

NWX-FDA OC

**Coordinator: Irene Aihie
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Operator: Welcome and thank you for standing by. All participants will be on listen only mode until the question and answer portions of today's conference. If you wish to ask a question on the phone line, you may do so by pressing star followed by the number one. This conference is also being recorded. If you have any objections, you may disconnect at this time. I will now turn the conference over to Owen Faris. Thank you and please begin.

Owen Faris: Good afternoon and welcome to today's FDA webinar. I'm Owen Faris, Director of the Clinical Trials Program within CDRH's Office of Device Evaluation. I'm very excited today to be able to provide some updates on two important activities within our program. First we will discuss early feasibility study, investigational device exemptions or IDEs. And second, we will discuss the draft guidance FDA categorization of IDE devices who assist the Centers for Medicare and Medicaid Services with coverage decisions, a guidance which is currently available for public comment.

After each presentation, you'll be given the opportunity to ask questions and I'd like to encourage you to do so. We're hoping for a lively and informative discussion today. Carla Wiese, a policy analyst in the clinical trials program

will be primary presenter today. We're also pleased to have Rosemarie Hakim from the Centers for Medicare and Medicaid Services to assist with questions. Also with us is Irene Aihie from the Office of Communication and Education who will help facilitate today's discussion. Now I'd like to turn the presentation over to Carla.

Carla Wiese: Thank you Owen. Again this is Carla Wiese. I'm the acting policy analyst for the early feasibility program. And for the first topic today, I would like to talk about early feasibility study investigational device exemptions which are a valuable regulatory tool for medical device development. I'd like to cover the following in this presentation: what an early feasibility study is and how it can benefit sponsors, what some key elements of the early feasibility guidance document are including what does doing the right testing at the right time mean, what a successful pathway to an early feasibility IDE approval looks like. I would like to go over some common questions we have received about the program as well as some tips. And I'd like to provide you with some helpful links.

First I'd like to talk about what an early feasibility study IDE is. An IDE is an investigational device exemption. An IDE submission allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data. An EFS IDE is a standard IDE except for there are significant unknowns about how the device will perform. This may be because the device is early in development or because it has a new intended use. Therefore, a small number of subjects are included in these clinical investigations, an intent of which is to develop an initial evaluation of safety and effectiveness or to establish a proof of concept.

Of note, EFS is an informal designation. And by this I mean it's not necessary to submit a request for a designation or apply in any way. Although it is

helpful if you note in your submission and cover letter that you are proposing an early feasibility study as a means to inform the review team of the type of submission they will be reviewing.

Next, I would like to discuss how conducting an early feasibility study in the United States can benefit sponsors. First, it can (unintelligible) a more efficiently pathway to U.S. commercialization and this can happen in a few different ways. First, FDA feedback early in product development may help a sponsor improve their development strategy and reduce the chances that unnecessary testing is completed. It can also increase the predictability of data requirements for a future study or commercialization needs. Also data collected in the U.S. population may be easier to leverage to support later studies.

Some additional benefits include the following. There's an assurance of patient protection under the IDE regulations. You may have better access to technical experts and key opinion leaders in the United States. You may have better access to technical experts and key opinion leaders in the United States. There's a logistical advantage in proximity to U.S. innovation centers. And this program allows for device iteration including during the early feasibility study which may result in higher quality products.

Now there's a lot of information on this slide and I won't go through it all in detail but I've included it for your reference. The table points out the differences between early feasibility studies and other common types of studies. I'll just go over the text in red in the left most column that is relevant to early feasibility studies.

So early feasibility studies again contain a small number of patients. They are fundamental questions about device performance and safety. The device

design may change. There may be limited non-clinical data available and the purpose of this study can be for multiple reasons including to demonstrate a proof of concept, determine what design or procedure changes could optimize the therapy and many more. Of note, not all of these phases are required for market approval and what I mean is there may be situations when a device is evaluated in an early feasibility study and then a pivotal study without the need to conduct a traditional feasibility study.

Next I would like to talk about some key elements of the early feasibility guidance document. A link to this guidance is provided at the end of this presentation for your reference. The first key element is doing the right testing at the right time. FDA understands that comprehensive testing during early phases of device development may add cost without significant return and some testing may be deferred. However, EFS is not to take the place of informative non-clinical testing. A second key element is that unknowns and risks can be addressed in several ways including using clinical mitigations to provide patients with extra protection, the use of more frequent and detailed reporting and the guidance to give specific informed consent recommendations that are relevant to early feasibility studies.

Another key element is that the guidance allows for timely device and clinical protocol changes. More changes can now be made during the study through a five day notification rather than FDA approval and there's a contingent approval option. This is the approval of anticipated or proposed device changes that can be obtained contingent on the completion of an agreed upon test plan and acceptance criteria. And lastly, the guidance contains recommendations on pre-submission content including an example risk assessment method is provided.

Next I would like to talk in more detail about one of the key elements of the guidance document which is doing the right testing at the right time. I believe there has been some confusion about how and why less non-clinical testing may be needed to support an early feasibility study. For the next few slides, I would like to discuss this in some detail which will hopefully provide some clarity.

FDA recognizes the value of alternative non-clinical test methods in leveraging data. For example, different test methods may be more relevant for small batches. An example of this is the single lot ethylene oxide sterilization versus completing a full ethylene oxide sterility validation. Also, some test data could be leveraged. For example, some biocompatibility and points could be leveraged from an animal study if one is conducted. And some test data could be leveraged from a previous version of the device.

FDA also recognizes that some non-clinical testing could be deferred. The most important concept to keep in mind here is the risk presented to the patient after clinical mitigations are considered versus the potential benefit. Some relevant questions that could be asked include the following. That the probability of failure or patient harm understood and can this be mitigated? For example, perhaps there is a low risk of irritation to a material and should if irritation develops this will be evident by evaluating the patient. A possible mitigation could be incorporating timely clinical assessments into the clinical protocol or use of an appropriate intervention.

Another relevant question may be can a potential failure or harm be detected and mitigated? Let's say that there is some risk that the patient may experience pain in a given procedure and an animal study will not sufficiently inform us about this. An option could be added to the clinical protocol to titrate the therapy while evaluating signs of discomfort or reverting to standard of care.

Another relevant question that could be asked is can the clinical study be controlled to further protect patients? For example, it may be possible to first evaluate a device in a hospital setting for the early feasibility study instead of the home where it may eventually be used, which could change the electromagnetic compatibility testing need.

And another question that could be asked is, is the clinical situation emergent and/or are there no alternatives available? For example, if the patient's condition is critical and they are not expected to survive very long it may make sense to defer long term durability testing due to the criticality of the short term benefit.

And lastly, will the non-clinical test data provide valuable information on how the device will perform in this proposed clinical study? For example, if test data will not inform the clinical study today but will characterize the device and will be important for developing specifications prior to a marketing approval, data could be gathered in parallel with the clinical study and submission of this data to FDA could be deferred. Of note, if the clinical situation is non-emergent and there are therapeutic alternatives, the amount of non-clinical testing may need to be comparable to other available therapies.

When assessing the appropriate non-clinical testing needed to support an early feasibility study, understanding and explaining the utility of the non-clinical test is important. It is - if it is animal study, which device performance data will inform the human clinical study. Is the test conservative or not? Is the test validated? Does the test have historical value? And will the test be used for quality control in the future? In summary, what will the data tell us? Are there options to protect patients when non-clinical testing has limited utility?

Next I would like to talk a little bit about what a successful pathway to an EFS IDE approval looks like. Our first recommendation is that the sponsor is well prepared. And by this I mean the sponsor knows what information they want to learn from the early feasibility study and have utilized their resources including FDA guidance documents and recognized standards, CDRH learned modules and external experts if needed, and they have also reached out to an early feasibility representative to discuss their submission strategy. I have provided a link to their early feasibility guidance and CDRH learned modules at the end of this presentation for your reference as well as a list of early feasibility representatives for each division.

Second recommendation is that the submission are well planned. An informational meeting may be useful for novel ideas in particular. An initial pre-sub should include all the information described in the guidance with the goal to agree upon the risks in the test plan. Additional pre-submissions should be submitted as needed, for example, if test requirements are uncertain or discuss the clinical protocol. And in order to help ensure an expeditious review, it is important that the IDE submission contains all required information. Again I have provided a link at the end of this presentation which contains the recommended content of an IDE submission.

I just wanted to make a quick note here. The use of pre-submissions to discuss the test plan and the clinical protocol can be very useful in the following ways. It can be useful when the non-clinical testing needed is unclear and be used to agree upon the test plan that will support an IDE submission with FDA and you avoid the need to redo expensive and time consuming testing. And it may help determine appropriate clinical mitigations and reporting requirements in the patient population for whom the benefit risk profile supports inclusion into their early feasibility study. In summary, these are highly recommended.

Another recommendation is that the submissions be of high quality. And by this I mean they contain enough information for the FDA to provide valuable feedback, the contents are well organized and navigable and high quality scientific discussion and evidence has been provided. =

And our last recommendation is that the sponsor is able to describe why additional non-clinical testing will not be informative and that a human clinical study is appropriate. There is a clear identification of potential risks and how they will be addressed be that be it non-clinical testing, clinical mitigations and/or reporting. An explanation is provided for why the plan is sufficient and it's helpful to explain what can and cannot be learned from the bench test and animal models and why any information to be leveraged is directly applicable to this study. And lastly it may be helpful to list which tests will be done to support the early feasibility study versus which will be done to support a later study if applicable.

Next I would like to go over some common questions that we received. The first question is, is EFS for novel technology only and the answer is no. Early feasibility studies are just small studies used to gather information when there is significant unknowns and they can be used for a variety of reasons: to study a novel device, to study an expanded device, expanded access or to support new indications for a marketed device. When is a good time to talk to FDA about an early feasibility study? The good time to talk is after you have established through general device design intended use and what information you would like to gather from the early feasibility study but before expensive and time consuming non-clinical testing has been started. Also, it is recommended to communicate with FDA informally throughout the development process to optimize submission efficiency.

The guidance document contains an optional risk assessment template. When and how is this used? This is called a device evaluation strategy table. This table describes what the device is supposed to do, how it may fail, what would be the result of the failure and how the chance of failure has been reduced and clinically mitigated. It can be helpful if you do not currently use another method for assessing risk. It should contain a high level description of risks not as detailed as an FMEA but more from the clinician's perspective. And the intent is to link primary risks together with risk mitigations.

Next I would like to go over some tips. First tip is that if you're iterating your device to keep samples of previous generations. They may be useful in the future for establishing biocompatibility equivalents, for example. Second tip is to keep clear and detailed records of the testing completed with each device iteration. This ensures that a detailed description of the device iteration is included in the protocols and this may help leverage information in future submissions.

If you would like to use test results that were not obtained per standard FDA recommendations, we recommend that you provide an explanation for why the data is sufficient. For example, if your animal study is intended to support device safety and deviates from the good laboratory practices, we recommend that you tabulate each part of the regulations, list how the study deviates and how you will ensure data integrity and minimize bias. Of note, only animal studies intended to support device safety are required to address the good laboratory practices and the EFS guidance this discusses how non-GLP data may be used as long as the deviations from GLP do not compromise the ability of the results. And I've provided an FDA guidance link for your future reference.

I'd like to expand on this a little bit more. Again if your animal study is intended to support device safety and deviates from GLP, FDA has some specific recommendations. And that is to include a protocol signed and dated by all key parties prior to initiation of the study. This would include the objectives, acceptance criteria and detailed procedures. It's also helpful to include the (unintelligible) protocol with amendments and include description of the animals enrolled in the study and their final designation.

It's also helpful to include the quality measures that have been taken and an explanation of how data integrity has been ensured. QA personnel to monitor the study are important and may be in the some company but organizationally separate and independent of those engaged in the study. And lastly, it can be useful to provide animal facility licenses, accreditations and assurances.

My last tip is to understand that FDA feedback is not a directive. It is information for your consideration into this (unintelligible) for further discussion. Frequently, further explanations provide clarity around a given FDA concern or context around the decisions made by the sponsor. So when FDA sends feedback or deficiencies it should be seen as the start of a conversation and an opportunity to provide clarity.

This slide provides several links for your reference. The early feasibility guidance provides a general overview of the program. The CDRH learn modules provide more detailed information about the program and there are several additional links that you might find useful. This slide contains contact information for all members of the early feasibility studies program including myself, our EFS medical advisor Dr. Andy Farb, and representatives from each division as well as the Office of Science and Engineering Labs. The acronyms in the left most column represent the various divisions. That's all I have for our first topic and I am happy to take any questions at this time.

Irene Aihie: Thank you Carla. We will now open the line for questions on early feasibility studies. We have approximately 25 minutes for questions before we begin our next presentation.

Operator: At this time if you wish to ask a question on the phone line, please ensure your phone is unmuted, please press star followed by the number one and record just your name clearly when prompted. Once again please press star followed by the number one if you wish to ask a question and questions will take one moment to come into queue. Please stand by. Questions are coming into queue. Please stand by for our first question. Our first question will come from (Raj Patal). Your line is open.

(Raj Patal): Yes currently how are you protecting and promoting public health right now?

Carla Wiese: Maybe I think perhaps you're referring to how are we ensuring patient safety in these studies? And I can certainly answer that question. The early feasibility studies are conducted still under the standard IDE regulations and the early feasibility guidance talks about some specific provisions that are used to ensure patient safety. For example, there's very specific language in the early - in the informed consent document that about what type of study this is, about regarding the fact that there's some limited information currently known about how the device will perform, etcetera. There's also usually more patient monitoring procedures and assessments that are conducted during the study and a lot of times more frequent reporting to the FDA is needed in order to reach an IDE approval. So in that way, we help ensure patient safety. And I hope that answers your question.

Irene Aihie: Thank you.

(Raj Patal): Okay thank you.

Operator: Our next question will come from (Jennifer Farrington). Your line is open.

(Jennifer Farrington): Hi. On one of the slides you indicated that it's helpful to contact the FDA informally throughout the process. How do you go about doing that?

Carla Wiese: That's a great question. As soon as the FDA submitted a submission, you know, your file will go to a specific branch with a specific lead reviewer who's responsible for managing your file. So what we usually recommend is for you to reach out to her if you have any questions about say what the next logical steps are is a good starting point.

(Jennifer Farrington): Okay great. Thank you.

Operator: And once again as a reminder, do please press star followed by the number one if you wish to ask a question. Please stand by for our next question. Our next question will come from (Abdel Haline). Your line is open. (Abdel) your line is open. You may be on mute.

(Abdel Haline): Yes sure. So my question is does this apply to companion diagnostics for drugs? For example, can this early feasibility study - can early phase one clinical trial be used as early feasibility study of companion diagnostics?

Carla Wiese: Yes I would suggest that you reach out to OIR for more specifics. It's somewhat of a detailed question that may be a little bit out of the scope of the talk today.

(Abdel Haline): Sorry what did you say? I didn't hear you.

Carla Wiese: I would recommend that you reach out to OIR for more specifics.

(Abdel Haline): No I'm trying to say, for example, if we are developing a drug in phase one and would like to use a develop test for patients enrollment. Does early feasibility - does this phase one serve as early feasibility study and do we need to do any submission to FDA?

Carla Wiese: Well I mean it sounds like you might be talking about a combination product.

(Abdel Haline): Yes.

Carla Wiese: So in that case, the different centers operate a little bit differently and I think that's somewhat of a specific question. What we can do is we've attached - we've included a Web site that you can go too - sorry an email link that you can go to with questions via our Division of Industry and Consumer Education. It's included in this presentation. But I think that your - it would be best to direct your question there to get a better answer.

(Abdel Haline): All right. Thank you.

Operator: Please stand by for the next question. I do believe our next question will come from (Paris Chowdry). Your line is open.

(Paris Chowdry): Thank you. If a clinical trial is planned are early feasibility studies still required?

Carla Wiese: Could you repeat the question? I couldn't hear you very well.

(Paris Chowdry): If a clinical trial is planned for a product, is the early feasibility study still required?

Carla Wiese: So I guess the answer is sometimes it is and sometimes it isn't. It depends sort of on the specific situation.

(Paris Chowdry): Thank you...

Owen Faris: This is Owen Faris. So there are certainly times when we feel that we know enough about the technology that's being studied, the way it's going to be studied, the general safety and effectiveness profile of the device such that it's appropriate to move straight into a pivotal study. That might be particularly common say if it's evolutionary change from a product that we're already relatively comfortable with. But there are many other products which are more novel in their nature where an early feasibility study or some sort of small study is needed to establish basic safety and usability and sometimes the patient populations for the device where by a small study is needed before it would be appropriate to move into that larger study. So it's really a case by case sort of situation.

(Paris Chowdry): Okay. Thank you.

Operator: I do believe our next question will come from (Catherine). Your line is open.

(Catherine): Yes. Out of the potential to reduce some of the pre-clinical or non-clinical study requirements for an EFS, is there any difference in the review process between an EFS and a normal feasibility study IDE?

Carla Wiese: Yes there's really no difference between the review processes. We try to be more interactive but besides that we're - it's really run like a standard IDE.

(Catherine): Thanks.

Irene Aihie: Thank you for your question. Operator do we have any more questions on the line?...

Operator: Our next question - we do. Our next question will come from (Diana). Your line is open.

(Diana): What is the expectation for researchers or sponsors to develop their investigational device using design controls? How thorough and to what extent are you expecting design controls to be implemented and documented for early feasibility study clinical devices?

Carla Wiese: That's an excellent question actually. There isn't currently a set standard or expectation for the level in which that documentation needs to be completed and I think it also is a little bit case dependent on depending on what type of device and what types of quality control mechanisms should be in place etcetera, etcetera. So actually today it's really left up to the sponsor to determine at what level of documentation they need. So I hope that answers your question.

(Diana): Thank you.

Operator: Our next question I believe will come from (Karen). Your line is open.

(Karen): Hi. My question is for software in early feasibility. Is there any type of delineation between how much software is required to be submitted for an early feasibility study for a device that has software in it? It's not a total software product but it's a part of the device versus a straight feasibility IDE. So how much - is there a list of documentation that's required for an early

feasibility study for software versus an IDE for a feasibility study for software?

Carla Wiese: So again it's going to depend a little bit on the risk profile and whether or not the risk can be mitigated in the clinical study. So there's always an option to potentially defer a little bit of the testing later on. There just has to be kind of a rationale set up for that, sort of what we talked about a little bit about this earlier in the presentation. So again it's a little bit case dependent but there's an option for that such as, as long as there's an adequate rationale provided for deferring any type of testing.

(Karen): Is it dependent on the level of concern?

Carla Wiese: The level of concern, whether or not patient protection measures are in place or different clinical mitigation strategies and etcetera.

(Karen): Thank you.

Operator: And once again as a reminder, do please press star followed by the number one to ask a question here on the phone line. And again do please unmute your phone and record your name. Our next question comes from (Harvey). Your line is open.

(Harvey): We had requested an early feasibility study from the FDA and they insisted that an animal study be done instead. The problem with doing an animal study is there is no animal model. And if we were to do an animal study, we would have to redesign the device to fit the animal in which case the results in the animal study would not equate to the design for a human. Where do we go from here? Is there anybody we can talk to like an ombudsman or somebody?

Owen Faris: So this is Owen Faris. I'll take that. So, you know, I think this gets back to a point that Carla made about deficiencies in letters from IDEs and feedback and pre-submissions. It's not necessarily directives. It's based on the information we have at the time providing feedback hoping to engage in a conversation. Sometimes our perspective is altered by feedback that we get from sponsors like you. And so, you know, the first thing I would strongly urge you to do is engage with the review team that you received that feedback from and try to understand their perspective, convey your own perspective. That may be best done through the pre-submission process.

But, you know, our teams are very eager to get to the right answer. And if you have information that shows that we haven't gotten there yet, we're definitely open to hearing that. There is a formal appeal process to engage in if you've explored the working with the review teams and that didn't get you to the end goal. But our first encouragement is really to work with the review team, provide them more information if you think that there's information that they haven't had yet and go from there. And we're happy to engage and Carla's email is on the slide that's up right now. And if you'd like to engage with us, we can certainly make sure that that conversation with the review team can happen.

(Harvey): Thank you.

Operator: Again do please press star one if you wish to ask a question. Please stand by for any further questions.

Irene Aihie: Operator are there any further questions?

Operator: We do have some additional questions coming into queue. Please stand by. We do have a question on the line from (Debbie). Your line is open (Debbie).

(Debbie): Yes. I'm wondering once the EFS IDE has gone in, how do the EFS staff participate in the process? Are they in the phone calls, at the meetings? Are they the project managers or participants? What's the role of the EFS staff?

Carla Wiese: So right now we ask the review teams to include their early feasibility representatives in all of the meetings associated with their early feasibility study files. And in that way they can sort of ensure that the EFS spirit is taken into consideration, communicate any issues to me that may be resolved and help the team in the decision-making processes.

(Debbie): Right. Thank you.

Operator: And next we have a question from (Fletcher Wilson). Your line is open.

(Fletcher Wilson): Hi. Thank you. Assuming a company has gone through the pre-submission process and has agreed on a test plan with the FDA, is there an opportunity for the purpose of timeline contraction to actually have the submission of the IDE occur while some of the longer term testing items are still ongoing with the understanding that no, you know, testing will begin until all tests have passed?

Carla Wiese: So there certainly is an option and there's also the contingent approval option, which is if you agree upon the test protocols and test methods and acceptance criteria you may be able to implement something during the early feasibility study assuming you've already come into agreement between the sponsor and the FDA. So there's some options to facilitate what I think you're going for there.

(Fletcher Wilson): Okay. Thank you.

Carla Wiese: Sure.

Operator: Our next question will come from (Eric). Your line is open.

(Eric): Hi. Thanks. What type of labeling is required for an EFS? And I'm talking in terms of aside from a part number or a serial number for say an implantable device. I'm talking in terms of either an IFU or a manual or instructions.

Carla Wiese: Yes sure. The labeling requirements are the same as for any other investigational device.

Owen Faris: So the device would need to be labeled as investigational. We would certainly look at any instructions that are provided to investigators to make sure that they are adequate. You know, really it's the same as what we would look for in any other study to make sure that patients are protected and that adequate information is being provided to ensure this application.

(Eric): Perfect. Okay thank you.

Operator: And we additionally have a question from (Hasan). (Hasan) your line is open.

(Hasan): Yes. My question is (unintelligible) the early feasibility study for it seems like the guidance is specifically targeting the non-finished device. So you can do a feasibility study and get some feedback from the FDA. What if you have a final device, it's considered the final device? Can you just go to an IDE directly without doing a feasibility study?

Carla Wiese: Do you mean going directly into a pivotal study?

(Hasan): That's correct yes.

Carla Wiese: In some cases that's possible. It's a little bit case dependent. But there are situations where that happens certainly.

Owen Faris: Yes really it depends on what is our knowledge base in terms of our knowledge of the risks and the benefits of the device. Do we know enough at this point to say that it's appropriate to expose subjects, many subjects, in the, you know, in a pivotal study to that device in the way that it's being proposed? Or do we need to see that device being evaluated in a smaller patient cohort under very tight controls and maybe additional risk mitigations to make sure that patients are protected as we learn more. And that's really the model of early feasibility and traditional feasibility studies. Sometimes they are required by us before a pivotal study would start even if you know what the final device design is simply because we need to be assured that you are - have learned enough to move into that larger study and under particularly tight controls generally is the nature that we're protecting patients.

(Hasan): Thank you. And a follow-up question to do an early feasibility study I guess. I'm assuming the process we should just go through the pre-submission process to start a discussion with the FDA?

Carla Wiese: Yes that's recommended.

Owen Faris: You know, and we've heard a couple of people say early feasibility study or an IDE. We just want to clarify an early feasibility study is an IDE. It's one type of IDE but it goes through the same IDE process as every other IDE.

(Hasan): Thank you.

Irene Aihie: Thank you. Thank you for your questions. If you had questions about early feasibility studies that we were unable to get to, please use the contact information provided on the slide presentation to reach us. Carla will now present on the draft guidance FDA categorization of investigational device exemption, IDE devices to assist the Center for Medicare and Medicaid Services, CMS, with coverage decisions. Following the presentation, we will give you the opportunity to ask a question about this guidance. As a reminder, available to assist with the Q&A portion are other subject matter experts from the Office of Device Evaluation here at CDRH and Rosemarie Hakim from the Centers for Medicare and Medicaid Services. Now I give you Carla.

Carla Wiese: Thank you very much. So the agenda for this presentation is the following. I would like to discuss why IDEs are conducted and why they are categorized, why there is new guidance related to CMS categorization, what the changes are between the old policy and the new policy are, considerations when changing from category A to category B, how a category designation may affect coverage in a study, and other factors that may impact coverage. Of note, I've also included links to this draft guidance and a relevant CMS Web site for your reference at the end of this presentation.

So why are IDE studies conducted? An investigational device exemption allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data. FDA approval of an IDE submission indicates that FDA has determined that the follow - the sponsor has provided adequate data to support initiation of the study, there are no subject protection concerns to preclude initiation of the study after IRV approval, and that the benefit risk profile for the study is favorable.

Generally an IDE study is conducted to answer outstanding questions about safety and effectiveness. However, the extent to which initial questions of

safety and effectiveness are already addressed depends on many factors and this needed to be communicated from FDA to CMS. For this reason an Interagency Agreement between CMS and the FDA was made in 1995 to support CMS' decision making for coverage. As part of this agreement FDA signed the device with an FDA approved IDE to one of two categories. Experimental investigational which is Category A; or a non-experimental investigational which is category B.

This agreement allowed for expanded coverage to include some investigational devices.

A category designation was to be based on the extent to which initial questions of safety and effectiveness have been answered. Specific criteria were defined in the 1995 Interagency Agreement for how FDA would determine the appropriate category.

The categorization has been used by CMS as part of its determination of whether or not items and services meet the requirements for Medicare coverage.

So why is there new guidance related to CMS categorization now? The previous FDA policy regarding categorization did not adequately articulate criteria that are relevant to certain studies such as feasibility studies.

The previous policy did not contain sufficient guidance regarding how a category designation may change from A to B. And the previous criteria did not consider all regulatory pathways such as the de novo submission.

Some additional factors include that CMS changed from local Medicare administrative contractor review and approval of IDE studies to a centralized review and approval of IDE studies effective January 1, 2015.

Interactions between FDA and CMS since that time have highlighted a need for changes to categorization in order to improve consistency.

This table shows what has changed or remains the same between the old policy and the draft guidance. The changes include the following.

In the 1995 Interagency Agreement, detailed criteria were used to designate an IDE device category. In this draft guidance the proposed criteria have been simplified to ensure that devices fall into the correct category.

In the 1995 Interagency Agreement there was limited or no visibility to how a category change may occur as knowledge is gained. And this draft guidance provides an explanation of how a category change may occur.

And in the 1995 Interagency Agreement no examples were provided. In this draft guidance we provided several examples that provide clarity.

There are also several items that remain the same. First the FDA review Team still makes the category designation. The category designation is still to be based on the degree to which initial questions of safety and effectiveness are resolved.

And the categorization will then be used by CMS as part of its determination of whether or not items and services will be covered. And this has not changed.

As a reminder, draft guidance is proposed documentation not yet ready for implementation. This draft guidance was issued on June 1, 2016 and the comment period closes August 1, 2016.

If you would like to provide comments to the draft guidance please go to www.regulations.gov and the docket number for the guidance is FDA-2016-D-1159.

Next I would like to discuss the policy included in this draft guidance. The draft guidance includes definitions of Category A and Category B which has been copied from the regulation and had not been changed in any way. A Category A definition, according to the regulation, is the follow.

A device for which absolute risk of the device types has not been established. But its initial questions of safety and effectiveness have not been resolved and the FDA is unsure whether the device type can be safe and effective.

Some of the next slides are challenging to digest so I will read through them and pause after some of them so that you may absorb the material.

Regarding Category A, FDA intends to consider a device to be in Category A if one or more of the following criteria are met.

No PMA approval (unintelligible) clearance or de novo request has been granted for the proposed device or similar devices. And non-clinical and/or clinical data on the proposed device do not resolve initial questions of safety and effectiveness.

The second criteria is that the proposed device has different characteristics compared to a legally marketed device. And information related to the

marketed device does not resolve initial questions of safety and effectiveness for the proposed device.

Available non-clinical and/or clinical data on the proposed device also do not resolve these questions.

The third criteria is that the proposed device is being studied for a new indication or new intended use for which information from the proposed or similar device related to the previous indication does not resolve initial questions of safety and effectiveness.

Available non-clinical and/or clinical data on the proposed device relative to the new indication or intended use also do not resolve these questions.

Next I will go over an example of a category situation. A device is completely novel and has no or limited previous human use and our initial questions of safety and effectiveness.

There is adequate non-clinical information to support initiation of an early feasibility study that will provide data to inform potential device design or procedural improvements.

Now I'll go over a second example. An already approved or clear device is being evaluated for a new intended use or indication wherein the device will be placed in a different anatomical location.

The device's technology is unchanged from what was initially approved. However, it is uncertain as to whether the device can be safely placed in the new anatomical location and whether the device can also be effective in the new anatomical location.

Therefore there are inadequate data to resolve the initial questions of safety and effectiveness relative to the new intended use or indication.

Next I'd like to go over Category B. The Category B definition, according to the regulation and as stated in the draft guidance is the following.

A device for which the incremental risk is the primary risk in question, that is initial questions of safety and effectiveness of that device type have been resolved or it is known that the device type can be safe and effective because for example, other manufacturers have obtained FDA pre-market approval or clearance for that device type.

FDA intends to consider a device to be in Category B if one or more of the following criteria are met. No PMA approval; 510(k) clearance or de novo request has been granted for the proposed device or similar devices.

However, available clinical data, for example feasibility study data and/or non-clinical data for the proposed device or a similar device solve the initial questions of safety and effectiveness.

The second criteria is the following. The proposed device has similar characteristics compared to a legally marketed device. And information related to the marketed device resolves the initial questions of safety and effectiveness for the proposed device.

Additional non-clinical and/or clinical data on the proposed device may have been used in conjunction with the leveraged information to resolve these questions.

And the last criteria for Category B is that the proposed device is being studied for a new indication or new intended use. However information from the proposed or similar device related to the previous indication resolves the initial questions of safety and effectiveness.

Additional non-clinical and/or clinical data on the proposed device may have been used in conjunction with the leveraged information to resolve these questions.

I'll now go over two examples of Category B. First example is that adequate data has been gathered from non-clinical testing and the clinical results of a feasibility study such that initial questions of safety and effectiveness have been resolved.

A pivotal study will be initiated to provide the primary clinical evidence for the safety and effectiveness of the device in support of a future marketing application.

A second example of Category B is that an improved device will be evaluated for a new indication. Data exists on an approved device for another similar indication, and non-clinical data has also been supplied such that the initial questions of safety and effectiveness related to the new indication have been resolved.

The new study to be conducted will provide further data regarding device performance for this new indication.

Next I'll discuss when IDEs are categorized. The FDA Review Team will make a categorization decision at the time of the first approval, be it full or conditional approval, of an IDE study. A categorization change will be

considered for study expansion or upon a request for redesignation. The category is included in FDA's approval letter for the IDE.

So a few types of information that might support a category change. One is, non-clinical test data or external data on the technology. For example data from other similar devices or preliminary clinical data on that device.

Next I would like to go over an example of a change from Category A to Category B. Adequate data has been gathered on a device from non-clinical testing to completion of an early feasibility study within the U.S., as well as a small non-U.S. clinical study such that initial questions of safety and effectiveness have been resolved.

Additional data are needed to help inform a pivotal study design. Therefore a traditional feasibility study will be initiated.

Although the early feasibility study was originally designated as Category A, adequate data, as described above, has since been gathered to support a change to Category B for the traditional feasibility study.

In this particular example multiple studies were conducted prior to completing a feasibility study. However many times (unintelligible) single U.S. early feasibility study is completed prior to starting the next study.

Next I'd like to talk about how a categorization designation may affect coverage in a study. If the study is designated Category A, the device may be covered but routine care and services may be covered.

If a study is designated a Category B then the device and routine care and services may be covered.

There are other factors that may affect coverage in a study. Some questions to be asked include the following.

Has a previous national coverage been made for the device type and/or procedure? Because a coverage decision may supersede the category designation.

Will the device be adjunctive to a procedure in which a coverage decision has been made? Again, a coverage decision may supersede the category designation.

Is the device relevant to the Medicare population, and have other CMS criteria been met? And I've included a link to a CMS Web site on the following slide for your reference. And of course there may be other factors that impact coverage.

Here are two links for your reference. A link to the FDA draft guidance we discussed in this presentation, and a link to the CMS Web site titled, Medicare Coverage Related to Investigational Device Exemption Studies.

I will now take questions. And as a reminder, we have (Rosemary Hakeem) here from CMS as well. Thank you.

Carla Wiese: Thank you (Carla). We will now open the lines for questions related to the draft guidance. Operator?

Operator: Thank you. Once again at this time to ask a question do please ensure you have your phone unmuted on your end. Please press star followed by the

number 1 and record just your name clearly when prompted so I may introduce your question.

Once again please press star followed by the number 1 if you wish to ask a question. And questions will take one moment to queue up. Please stand by.

Our first question will come from (Abdel Helene). (Abdel), your line is open.

(Abdel Helene): Thanks. So my question is, how this applies to companion diagnosis in clinical trials? My interpretation of your guidance is, companion diagnostics IDE is for clinical trials can be considered within Category A which is not reimbursed, but if the test has been already approved

For example, if you apply HRSA test for a new indication where the test has been approved this - can this be within Category B which can be reimbursed for clinical trials or not?

Carla Wiese: So the guidance applies to all IDEs. And if you have specific questions which it sounds like you do, I would recommend that you send via the email provided in the presentation.

(Abdel Helene): Thank you.

Operator: Our next question will come from (Trang Quen). (Trang), your line is open.

(Trang Quen): Hi, I'd just like some clarification. If we have - if we are trying to add in a new indication, that requires a clinical trial?

Owen Faris: So this is Owen - yes. So if you are studying a device or a new indication that's not approved then if it does fall under the purview of something that

may require an IDE, depending on the risk profile and whether there are other reasons that the study be exempt.

But generally, if it is considered a significant risk device - significant risk study for a new indication for an approved device, yes it would require an IDE.

Carla Wiese: Operator, are there any further questions in queue?

Operator: Yes, our next question will come from (Debbie Brown). (Debbie), your line is open.

(Debbie Brown): Thank you. I have two questions. One is, does the FDA give an automatic designation of Category A and B even if the company doesn't provide any information related to this topic?

And then my second question was, if you get product approval after conducting an IDE and you have a Category a designation, to what extent does that affect reimbursement after approval?

Owen Faris: I will take the first part of that question and maybe (Rosemary) can take the second. So the first part is, every IDE that we approve or approve with conditions, we assign a designation.

So regardless of whether you make a case for one or the other, we're going to assign a designation in that letter.

(Rosemary Hakeem): Hi, this is (Rosemary Hakeem). The question about reimbursement, so reimbursement is an automatic - has an FDA approval (unintelligible). So...

(Debbie Brown): I'm sorry, we can't hear you very well.

(Rosemary Hakeem): Can you hear me?

(Debbie Brown): No - yes. Could you try again?

(Rosemary Hakeem): I could try.

(Debbie Brown): Thank you.

(Rosemary Hakeem): Yes, so the initial - after the FDA has approved the device, the initial category designation doesn't affect the reimbursement. In order to get it reimbursed you have to go to CMS and ask for a billing code and that's how you get reimbursed.

Carla Wiese: I'm sorry, we still couldn't hear that last sentence I think.

(Owen): We're going to pass over a different microphone. Hold on one moment, we're going to give it one more shot.

(Rosemary Hakeem): Okay, so the initial FDA ID designation no longer applies to billing after the FDA approves the device. You have to go to CMS to get a code in order to go to reimbursement for whatever it is that you're doing.

(Debbie Brown): That answers my question. Thank you.

Operator: Our next question will come from (Laura Lund). (Laura) your line is open.

(Laura Lund): Thank you. I also have two questions if that's okay? The first question is, how - to what degree will FDA consider OUS feasibility study data or post-market surveillance or registry data in making a category decision?

The second question is, if a sponsor is approved for a pivotal trial, however FDA believe that beginning the trial, the device should be categorized as A, is there a potential process for pre-agreeing on a point during the pivotal trial at which a device can change categorization from A to B?

Owen Faris: So the first question was I think, what extent would we consider OUS data and registry data; other data in our decision as to what we know about initial questions of safety and effectiveness?

And I think the answer to that is pretty clear that we absolutely will consider that information that we are always trying to take a least burdensome approach to make best use of the information that's available.

And so if you have meaningful information that didn't come from a U.S. clinical study, that's perfectly fine. If it's meaningful and we can rely upon it we will do so. So I think that part is relatively clear.

The second part of your question was asking if we're going to transition from an A to a B. Somewhere along the way, is there a clear cut point where that might happen? And I think the answer to that is, maybe.

So you know we are always willing to consider a Change Request in designation. So there certainly would be times when you might conduct a feasibility study it's an A. You come in with your total study proposal, we now know more because of the information gained in the feasibility study and we determine that that's B.

There might be another situation where you are proposing a pivotal study, maybe without having done a feasibility study. Maybe we think that's appropriate, but we do what we call a phased or staged pivotal study where a certain number of patients are exposed to the device through the investigation initially. We see what happens with that before we broaden that study.

That may be a reasonable transition time to consider changing from an A to a B as well.

But then there are also times when new information becomes available and you as a sponsor could come to FDA and say, new information is available. We'd like to make a case that this should be a B now. And we would definitely entertain that discussion.

(Laura Lund): Thank you.

Carla Wiese: Hi this is (Carla). I just wanted to add one thing. I think just keep in mind that we can always - you can always communicate with your review staff and discuss which open questions there are about safety and effectiveness in order to help with predictability.

(Laura Lund): Okay, thank you.

Carla Wiese: We'll take our next question.

Operator: Our next question will come from (Cathy). Your line is open (Cathy).

(Cathy): Hi. I was just wondering if you could give us an example of what answering an initial question of safety and efficacy is. I know in certain final questions

regarding safety and efficacy would require a pivotal. But is there any guidance on what threshold you might have to meet to answer an initial question of safety and effectiveness?

Carla Wiese: There is no guidance or threshold because it's such a large variability in the questions of safety and effectiveness that could potentially need to be answered.

I can give you an example of like a relatively easy question of safety that could be answered. Let's say for example you are investigating an implantation method and there's a concern about whether or not that specific method for implanting that device in a specific location will be safe.

That's something that you may be able to easily answer by verifying throughout the clinical study that the implant will end up where it was intended. And that is the one question of safety. There are probably, you know, several in any given study.

But that particular question could potentially be answered relatively quickly. And of course there are other questions that may take much longer to resolve.

Owen Faris: So this is Owen. I think I'll expand on that a little bit. Thanks (unintelligible).

So I think - you know I think you're getting to sort of the core question here about what does it mean to answer initial questions on safety and effectiveness. And I think, you know, we have many examples that are easy on either side of the fence. And then we have some that are right on it.

And so, you know, when we have - when we see a novel device in a feasibility or early feasibility study, there are many new questions. We may not know

exactly how it's appropriately going to be tested. We're going to be learning a lot along the way. That's a pretty clear no, we don't know the answer to initial questions of safety and effectiveness.

We also see many studies that are iterative changes relative to very established products. And so sometimes those studies go right into pivotal. We know a lot about how to design them. We know a lot about the end points, and we know a lot about the kinds of things that might go wrong.

And we tested a lot of that through animal and bench data. And so those kinds of devices are pretty clearly in the B category.

And then we have a lot that are in the middle somewhere. And those are the ones that, you know, we are trying with the design of this guidance to give some flexibility and interpretation and room to have a discussion with sponsors to figure out whether we know enough to go from an A to a B or whether we're still in the place of saying we don't know enough yet and we're going to have it stay in the A category.

And so we have a lot of devices that are substantially different from the technologies that are out there but also have some similarities. And so the extent to which we can rely on what we know or the extent to which things remain unknown and must be answered vary to a great extent and can - you know, requires a great deal of consideration and discussion.

And one of the ideas about this guidance is that we wanted to be flexible enough such that that discussion can be held and the right decision can be reached.

Carla Wiese: Okay, thank you.

Operator: Our next question will come from (Laura Hinsey-Russell). Your line is open.

(Laura Hinsey-Russell): Yes this is a question regarding the safety and effectiveness. Will IDE and other testing start to move towards recognizing variation in biocompatibility among patients under a precision medicine framework?

In the future, will you be looking at basket studies to look at allergic and autoimmune reactions to device materials which can help minimize the cost of adverse events to patients and recalls to manufacturers if certain people can't tolerate them and others can?

Owen Faris: That's a great question but I'm going to say that that's a little bit out of scope of the talk we're giving today. And to answer that question I think we'd want to have other experts in the room. So I would say that if you have a specific question in that area that you send it to that e-mail address on the last slide there, and we'd be happy to engage with the right people.

(Laura Hinsey-Russell): Okay, thank you.

Operator: Our next question will come from (Catherine). Your line is open.

(Catherine): Yes, if the investigational product is covered by CMS and then that product goes on to be approved or cleared, is there an automatic CMS coverage for the commercial product or is it more likely to be covered? Or are the two coverage decisions independent from each other?

Carla Wiese: Okay so in order to be covered in CMS, not only do you need to go through the IDE process for approval but you also have to have a payment code. And so once the IDE is FDA approved or is no longer an IDE, you use that code

for billing. Sometimes things rise to the attention of our Medicare contractors or to our central office and we do a national coverage decision or a local coverage decision.

And in that case, we may re-evaluate whatever it is that was tested under the IDE and apply conditions to coverage. But in general things go through and get billed if they have a billing code. And that's up to the sponsor to get that code.

Owen Faris: So it'll be covered.

(Catherine): So for example if we get an ICD-10 code and we are - the investigational product is covered for the study, if the product is approved or cleared, then the coverage is automatic for commercial products?

Carla Wiese: As long as there aren't any Medicare policies that restrict coverage.

(Catherine): All right. And a second related question is getting CMS coverage for the investigational product, is that less lengthy than going through like an NTAP application or whatever applications you need to go through to get coverage for a commercial product? Is it a quicker process?

Carla Wiese: Well since I don't work for the FDA, I can't do that comparison for you.

(Catherine): All right.

Carla Wiese: So are you talking about coverage during a study or coverage...

(Catherine): Yes, yes.

Carla Wiese: ...after the (unintelligible)?

(Catherine): Yes, yes, it's coverage - is it a quick process to try and go through the process and learn whether or not you're going to be covered or not covered for an investigational product during the study? How long does that typically take?

Carla Wiese: Well we had tried to do it within 30 days. Sometimes there are problems and issues and we have...

(Catherine): All right.

Carla Wiese: ...to have discussions, but...

(Catherine): All right.

Carla Wiese: ...once you submit it and that - it was in the previous slide - (Carla) gave you the address, the instructions on how to submit an IDE study for approval and the materials you need to submit to the IDE site. That's all on our Web.

(Catherine): All right, thanks.

Carla Wiese: You're welcome.

Operator: As a reminder, to ask a question please ensure your phone is unmuted. Please press Star followed by the number 1 and record just your name clearly when prompted. Our next question I believe will come from (Mary Ann Bruner). Your line is open.

(Mary Ann Bruner): Hi, thank you. How does this apply to non-significant risk devices that don't require an IDE to the FDA?

Carla Wiese: So the FDA doesn't assign a category to those. If it's a non-significant risk device, and the FDA has not assigned an IDE, then what you generally have to do is to go to the Medicare contractor to ask for coverage.

(Mary Ann Bruner): Okay, thank you.

Operator: And our next question will come from (Debra). Your line is open.

(Debra): Thank you, and I'm sorry I didn't quite hear the last question so maybe it's already been answered, but for IVD studies in which it's exempt from the IDE regulations, will CMS still entertain coverage? And how would we get some kind of designation?

Carla Wiese: So again I think you're referring to non-significant risk devices that we were just talking about. If it's in a clinical study, you should go to the local Medicare contractor to discuss coverage.

(Debra): Okay, so even if it's exempt from IDE regulations altogether, we could still go to CMS.

Carla Wiese: Yes. But we don't review it in the IDE process.

(Debra): Okay, thanks.

Operator: Once again to ask a question please press Star followed by the number 1 now. Please stand by for further questions. Once again please press Star 1 for questions. Please stand by for additional questions. Additional questions are coming in. One moment. Our next question will come from (Jessica Stern). (Jessica) your line is open.

(Jessica Stern): Thank you. With regards to submitting a request to CMS for review and approval of an IDE study, whose responsibility is that for the submission? Is it the study sponsor or the study sites that are participating in the study?

Carla Wiese: Okay so I think you're asking this because in the old process, the study sites submitted a request to a local Medicare contractor.

(Jessica Stern): Yes.

Carla Wiese: Well nowadays the most efficient way to do it is for one entity to submit it under one IDE number. And then if we approve it, we put that IDE number along with a ClinicalTrials.gov number onto our Web site and that study is now approved for every site.

So if we've seen that another site is already submitting something that was submitted by the sponsor, we'd already approved it, we just say well you didn't need to do that.

(Jessica Stern): Okay, thank you. And a follow-up question to that, with the older system, the study sites were responsible for determining whether or not CMS coverage was required for the hospital and/or the institution and/or the physician for a particular study.

So within one study, sponsored study, some sites would have CMS approval and some wouldn't. Is that still the same case with the current system?

Carla Wiese: No. Everybody's covered if it's approved, if it's on our Web site. Some of the Medicare contractors will ask for material, but they can't override our decision so they can't non-cover it.

So what really happens procedurally is once we've put your study's IDE number up, the local contractors actually change their computer systems to accept it at each site individually, which is why they might want more material from each site just to ensure that that site's really in the study.

(Jessica Stern): Okay, thank you.

Carla Wiese: You're welcome.

Operator: And once again as a reminder please press Star followed by the number 1 if you wish to ask a question. Our next question will come from (Ashwini Jacob). Your line is open.

(Ashwini Jacob): Yes hi, I have a question. I currently have an IDE that's categorized as B-3, and I don't see any numerical designations in the guidance document, and I was wondering if you could elaborate on what the definition for that category is.

Owen Faris: Sure. So that was definitely part of the point for why we did what we did with this guidance. One of (Carla)'s early slides said that, you know, the old model from 1995, which you're referring to, had some very specific criteria under which something would be an A or a B.

And we found that frankly that those criteria weren't fully comprehensive and were a little bit limiting. And so looking back at it, you know, 20 years later, the feeling was that really they all come back to this fundamental question of what are the initial questions of safety and effectiveness and to what extent have they been addressed at the time of the IDE approval.

And so we very intentionally simplified this so that it would be an A or a B and not a B-1, B-2, B-3, B-4 because really we felt that that was really kind of confining and limiting from us having the right conversation reaching the right decision.

(Jessica Stern): Okay, thank you. That's clear.

Operator: Our next question will come from (Audrey). Your line is open (Audrey).

(Audrey): Hi, I have a question. Once you submitted the documentation that's needed for coverage from CMS to CMS, when does that information get available public viewed on their Web site? How long does it take to see that on their Web site?

Carla Wiese: Yes so we have scientific people review it. And it takes a few weeks. Once we make a decision, we send the letter to the sponsor, whoever made the request. And then every Friday, new approvals go up on our Web site.

So if you submitted something a month ago, and it was from Monday, and we decided to approve it on a Monday, you'll see your number appear on our Web site on Friday.

(Audrey): Okay, thank you.

Woman: But you'll get the letter on Monday, yeah.

Carla Wiese: Thank you. We appreciate your participation and thoughtful questions. Today's presentation along with the slide presentation and transcript will be made available on the CDRH Learn section of our Web site at www.fda.gov/training/CDRHLearn by Friday, July 22 under the tab How to

Study and Market Your Device in the section titled Clinical Studies,
Investigational Device Exemption IDE.

Please note the FDA is not able to provide continuing education credits or
certificates of attendance for today's Webinar.

If you have additional questions about medical device clinical trials program,
please use the contact information provided at the end of the slide
presentation. Again thank you for participating and this concludes today's
Webinar.

Operator: Once again, with that we'll conclude today's conference. Thank you for
participating. You may disconnect your lines at this time.

END