determinations.

So how does IDE benefit risk assessment differ from marketing applications benefit risk asssessment? Clinical investigations, by definition, are research studies with greater uncertainty regarding the relative benefits and risks of a given device, device technology, and treatment with that device. Less evidence is available for IDE applications compared to marketing submissions and the benefits of the research study are considered directly to the subject and to others. For example, indirect benefit might be the knowledge to be gained from research or contribute to developing treatments.

The real question is how much uncertainty to accept in a benefit risk decision. An effective benefit risk assessment will inform the risk management strategy which includes the application of risk controls and risk mitigation measures. This can result in a favorable IDE benefit risk determination.

So what should be included in a risk benefit assessment? Section five of the guidance takes a deep dive into the assessment of risk and benefit and the following several slides will highlight the important aspects of these two areas. In order to characterize the benefit-risk, it is critical to understand the degree of uncertainty around the benefits and the risks.

Starting on the risk side of the equation, sponsors must include a risk analysis in the IDE application. This includes a description and analysis of all increased risk to which subjects will be exposed by the investigation, the manner in which these risks will be minimized, a justification for the

investigation, and a description of the patient population including the number, age, sex, and condition.

FDA also compares the risks associated with the investigation with not participating in the study - for example, the risk of alternative treatments if available. In assessing risk associated with the investigational device use FDA recognizes ISO standard 14971, or the application of risk management to medical devices -- as an accepted and preferred method of risk assessment.

This ISO standard describes a process through which the medical device manufacturer can estimate and evaluate risks, control for these risks, and monitor the effectiveness of those controls through the product life cycle. The guidance incorporated principles from this standard and appendix (D) of the guidance provides definitions for risk management terms consistent with the standard.

Assessing risk during the investigation is very important and we want to emphasize that this involves describing the relationships between the hazard -- a potential source of harm -- and the ultimate harm in terms of injury or damage. This relationship should specifically describe how the hazard could lead to clinical sequelae -- including length of time experienced and residual effect if any -- or other harmful events.

This is important because it allows a more precise estimation of risk severity and likelihood. Focusing on severity of a risk along with likelihood is important for a complete estimation of that risk. Many identified risks are reduced to an acceptable level through effective risk controls.

FDA's benefit risk assessment of IDE applications focuses on completeness of risk control measures and whether residual risk outweighs anticipated benefits

to the subjects. So -- in general -- the sponsor's assessment of risks to IDE subjects focuses on risks supported by objective scientific evidence and are reasonably foreseeable, include a description and analysis of incremental risks subjects will be exposed to in the study, and how the risk will be minimized, and describe the relationship between hazards -- the potential source of harm -- and the ultimate harm which is injury or damage.

The next several slides will talk more specifically to the characterization of risk or the extent of - risks and harms in an IDE study which takes into account the following three risk factors individually and in aggregate. The type of risks -- such as basic safety -- which includes device-related serious and non-serious adverse events -- procedure-related complications due to the investigation, risks associated with the study itself, not resulting directly from the use of the device, and risks from false positive or false negative results for diagnostics.

The second assessment of risk is the probability or likelihood of risk. This can come from relevant historical data, prediction using an analytical or simulation techniques, the use of data from prior investigations, reliability estimates, production data and post production information, and the use of expert judgment.

During earlier device development stages this may be less certain. Probability levels within an estimated range may be acceptable here. This also includes the likelihood of the hazards resulting in a harmful event. FDA considers whether an event occurs once or repeatedly in assessing the probability of risks.

And the third characterization of risk is the duration of the risk. Is the exposure to subjects temporary, minor harm; cause repeated but reversible

harm; or cause permanent or debilitating injury. Duration or how long the adverse consequence lasts should be considered along with severity of risk.

The next few slides provide details on what is expected to be included in the risk management plan. There should be a summary and assessment of efforts to mitigate the identified safety concerns or ensure device use is directed to participants for whom the risk is considered acceptableso not to outweigh the potential for benefit.

Risk control measures -- including risk mitigation efforts -- should be applied where appropriate to reduce the likelihood and severity of harm to study subjects, improve the benefit risk profile of the proposed study, and intended to reduce the risk to an acceptable level. In an effort to reduce the risk to subjects to an acceptable level sponsors should conduct an initial determination of which risk controls are appropriate.

The benefit risk assessment should focus on residual risk and reduction to acceptable levels relative to the anticipated benefits to the subject. And finally provide a clear justification for the investigationconsidering risks for the intended study participants and plan for minimizing those risks.

The final risk management strategy is the residual risk evaluation. After risk control measures are applied the following measure may be considered when evaluating residual risk. Risk communication and disclosure of residual risk during the informed consent process -- for example how subjects can and should act to further control or mitigate risks, when reliable information is available -- consider subject perspective and tolerance for assuming risk relative to anticipated benefits and limit study subjects most likely to experience benefits.

Initially limit study subjects most likely to experience benefits or a subset where the benefit risk profile is more favorable, for example treatment-refractory patients. FDA believes that effective risk management -- including the application of risk control measures and risk mitigation measures -- can reduce the residual risk and result in a favorable benefit risk determination.

Assessment of other considerations. In addition to the previously discussed risk characterizations and management FDA may consider other risks as well -- such as risks related to interpretation of the study data, risks of drawing false conclusions based on clinical data obtained and the risk of data which are inconclusive or difficult to interpret. Risk to others to consider -- for example risk of radiation exposure - of the health care practitioner or treated subjects become drowsy while operating a vehicle.

So what about the benefits side of the scale? FDA's assessment of anticipated benefits of study participation includes the direct benefits to the subject and benefits to others. The type of benefit examples might include closer surveillance of the clinical management and quality of life.

For diagnostics, identify a specific disease for early intervention or identify patients more likely to respond to therapy. The magnitude of the benefits -- anticipated change in subjects' condition or clinical management -- and questionnaire analysis provides insight into subjects' preference.

Assessment of anticipated benefits to study subjects -- direct benefits or the probability of subjects experiencing one or more benefits. Based on evidence from prior investigations in early stages of device development it may not be possible to assess the probability of subjects experiencing one or more benefits.

The duration of effect -- or how long can the benefit be expected to last? – Some treatments are curative and others are repeated over time. To the extent the effect is known, the duration of the effect may influence how the benefit is defined over time.

The assessment of benefits to others i of the investigational study is the importance of knowledge to be gained. The societal benefit or increase the understanding of a disease condition, potential treatment, or diagnostic applications. The benefit is unique to research doesn't apply to marketing applications. And subject may not receive direct benefit but willingness to participate due to indirect benefits of increasing generalizable knowledge about the disorder or condition being studied.

So how does this all come together and what does it mean for your submission? The goal of the IDE benefit risk framework is to frame the submission content in a format that aligns with regulatory review and decision making.

The benefit risk assessment of an IDE study takes into account the uncertainty surrounding the knowledge and available evidence from different domains such as the clinical, non-clinical, and the patient. The contextual setting in which the study is being proposed -- which includes characterization of the disease or condition being treated or diagnosed -- and the availability of alternatives and risks associated with them.

When available information characterizing the subject’s tolerance for risk and perspective on benefit may provide useful context during this assessment. Such information should and could be derived from sources in the literature and or patient reported outcomes. The benefit risk analysis involves

explaining why the potential risks are acceptable when weighed against the anticipated benefits.

Also considering the limitations and risks associated with alternative treatments, patient tolerance for risk, and perspective on benefits. And how the clinical study mitigation strategies can reduce the risk to study participants. FDA believes that the use of a common framework and structured approach to assessing IDE benefits and risks will facilitate not only the submission of relevant evidence and knowledge but a clear and rational approach to justify the intention of the proposed study.

As stated earlier the application of the factors listed in this guidance can ultimately improve predictability, consistency, and transparency of FDA's IDE decision making and reaching a goal of conducting efficient and cost effective clinical trials while maintaining appropriate patient protections.

I'd like to finish with a sample format of what an IDE sponsor's benefit risk summary section outlining the benefit risk framework should contain, beginning with a detailed device description. Regulations do require that investigational plan includes a description of the investigational device. Appendix (C) in the guidance lists the device attributes that FDA recommends to include in an IDE application device description section.

And the deficiencies related to an incomplete or inadequate device description are the single most common type of non-protocol related deficiency and results in the failure to obtain full IDE approval. This and the following two slides duplicates the outline of the general benefit risk framework for an IDE application provided in appendix A of the guidance. Appendix B contains generic examples of IDE benefit risk determinations.

In the previous slides we talked about the details to include in each of these key elements. And went into some great detail in terms of the assessment of risk. Assessment of benefits -- including a summary of the benefits -- and a consideration of patient preference information. I will add -- with regard to patient preference information and the patient perspective plays a really important role within the benefit risk framework.

When available information characterizing the subject tolerance for risk and perspective on benefit may provide useful context for assessing the benefits and risks of the proposed investigation. Keep in mind as well that individual patient preferences vary and a patient may not assign the same values to risks and anticipated benefits as their physician or family member or other individual. Some patients are willing to take higher risks to potentially achieve a small benefit where others are more risk adverse.

The assessment includes the assessment of uncertainty -- again we went into this in some great detail -- and the conclusion should summarize how the consideration of the factors discussed in this summary justify the decision to proceed with the clinical investigation.

The quantity of information from clinical and non-clinical sources must be evaluated and considered by FDA reviewers is really substantial in a 30 day review period which makes regulatory evaluation a complex process. A framework for benefit risk decision making that summarizes the relevant facts, the uncertainties, and key areas of judgment adds clarity to the review - the regulatory review process.

As mentioned earlier this guidance does not change the way FDA handles IDE decisions but rather it outlines an approach that many of our review teams have used for years. Balancing the need to minimize risk and reduce

uncertainty while promoting public health and innovation by supporting the study of potentially impactful new therapies. For additional information please refer to the guidances listed here or you may contact the appropriate division representatives for your device type.

I would like to invite the panel discussants Dr. (Owen Faris) and Dr. (Soma Kalb) to join us for the Q and A portion of this webinar. But before beginning Dr. (Faris) would like to add a few remarks while the questions are loading.

Dr. (Owen Ferris): Thank you (Karen) and thank you for the presentation today. I just would like to make a few comments. As (Karen) noted in the beginning of her presentation the release of this final guidance is really part of a continuum of efforts in the clinical trial space that really began with the development of our CDRH vision. Which is to bring high quality, (effective) medical products to patients in the US first in the world.

And, you know, that's really an aspirational goal with the idea that bringing important products to patients is important. Bringing them quickly is also important. Patients really need to have the opportunity to access these devices as they become available.

And when we were developing that vision and thinking about strategic priorities for CDRH one of the things that became clear to us -- all the way back in 2013 and '14 as we were developing the strategic priorities for 2014 and 2015 -- was that there was work that CDRH could do in the clinical trial enterprise space to improve patient access to early technologies. And -- by extension -- bring those technologies into the marketplace sooner.

And we recognized back then that the IDE process -- and the time it takes for FDA to interact with sponsors and get our questions answered so that we were

all comfortable with the appropriate benefit risk profile for IDEs -- was simply taking too long. Back in 2011 it was taking over 400 days to reach approval for an IDE. And we identified that as a strategic priority.

And in 2014 and 2015 we sort of took an all hands on deck approach to say we are going to change this dynamic. And we did so quite dramatically. And now instead of 400 days to reach approval for an IDE our median time is 30 days.

And I would emphasize is not because we lowered our bar. It's because we shifted the dynamic about what an FDA review team is expected to do and what the conversation looks like between FDA and clinical trial sponsors. And in particular we want to shift the conversation to being one of we identified challenges potentially, we identified questions. But now let's sit in a collaborative setting and figure out how we come up with the answers to those questions and the solutions to those challenges.

And this guidance is an extension of that. These decisions are very difficult in terms of determining whether it's appropriate to approve an IDE. And this guidance is intended to lay out the framework to support the benefit risk conversation. That's really the fundamental conversation that needs to take place when we decide whether to approve an IDE.

And the idea is that this guidance should help us all hit the ground running so that we can immediately jump into those substantive questions. And this is good for all of our stake holders but most importantly it's good for our number one stakeholder, which is the patient population that will receive these devices and potentially benefit.

So, you know, every IDE involves some level of risk. Some are greater than others. But importantly there is a potential for meaningful benefits that might justify those risks. And you know, when we approve an IDE we accept certain risks. When patients agree to sign up for an IDE trial they accept certain risks.

But we all want to make sure that there is a potential for benefit that justifies those risks. And importantly -- and one of the things that (Karen) brought up toward the end of her talk is that we won't all see this balance in the same way. Not every FDA reviewer, not every sponsor, not every patient will see the benefits and risks in the same way.

But if there is a reasonable case to be made that the benefits justify the risk -- even for some patients -- then that should be part of our decision making process. So that's when patient preference information can come and inform that decision. It's also when the consent form can be enormously helpful in making sure that those outstanding risks are adequately conveyed -- the potential for benefit is adequately conveyed -- so that people can make informed decisions when there might be an array of different perspectives on the benefit risk profile.

Lastly I would just say that I view this guidance not as the end of a conversation but as the start of a conversation. This is a framework for individual sponsors to think about these issues. To think about their own processes and their own way of assessing benefits and risks and see if they believe the case is made.

But then also to use that framework as a way to start that conversation efficiently and effectively with the agency so that we can all start to see things from similar perspectives in as much as is possible. And again, the idea being

that we can hit the ground running with a common understanding of what those benefits are, what those potential risks are, and whether the equation justifies starting that trial.

So with that, I think let's turn to the questions.

Coordinator: Thank you. To ask a question unmute your phone, press star followed by the number one, and when prompted record your name clearly so I may introduce you. To withdraw your question press start two.

Again to ask a question star one. It will take a few moments for questions to come in. Please stand by.

Dr. (Owen Ferris): I want to also mention that we have another guest with us that will help with questions. (Elaine Katrivanos) is here and represents the Office of Invitro diagnostics and radiology.

Coordinator: Our first question comes from (Abby Marcucci). Go ahead your line is open.

(Abby Marcucci): Hi. Thank you for this presentation. It was very informative. I have a question on the guidance document. The benefit risk guidance document points to the early feasibility study guidance document for a device strategy table. When we are submitting the IDE application do we need to consider the device strategy table if the application is more around a pivotal trial where the device design is more final?

Are you expecting us to create something from a device strategy table perspective or just providing a risk document and using the framework that was presented today will be enough? Thank you.

Dr. (Owen Ferris): So -- hi this is (Owen) -- thanks for that question. So I'll start with saying that both the early feasibility guidance document and this benefit risk guidance document offer recommendations but not requirements for what needs to be submitted in an IDE.

Both documents offer some insight into our thinking about how we consider these questions. But by no means is there an expectation for you to apply -- all the elements of the early feasibility guidance -- into other studies. That said -- I think looking at that guidance and thinking about how elements of that guidance might apply to your study could be helpful.

(Abby Marcucci): Just a quick follow up to that, Dr. (Ferris). So in terms of the device strategy table -- it looks a little bit different in terms of how a typical risk document would look for a device where the design is more final -- so the strategy table doesn't have things like likelihood severity of risk.

So -- from a preparation perspective -- if the device design is more final and we have a risk document would you recommend -- and I'm just looking for your thoughts -- putting that in versus trying to look at and fit our risk document into a device strategy kind of table?

Dr. (Owen Ferris): I think that’s what we were hoping would come out of this discussion and this current guidance is, you know, that if you are proposing a study -- where there'd be a feasibility study or a pivotal study -- that you'll use the tools from this benefit risk guidance to have a section of your application -- as outlined in the appendix -- that talks about that. That describes your thinking on the benefits, the risks, and how you came to the determination that those benefits justify those risks. So I think using the outline from this current guidance would be the most helpful.

(Abby Marcucci): Thank you so much.

Coordinator: I show no additional questions at this time. But as a reminder if you would like to ask a question press star followed by the number one. One moment please for incoming questions.

Dr. (Owen Ferris): So maybe I'll just fill in some while we're waiting here? I'd like to take just a moment to reemphasize one of the slides that (Karen) had about device description. And really just make the point that we do sometimes lose an entire IDE review cycle because we have fundamental questions about what is the device, what is it comprised of, how was it tested.

And we're not starting with deficiencies, that we disagree, or we have concerns. It's basically we don't understand because it wasn't fully described in your submission. And before we reach that point of understanding of what is your device we're unable in many cases to make an informed benefit risk determination.

And so I would just emphasize that this is something to make sure - that when you are putting together an IDE application that it's very clear to someone who is not intimately familiar with your device and your development process what that device is, how it's comprised, and how it was evaluated in the non-clinical setting.

So again - the concept of hit the ground running. So just a little plug for that. Do we have any questions?

Coordinator: Again to ask a question it is star one. Our next question comes from (Matthew Albert). Go ahead your line is open.

(Matthew Albert): Hey, can you hear me?

(Karen Ulisney): Yes, we can hear you.

(Matthew Albert): Great. I was wondering if the panel sees any impact of this guidance on clinical trial design or conduct? I know it's mostly based on risk and benefit of the device and the contents of the IDE application itself. But specific to the trial design, data collection, or conduct of the trial. Any thoughts on that would be appreciated.

(Karen Ulisney): So - this is (Karen). I think that at any point in the study design you can incorporate principles of quality – or design by quality principles. Whereby in planning the trial– you know where the highest risks are going to be.

So in other words you might -- for example as you design your monitoring program -- you might want to include enhanced monitoring at certain points in the clinical trial that you know there might be a more likelihood of missing windows forpatient follow up that are critical. Particularly those where end points are collected.

I think the other aspect would be patient perspective. It's very important to build some of those constructs into your study design. For example, even when your - consenting patients it may be very difficult for folks to come to you but you might think of mechanism whereyou can go to the patient. Maybe where they are in the clinic.

Or look at using some of the more tools that we have provided in guidances. Like electronic methods of gaining informed consent where you enhance the

informed consent process by providing electronic tools such as graphs and charts. And a variety of different things that help engage patients in clinical trials. So I would say build by quality by design and also include patient perspective.

Dr. (Owen Ferris): I'll echo what (Karen) said. And I think that there are many elements of a trial that can either help to reduce residual risk or can in some ways help to increase the potential for benefits that justify those risks. There are many times when there's nothing else that can be done except what is done in the trial to address those needs.

So for example there might be a safety profile that is somewhat concerning but we don't fully understand it well now. Maybe we have some additional monitoring methods that are in the trial. Or a (DSMB) that is observing events as they occur. Or stopping rules that will say if that even happens even once or five times then the trial...

(Matthew Albert): Yes.

Dr. (Owen Ferris): ...will stop while we look at those results. There are also some times where -- to increase the benefit profile -- the study might be designed to focus on a certain patient population that has a higher likelihood of deriving benefit from that study compared to other patients who might be considered for the trial.

So there are ways in which the trial design itself is an enormous part of the benefit risk equation and factors in to whether that trial is appropriate to proceed.

(Matthew Albert): Great, that's very helpful. Thank you. One follow up question if I might. In terms of data collection and the piece on patient preference. Is FDA expecting more collection of data on patient preference in clinical trials?

(Karen Ulisney): This is (Karen) again. You know I think the message that we are imparting regarding that is that if it is available- if the product area itself lends itself to...

(Matthew Albert): Okay.

(Karen Ulysmee): ...collecting more patient preference information, then we would expect that you would consider including that in your application. If there are specific patient-reported outcome tools that may be appropriate to the particular patient population we would highly encourage you to include that in the study design and include that as a factor in considering the benefit risk determination.

(Matthew Albert): Okay thank you. That's very clear.

Dr. (Owen Ferris): So back in 2014, 2015, I mentioned that CDRH had a strategic priority around the clinical trial enterprise. For 2016 and 2017 we identified three new strategic priorities, one of which we termed partnering with patients. And the idea is that the patient voice -- and the entire clinical trial evaluation but also device approval decision making process -- could use some strengthening.

And that we want to move in that direction of bringing the patient voice -- again I mentioned that patients are our most important stakeholder -- but they don't always have the loudest voice in the process. And so we think that it should be at every stage. And so it should be, you know, if there are data that help us understand the benefit risk equation for whether to approve an IDE or not -- that some patients would accept a certain benefit risk profile that other

patients might not -- that would be helpful information if it's reliable data that we can use as part of our decision making process.

It's also the case that trials themselves can benefit from gathering patient preference information as part of the trial design so that that information can be used to inform future decisions around that product. So a trial could be designed to gather some patient preference information, some patient recorded outcomes, information about how patients experienced the benefit or the risks of a device.

And that information can be extremely helpful in informing the decisions we make later about whether that device should be (in) the market. And going even further, patients can be very helpful in determining what are the right end points for a trial. If we're saying that this is a particular success criterion for what determines study success -- well if that information is informed by patient input that's even better. And so there are many ways in which patients can and should be brought more into the conversation.

This guidance in particular focuses on the decision around approving an IDE and if there's patient information that helps us make that benefit risk determination as to whether that IDE should go forward. But I think that is just one segment of the whole scope of where patient information can and should be increased and it's something that we as an agency are trying to more towards.

(Karen Ulisney): And -- this is (Karen) again -- I will just add one follow up to (Owen)'s comment regarding PROs or patient reported outcome -- tools. I think the clinical investigational setting -- the IDE -- is a very good spot - place to try to validate some of these patient reported outcome tools. Sometimes these are

included in clinical investigations but we don't have a lot of validation data unless they are tested in the clinical investigation setting.

(Matthew Albert): Right. Thanks.

Coordinator: We have no additional questions at this time. I can now - like to turn the call back over to Irene Aihie.

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) webpage at W-W-W dot F-D-A dot gov forward slash training forward slash C-D-R-H Learn by Friday, March 3. If you have additional questions about the final guidance document please use the contact information provided at the end of the slide presentation.

As always, we appreciate your feedback. Please complete a short survey related to today's webinar. The survey can be found at W-W-W dot F-D-A dot gov forward slash C-D-R-H webinar. Again, thank you for participating. This concludes today's webinar.

Coordinator: This concludes today's conference. Thank you for participating. You may disconnect at this time.

END