FDA Webinar: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
Moderator: Irene Aihie
October 10, 2017
1:00 pm ET

Coordinator: Welcome and thank you for standing by. At this participants, will be on a listen only mode until the question and answer portion. If at that time you would like to ask a question, press star one. Today's conference is also being recorded. If you have any objections, please disconnect at this time. And now I would like to turn the call over to you host today to Miss Irene Aihie. Ma'am you may begin.

Irene Aihie: Hello and welcome to today's FDA webinar. I'm Irene Aihie of CDRH's Office of Communication and Education.

On August 31, 2017, the FDA issued the final guidance documents used as real work evidence to support regulatory decision making for medical devices. A guidance plan by policy agencies determines whether real world data making sufficient for use in regulatory decisions. To adopt changes to evidentiary standards we use to make those decisions.

It's also clarifies how you plan to evaluate real world data to determine whether it may be sufficiently relevant and reliable for various regulatory decisions and when an investigation of the extension IDE may be needed to

correct and use real world data for purposes of determining the safety and effectiveness of a device.

The purpose of this webinar is to help clarify the agency's recommendations to make it a constant to the guidance documents. Today Josh Chetta a biomedical engineer in the Office of Device Evaluation and Alex Hu a medical device epidemiologist from the Division of Epidemiology in the Office of Surveillance and Biometrics here at CDRH will present an overview of the final guidance.

Following the presentation, we will open the lines for your questions related to the information provided during the presentation. Additionally, there are other interest subject matter experts to assist us with the Q&A portion of our webinar. Now I give you Josh.

Josh Chetta: All right. Thank you for that introduction. So briefly our agenda for the talk. First, we'll go over background. Cover the differences between the draft and the final version of the guidance document, discuss the regulatory framework in which this information fits and then we'll cover some highlights of the final guidance including examples and issues of data quality.

But first we want to highlight the publication of this document is only part of a larger initiative to leverage non-traditional data sources for regulatory purposes. Increasing access to and use of real world evidence is a part of CDRH's strategic priorities and recent legislation includes sections addressing real world evidence as well.

The definitions from the guidance document are as follows, real world data is defined as data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. And real world evidence is

defined as clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real world data. Taken together a functional definition for real world evidence is an analysis of information collected from routine clinical care. And these definitions in the guidance make clear that for information to be considered evidence, care must be taken at multiple stages - during the data collection process in the approach to the analysis and in any use to evaluate how the resulting information may or may not prove to be adequate to support the regulatory decision at hand. And this is no different from a standard clinical investigation.

The structure of the guidance covers the scope, background, general considerations and then it goes into when an investigational device exemption may be needed and covers data quality and finally goes on to examples. We'll largely stick to this structure for our presentation today.

The guidance discusses how the FDA will evaluate whether real world evidence is of sufficient quality to inform a regulatory decision for a particular medical device, but the document is not all inclusive and we want to make clear that it does not address the use of non-clinical data, adverse event reports, secondary use of previously collected clinical trial data or systematic literature of these.

In addition, it does not endorse a specific study design, study conduct or analytical methodology that could be used for generating or interpreting real world data.

As background we would like to take a minute to consider where real world evidence comes from and why we're interested in it.

First we want to point out the vast majority of medical devices don't require clinical data to be provided to the agency before being marketed in the United

States. However, for devices where clinical data may be necessary to support a marketing application, for example novel or high-risk devices, the traditional pathway to collect clinical data is relatively linear.

The sponsor conducts a clinical investigation, sometimes under an IDE, and the information collected in that study is then evaluated in a marketing application that is subsequently submitted to the agency. Additional post market information such as confirmatory evidence may be collected in a post-approval study or safety issues maybe evaluating post markets surveillance activities.

These clinical studies tend to be well controlled trials conducted in a specific patient population with clinical endpoints designed to support very specific labeling claims and indications for use. These results may not be generalizable beyond specific patient population under study and new trials may be needed for label changes and device modifications.

We know that separate from medical research, the routine use of medical devices in the United States health care system generates a huge amount of data found in sources like electronic health records, laboratory test results and claims databases.

The agency recognizes how important these data sources are because they include information covering the experience of physicians and patients on the actual use of devices in practice and this may be different from what we see in research studies. This constellation of information sources are used to inform clinical decision making, develop new hypotheses for testing and drive device innovation.

This innovation may result in new clinical studies and in some cases high quality evidence generated from real world device use may be submitted directly in a marketing application. So rather than a linear pathway in which multiple one-off trials must be repeatedly conducted, the question is whether we can take advantage of this information being generated to evaluate device use dynamically as population and use change through the total product life cycle.

The guidance document makes clear that we will consider any valid scientific evidence regardless of its origin without preference, but for some regulatory questions, a traditional clinical study may be the most effective mechanism to collect the necessary information. There are benefits and shortcomings of traditional clinical studies, as well as information from real world device use and this document is intended to communicate our expectations to facilitate the use of these non-traditional data sources.

The draft guidance document was released last summer and many commenters provided feedback to the agency. It was important that these be addressed and incorporated into the final version of the document and we'll go over a few of the more common ones now.

The public comments that we received can be broadly summarized into four categories. We were asked whether this guidance applies only to certain classes or types of devices. We were also asked to provide a deterministic score sheet for when real world evidence is applicable to a specific regulatory question. There were concerns about the potential for the use of real world evidence to lower the evidentiary standard that we use to make regulatory decisions and we were also asked to clarify how the use of real world evidence impacts the IDE process.

First the final guidance makes clear that real world evidence may be provided as support for any regulatory decision related to a device and this includes diagnostics, software, class 1 and class 2 devices, as well as for pre-market and post-market decisions.

Second, it was not possible to develop a scoring tool or pass/fail criteria for the use of real world evidence. However, we added additional detail on what aspects the agency will consider when evaluating real world data and real world evidence.

Regarding the question of data quality, the guidance is explicit that the evidentiary standard for all regulatory decision remains unchanged. Using real world evidence does not lower the bar and we also expanded sections of the document that discuss data quality and applicability to a question and these will be discussed in more detail later in this presentation.

Finally, the guidance includes an expanded section on when the collection of data from real world use of device might require an IDE. We'll also discuss this is more detail later.

Now moving from the background information to the information contained in the guidance document, we want focus our attention now on what many of the public comments asked about mainly data quality. In this section we'll cover how the agency intends to evaluate the quality of information collected from routine care.

A reminder that the framework within which we make our evaluations is laid out in our governing statues and regulations. 21CFR makes it clear that a sponsor may submit any form of evidence to the agency but that only valid scientific evidence will be used to support a regulatory decision. This

regulation goes to list the range of potentially acceptable sources and this includes information from well-controlled investigations all the way down to reports of significant human experience. Finally, this regulation lists data sources which are insufficient to be considered for use in evaluating the regulatory decision.

And we've highlighted these sections to emphasize that in CDRH we've always accepted and reviewed clinical data from a variety of sources and part of that review has always focused on the quality of the data. This document does not change that rather it formalizes the process we've been using and lays out our expectations.

Simply put, information provided to us needs to be fit for purpose. It must be complete, consistent, accurate, and needs to contain all critical data elements to evaluate a medical device and any associated claims. Within any benefit risk decision, the information must be relevant and reliable such that an evaluation safety and effectiveness can be undertaken.

What this means is that certain decisions will require a higher-level data than others. For instance, the first of the kind class 3 device may require more information than post-market surveillance for a lower risk device. The guidance includes significant detail on how data relevance and reliability will be assessed and we'll spend some time walking through those ideas but we want to point out that quality needs to be built in into the entire evidence generating process: from primary collection through compilation analysis and use.

So relevance is the idea that the data adequately addresses the applicable regulatory question or requirement in part or in whole. In other words, is the information relevant to the question being asked? Broadly the data should

include appropriate variables collected with sufficient detail to capture the device exposure and outcome of interest. For example, the endpoints must be clinically relevant and be well-defined in a consistent and meaningful way.

The patient population should be appropriate and representative of any potential labeled use and finally the data must be amenable to sound clinical and statistical analysis and the results must be interpretable using informed clinical and scientific judgement. If the data are considered relevant to the specific regulatory question, then we'll evaluate whether we can have confidence in the underlying data and data analysis used.

The data refers to (unintelligible) which play into overall reliability. Data accrual and data assurance. We'll first discuss data accrual which refers to how the data were collected. We'll consider multiple aspects of the collection process in our evaluation. For example, we'll look for pre-specification of standardized data elements, the use of the common definitional framework and data dictionary, and the timeframe for collection.

In addition, we'll consider the data sources and technical method used to capture the data. The patient selection process should be appropriate and should limit bias in the study population and the appropriate patient protections must be in place to protect the rights, welfare, safety and privacy of the patients.

The other aspect of data reliability is data assurance and quality control. And this refers to ensuring adequate people and processes are in place to minimize bias and errors and to ensure data integrity. One consideration is the process used to populate data elements. Were they abstracted manually or was an algorithm used to automatically populate them? Additionally, there needs to be documentation to, documentation of and adherence to source verification

procedures. The data should be complete and consistent for the specified analysis. The data should be consistent and poolable across site and over time and there should be ongoing training programs to ensure personnel are knowledgeable of the data collection, handling, and transmission procedures. These lists of example considerations are not intended to be exhausted by any means. We encourage you to look carefully through the guidance document and contact us with any questions through pre-submission process.

Additionally, although they tend to be focused on registries we encourage you to consult the published resources from other stakeholders that include best practices and recommendations for addressing issues related to data quality. The guidance document lists a number of resources for reference.

We'll now move on to a discussion of when collection of data from routine clinical care might require an IDE. In general, whether the collection of real world data requires an IDE depends on the intended use of that information. The FDA does not regulate how health care practitioners use legally marketed devices or make health care decisions within the context of the legitimate patient practitioner relationship.

Health care practitioners regularly use medical devices off label in the course of normal medical care and we consider these types of interactions to be an important source of real world data. These data may be adequate to support regulatory decisions if found to be of sufficient quality.

It's important to point out that the FDA's regulations are only one part of the legal framework governing protection of patients and the patient's protected health information in the U.S. It was not within the scope of this guidance to address the entirety of human subjects protection questions related to real world data collection. Rather the guidance document focuses on when an IDE

might be needed for activities related to the collection of real world data or real world evidence.

21CFR812 gives the agency authority to grant an investigational device exemption allowing clinical investigations of medical devices to determine safety and effectiveness. Whether the collection of real world data for a legally marketed device requires an IDE depends on the particular situation and use. If the device is being used in the normal course of medical practice, an IDE would likely not be required.

However, if data are being gathered to determine the safety and effectiveness of the device and the process for gathering the data would include treatment decisions is likely not within the normal course of medical practice and an IDE may be required. Given the complexity and nuance of these issues, we strongly encourage sponsors, investigators and IRBs to contact us with questions regarding what activities might require an IDE.

We welcome the opportunity to work with external stakeholders on these issues.

Alex will now discuss examples of how real world evidence has been used for regulatory decision making.

Alex Hu: Okay. Thank you Josh. We believe that real world evidence can be used to aid FDA in our regulatory decision making under the right conditions in areas including but not limited to clearing or approving new devices, supporting labeling expansion, supplementing the total evidence required for clearances or approvals, and in a postmarket setting.

My name is Alex Yuzhi Hu and here I'm going to talk about four cases that were generalized from the actual use of real world evidence.

Labeling expansion is a big deal and it is usually supported by trials with limited sample size and in many cases it can be hard to yield sufficient data that is needed to support such a decision.

There was a class 3 device. We approved it based on traditional clinical trials with focused patient selection criteria. And, due to this reason, we approved indications for use that was quite focused as well. But after the device entered the market, it has seen an expansion of clinically acceptable use beyond what was approved. We discussed with the sponsor about labeling expansion but the scarcity of clinical study data made approval through traditional venue unlikely.

To address this lack of information, we worked with the company and successfully identified an existing national registry that collects clinical information for all patients with this device and other similar devices as participating institutions. It was also linked with claims data through a validated matching algorithm such that it made possible the evaluation of long-term performance. Right now, a study using the data collection and analysis infrastructure of this registry was already initiated to support this labeling expansion.

As for control group, it needs to be there for us to make various regulatory decisions. But it doesn't mean that a control group has to be created based on randomization or it has to be enrolled prospectively. Here in the next example, I will show you such a case. In this example, we determined that clinical data was needed to support an approval decisions for a significant change to an existing device and we decided that we would like to see the

comparison between this device and other clinical alternatives that were already on the U.S. market, and this rendered a use of routine care data possible. To our knowledge, a registry is already out there capturing data on all uses of medical devices with similar intended uses.

From this registry, we drew a non-randomized concurrent control group consists of targeted on-marketed devices as comparator. To make sure that the registry would provide sufficiently relevant and reliable data to the control population. The quality of this registry was evaluated by us and also by the sponsor according to the factors cited in the guidance.

We determined that the quality is sufficient enough for making such a decision, The sponsor did not have to collect additional data from these patients or influence the course of their clinical care in any way. So even though the patient's that received the investigational device were enrolled under an approved IDE, the control group did not need an IDE because the registry was just collecting data on patients with FDA approved devices under the normal course of care.

No study is perfect, there will always be a need here and there for additional data. In many cases, more evidence will lead to decision making that is better and faster. Here in this example, let's talk about where the use of real world evidence provides supplementary evidence. There was a groundbreaking class 3 device under review for a new indication, to which, the sponsor provided FDA with somewhat limited data from a prospective clinical trial particularly in the sense that it did not enough follow-up information and less than clear information on a control population.

To overcome this, we identified a pre-existing data source that was already collecting and reporting data on the control therapies. The registry data was

used to supplement and help interpret the original study results allowing the FDA to come to an appropriate regulatory decision without requiring additional clinical trial data. In this case, real world evidence provided crucial clinical information that is otherwise unavailable to us. It expedited the decision-making process, protected the patient's health while also facilitated medical device development.

As we know, postmarket requirements could serve the patients well but also reduce the pre-market burden while still ensuring that the statutory standard of reasonable assurance of safety and effectiveness is met. But how could a post-marketing requirement also be very helpful for the regulatory decision making on many other devices? In this last example, let's take a look at a postapproval surveillance case where the use of real world evidence made earlier device approval possible and much more.

It was a first of a kind class 3 device approved based on prospective randomized controlled clinical trial data. Early in the PMA review process we began to consider postmarket commitments. We decided to use data generated from routine care to support the postmarket requirement as opposed to resorting to a traditional stand-alone post approval clinical trial. With the help of FDA, a registry was launched that generated real world data that could meet FDA's data requirements on this case. Because the new registry is able to capture information on all patients receiving devices with similar design and indications. This data source provided not only an earlier approval decision for this device but also the necessary infrastructure for making regulatory decisions in many other similar devices. This registry has since been used to collect surveillance data, support indication expansion, even embedded prospective clinical investigations under IDE for subsequent devices with similar designs and indications all because we started using real

word evidence on one single case. All of this cannot happen if a traditional stand-alone post-approval study was required instead.

To sum it up we believe that there is opportunity for greater use of real world evidence and this guidance is designed to provide the framework to help all stakeholders assess relevance and reliability of real world evidence. The center has been supporting various efforts to facilitate the development of infrastructures and tools to better access and use real world evidence for regulatory decision making including the development of NEST. Please contact us through pre-submission or let us know how we can help you through the email addresses provided below. Thank you for your time.

Irene Aihie: We'll now take questions.

Joshua Chetta: And while we're waiting for those questions to get queued up, we've mentioned a few times the pre-submission process and we wanted to point out that there is a guidance document: Requests for feedback on medical device submission, the pre-submission program and meeting with Food and Drug Administration staff. This lays out the process and recommended structure for pre-submission requests and the types of questions that should be and would be appropriate for that type of submission. So we encourage you to contact us early if you have any question about a specific submission.

Coordinator: Thank you and for audio questions, if you would like to ask a question please press star one and record your name at this time. One moment we have an audio question and thank you the first question comes from (Chris) your line is open.

(Chris): Hi I was wondering if you could describe a process for post-approval commitments for class 2 devices.

Joshua Chetta: Thanks for the question. I think that's a little bit out of scope for what we're talking about today.

(Owen Faris): Hi this is (Owen Faris), and I'm the director of the clinical trials program in CDRH. So I agree with (Josh) that if we're talking generally about post-approval requirements for class 2 devices out of the scope of today's conversation and we won't touch on that directly. I will say that I think real world evidence can be used to support regulatory decisions for any class of device. So class 2 and class 3 devices are certainly the subject of this guidance and the principles apply in terms of obtaining quality data that can answer the right questions.

Chris: We have another question in the room.

Woman 1: So just a follow-up on that, is there any example that you could give on real world evidence of what would be acceptable for a class 2 device that doesn't have, for example, device registry or something like that.

Josh Chetta: Again there have been decisions made for class 2 devices in the center using real world evidence. After that information, the information included in that submission was found to meet the kind of the parameters that we laid out here for quality, relevance, reliability, informed consent - all of those things, if necessary.

(Owen Faris): This is (Owen Faris) so I will say that you know this is an area where the use of real world evidence is an evolving landscape and certainly I think this gets to the point of your question, certainly some of the earliest experiences with using real world evidence and regulatory decisions came from (PMA) devices.

But there is a strong interest in the agency to support the expanded use of real world evidence into the class 2 space.

We have seen early examples of that in certain places but we strongly encourage you - if you're a manufacture of a class 2 device and would like to think about how real world evidence can be used to support regulatory decisions in that space, please come talk with us. We're very interested in engaging - particularly through the pre-submission process to talk about how we can make that work.

Chris: Great. Thanks for your help.

Coordinator: We do have another audio question. It comes from (Wade) your line is open.

(Wade): And thank you. I have two questions. The first question is that I'm working on oncology and can you comment on how this guidance will apply for the companion diagnostic in oncology. My second question is regards to that, you gave lots of examples of using the registry data. I'm wondering if any examples using some other data sources, like a EHR databases or claim databases which has been used before in your experience? Thank you.

Mike Waters: Yes, hi this is Mike Waters from the Office of In Vitro Diagnostics and Radiologic Health (OIR). There have been a lot of efforts to help figure out how to leverage realworld evidence from electric health care records (EHRs) and registries when it comes to companion diagnostics. This is an ongoing active space of development.

There have also been some submissions that have gone through the process of leveraging data from appropriately curated next generation sequencing databases in the area of companion diagnostics which (at some levels) fits into the concept of realworld evidence. But this is like I was saying before, this is a

space that's currently under development. If you have something that you would like to utilize, then engaging through the pre-submission process would be an extremely valuable effort.

(Owen Faris): So I'm going to take this. This is (Owen Faris) again, so I'm going to take the part two of your question and you know that much of the example information we provided was related to registry data and I think it's clear that's where our earliest experiences and our most extensive experience with real world data have been because registries are generally systematically designed to gather consistent high quality information that may be more complicated to gather in other ways but I'll say a few things about that.

So one is that many of the registries that gather information are actually linked to claims data to gather later data points that the registry itself doesn't gather and so we do have experience with linking registries to claims data to gather some of that information. There's also a lot of interest in how can we start using electronic health records as the primary data source for real world evidence and how do we gather that in a high-quality way.

So that's a broad effort. The agency's very engaged and very interested in and we've seen some examples of that, but I think we're going to see a lot more in the future. The National Evaluation System for Health Technologies which is just getting off the ground this year, just recently announced a couple of pilot projects which are directly focused on that question of how do you get high quality data from an electronic health care system and translate that into information that can be used for regulatory purposes.

So, I definitely think that's where we're going. We're seeing some of the earliest signals there. But our experience with using real world data with high

quality submissions thus far has a lotof Registries that have played a major role.I think we're going to start seeing that shift in the future.

(Wade): Thank you.

Coordinator: Thank you. As a reminder if you would like to ask a question, please press star one. All questions will be taken through the phone. Again if you would like to ask a question, please press star one. The next question is from (Julie), your line is open.

(Julie): Hello thank you. I was wondering if there was any previous examples or thoughts around the use of international data. So given that quality is all controlled and the other considerations are met, are there any thoughts on using for example UK data as part of a (unintelligible).

Josh Chetta: Thanks for that question. So the center has used information from outside the United States to support regulatory decisions in the past and that doesn't change with this. We would still want to see that the all those parameters that discussed are met. We'd also look for an evaluation of whether the patient population from which the information was collected is relevant to the United States population. There are certain you know depending on the device space there may be differences in considerations that would be specific to that. The broad answer to your question is that yes, we do accept that information and we have used it in the past.

(Owen Faris): I'll just add just a little bit. That (Josh)’s answer extends not to just real world data but also to clinical trial data. We're looking for high quality data that is relevant and applicable to the patient population of interests for U.S. indication. And so if that information comes from the outside of the U.S. whether it's a clinical trial or it's high quality real world evidence, we are

completely open to having that be part of a pre-market submission or other regulatory submission.

Irene Aihie: Are there any more questions?

Coordinator: Yes ma'am. The next question is from (Randall). Your line is open.

(Randall): Yes hello. So my question is regarding along the same vein and it's a good Segway. It's regarding the quality of the data. As a sponsor company, how do we - what mechanisms do you recommend for us to ensure or looking for to ensure the quality of data is being submitted to support an IDE or PMA.

(Owen Faris): So, I'll take a first crack. This is (Owen) and I'm director of the clinical trials program. You know there are a lot of nuances to that question and in many cases, it depends on the particular situation in front of us. But what we find really is of most benefit is having a conversation with us early. You know before - as early as possible really. Before you've opened up that data set, talking about your plan with us. Figuring out what we think the obstacles may be.

We really find a lot of value in sitting down with you and mapping out a strategy. We all recognize that you know while the guidance lays out, the ways in which a high-quality dataset can be constructed there will be limitations and pros and cons to any dataset and any question in front of us.

We recognize that it will not be perfect. It almost never is and we will have some level of uncertainty and the question is how do we get to the acceptable level of uncertainty to support that particular regulatory decision. And so the earlier you can come and talk with us the more aligned we can be and set expectations appropriately the better., and I think you'll find that we're very

flexible and open to these ideas. This is a new ground that we're all breaking here. But, at the same time, the questions are the same questions. How do you provide credible data that's relevant and that's reliable to the question at hand and we believe there's a real opportunity to gather it in a real world space.But coming and talking with us and mapping out a plan is really how we get started.

(Randall): So, I'd just like to add to that. So as a sponsor I have monitors I have CREs that go out and look at the data and do source data verifications so I can stand behind the data that I'm providing. Because I have those mechanisms in place. But in these particular cases when we were using real world data and this data is being collected by a third party, an investigator, an academic, people that don't have the same mechanisms in place that don't have data monitoring or don't have the standard operating procedure sin place, that's where I'm looking for that guidance and that's where I'm struggling to understand which way do we go. What do we do as a sponsor?

(Ben Eloff): Hi this is Ben Eloff, Deputy Director of the Division of Epidemiology at FDA. The section in the guidance within reliability discusses the need for the concept of quality by design and that is that the registry or other data source being considered will generally have some operating procedures along with it. And understanding the design of the operating procedures and the adherence to the design is going to be a critical factor in understanding the reliability of the data and how well it has captured the actual clinical experience. This is different than a traditional bioresearch monitoring inspection and individual source data verification. But the - a well-designed well executed third party data collection and analysis system can be just as reliable under the right circumstances as a traditional standalone clinical trial.

(Randall): Thank you.

Coordinator: Thank you. The next question comes from (Robert) your line is open. Hi there. Thank you.

(Robert): My question relates to the more understanding about the off label use and getting approval for new uses for a device. So as a sponsor what is the line between promoting an off label use and setting up a real world study to determine whether something can be cleared for new use?

(Owen Faris): Hi this is (Owen) again. So, I think the fact that you're getting into a territory that is tricky and you know we try to navigate part of the answer to that question and the guidance around when do you need an IDE. But certainly, there are questions that this guidance doesn't directly take on about promotions. So , generally, when we approve a device, it has a specific indication, particularly for class 3 devices at a clinical trial that indication is generally focused on the patient population that was enrolled in that study that supported its approval.

And we all know that those devices, very frequently, get used for indications that are beyond the scope of what they were originally approved for and this is part of how we have a learning health system, right? Physicians and patients and other care providers learn more about how to use that device better in terms of the ways they use it and the patients that use it, etc. and we don't want to blind ourselves to learning from that information.

With that said, it's certainly not appropriate for a manufacturer to promote for that use which is outside of the scope of its approved indication and that's a tricky water to navigate. But the kinds of questions we ask when we're looking at can you use a registry that gathered information that was beyond

the scope of the approved indication for example to support marketing applications are around,
Well, did you influence care? Did you recruit patients for that use? Did you promote in a way that was inappropriate? There are lots of questions around that - that really have to be taken on in a case-by-case basis. It's hard to give you a clear roadmap in a few sentences and the answer to the question. But these are the kinds of considerations that go into with how we deal with those.

(Robert): Okay. Thank you. So just to summarize I think what I heard was we should probably seek your input first. That would be the most appropriate way to handle those situations?

(Owen Faris): Absolutely. We handle those sorts of questions every day.

(Randall): Okay. Thank you.

Coordinator: Thank you. The next question is from (Andy). Your line is open. Please check your mute button, your line is open. (Andy) we're unable to hear you.

(Andy): Hello.

Coordinator: Your line is open sir.

(Andy): Well hello.

Coordinator: Yes, did you want to ask a question? You pressed star one.

(Andy): Could someone just perhaps discuss the potential use of meta-analysis? Published meta-analyses and which papers that were obviously used to

comprise that we're all investigator sponsored kind of perspective clinical trials?

(Owen Faris): This is (Owen). I'll take the first crack at the question and see if I miss anything. So, I would say, in general, meta-analyses would be outside of the scope of this guidance in the sense that we're generally talking about a Meta-analyses of clinical trials rather than real world evidence. With that said, I think the same sort of principles apply that we're looking for a high quality, relevant, reliable data to support regulatory decision making.

And there are times when Meta analyses can form part or all of that dataset. So I think you can think of similar principles applying but that's not specifically the scope of this guidance or these discussions.

(Ben Eloff): This is Ben Eloff, from the Division of Epidemiology again. Indeed as (Owen) mentioned, meta-analyses, when used appropriately and designed appropriately, can provide additional information as a part of any regulatory decision making. With regards to the real world guidance that we're discussing today, where we consider the literature and presentation to be just that: a presentation of data. The discussion focused in the guidance as the data itself and how it was generated. So an meta-analysis of clinical trial data would not be covered under the scope of this guidance.

The guidance and the principles in this guidance relating to the relevance and reliability are based on sound scientific principles that are really a part of the underlying understanding of any scientific data source. So, we would apply the same principles regardless.

(Andy): Thank you.

Coordinator: Thank you. The next question is from (Anne Marie). Ma'am your line is open.

(Anne Marie): Hi. In the final guidance, FDA states that, in certain circumstances, RWD may be used for generating summary reports and MDRs and unique post-approval studies both of the study and the adverse event reporting are submitted to the Office of Surveillance and Biometrics. So, my question is, in what circumstances, are MDRs required, specifically if the registry date are provided to a class 3 manufacturer by a third party meets the study and points, but is de-identified when there's no possibility of one event investigation or two, identification and removal of duplicate adverse events that have already been reported, then does 21CFR803 still apply to require MDRs for these registry data?

(Ben Eloff): This is Ben Eloff again from the Division of Epidemiology. Thank you very much for that question. The bottom line is like many of these questions it depends on the specifics. The process for doing summary reporting, is out of scope of this specific guidance and is covered by a different set of procedures.

When we have used summary reporting within a registry it has been on a specific case-by-case basis through a waiver process, so you would have to go through that process. And again, we're happy to discuss this on a case-by-case basis.

(Anne Marie): Okay. Thank you.

Coordinator: Thank you. The next question we have is from (Archita). Your line is open.

(Archita): Hi. I just have a quick question. It's actually a follow-up to one of the previous questions. Let's say you do have a (unintelligible) of evidence that it

is connected from our connected product as a medical device company. How do you think it's going to affect reimbursement if we were to use that in patient outcome?

Josh Chetta: This is (Josh). Unfortunately, you're kind of muffled. Could you repeat the question again? I'm sorry, we didn't quite catch it.

(Archita): I'm so sorry. Can you hear me all right?

Josh Chetta: Yes, that's better.

(Archita): So, I was wondering, currently, you know as a medical device company we have a good amount of real world data. How exactly can we use that for improving reimbursement as we're looking at improving patient outcomes but we're not actually able to figure a way for reimbursement for it?

Josh Chetta: Hi this (Josh) again. Thanks for the question. Unfortunately, I don't think we can address reimbursement in this discussion right now. We're focused on regulatory decisions that the FDA would make and those would be outside kind of the scope of what we do.

(Archita): That's all right. Thank you.

Coordinator: Thank you. The next question is from (Rob) your line is open.

(Rob): Hi do you have any guidance or thoughts on collecting patient reported outcome data for post-market commitment studies using mobile devices?

(Ben Eloff): Hi this is (Ben Eloff) from the Division of Epidemiology. With such an open-ended question I can provide a few different avenues for consideration. One,

patient reported outcomes are a very high priority for us here in CDRH for a variety of reasons and we have indeed relied upon them in post-approval settings and in pre-approval settings for many devices over the years.

In a real world setting, the qualification and evaluation of a PRO instrument and its fitness for purpose for evaluating the endpoints that it's supposed to evaluate are part of qualification document for that instrument would be submitted via the PRO guidance processes and the medical device development tools process. Once appropriately qualified within the space, it could then be used as an appropriately robust endpoint data collection tool for measuring that outcome.

Coordinator: Thank you.

Irene Aihie: We'll take our next question.

Coordinator: Yes, the next question is from (Kim) your line is open.

(Kim): Hi. Thanks for doing the teleconference. In one of the examples, this morning, FDA performed a study evaluation of a registry - will this be the standard for the Agency going forward and if so will it be done in conjunction with the sponsor or will it be independent between the agency and the registry?

(Owen Faris): Hi this is (Owen). You know I think right now frankly we're seeing both. We are seeing sponsors come to us and say we'd like to use this registry or we'd like to take part in developing this registry. Here's the purpose that we have in mind for a regulatory use and can we work with FDA to talk about how we can make this happen? We're definitely seeing that. We're also seeing patient groups, physician groups saying ‘this is happening in this space right now and

we'd like to have a better way of gathering this information; FDA, we know you have some experience in this, Can you help us? And can you help us form a registry that can gather information that can answer these kinds of questions'. We may want to help answer and work with you know manufacturers with in the future.

And so, really it can come from anywhere. There are times when manufacturers have the interest in that and there are times when patients or physician groups have interest in that information. And we're happy to engage with either of those groups or together.

(Ben Eloff): Just to add to Owen's comments, much of the engagements with real world data sources and qualifying these sources as evidentiary is going to be covered and rapidly evolving through the National Evaluation System for health technologies. We do not right now have a clear one size fits all standards or route map that would cover every conceivable source. However, what we do have is a long-standing commitment to partnering with all of available and interested stakeholders in the interest of advancing public health.

Mike Waters: And if I could add to that, (this is Mike Waters from OIR (the Office of In-Vitro Diagnostics and Radiologic Health)), we have several examples and efforts that we're actively engaged in right now throughout CDRH to develop the harmonized and interoperable infrastructure to access real-world evidence in both the therapeutic and diagnostic spaces. In the diagnostic space, we've engaged multiple stakeholders including CDC, NIH, ONC, CMS, device manufacturers, labs, electronic healthcare record (EHR) vendors and standards developers to adopt and develop semantic standards and structured data formats to improve access to harmonized and interoperable real-world evidence. So, if you want to help in enhancing the ability to access RWE, you can contact us at OIR-Policy@fda.hhs.gov or

CDRHClinicalEvidence@fda.hhs.gov and you can get involved in some of these developing efforts.

(Kim): Excellent. If it's okay, I have a couple of other specific questions. One is regarding in the irrelevance category and real world data study designs and study protocol and analysis plans, it goes on to say whether or not it's capable of being accomplished in efficiently timely manner. Could you provide more specifics on what that means? Are you saying its treatment may be device/treatment affect specific and who would determine the timeliness?

Josh Chetta: Hi, this is Josh. I think that again we've answered a number of times, it's going to be handled on a case-by-case basis but the intent is to ensure that the information is collected in a timely manner, the patients are and that the information can be used and it's going to be fit for purpose. So I don't if there's additional - if you had another question about that or what specifically you were asking.

(Kim): I was trying to understand better what the temporal nature of that part of the sentence that relates to? Is it relating to actual collection - like the timely collection of the data itself or is it implying something about the timeliness of the study designs somehow?

(Ben Eloff): This is (Ben Eloff) again, I think a good way to understand that question is the condition that it's attempting to mitigate. As we all know science and clinical practice moves fairly rapidly and evolves and the concern with using especially a retrospective design would be that you would be analyzing results that are not necessarily applicable to the current state of affairs or events. So understanding whether or not a trial can be performed or analysis can be performed in a time that's still able to address the question that is relevant. It is the concern that we're trying to mitigate.

(Kim): That's very clear. Thank you so much for that answer. And the last one from me at least is on the data accrual and reliability. Again, there's a bullet related to establishing the steady plan and protocol relative to the collection of the retrieval the real world data. Maybe this is a can to, but we just discussed on the relevance side I wasn't sure it's the same thing. I didn't know if implied prospective versus retrospective and if you have RWD that was already pre-determined and there was a common definitional claim work, as well as a data capture form. What difference would it make if it was retro versus PRO? If you can comment on that.

(Ben Eloff): Right. This is actually a little bit different than the prior case. The concern here that we're interested in is whether or not the data have been accessed or if there is an understanding or look at the data prior to the plan going into place that would affect the development of that plan. One can do a prospective evaluation of retrospectively collected data if you don't know what is necessarily in there. However, if the data has already been analyzed, retrieve and then the study plan is put in place, the scientific value of that analysis is reduced more to a hypothesis generating status than it would be to a definitive conclusion.

(Owen Faris): This is (Owen) to add a little bit to (Ben)’s response. You know there are times when retrospective data that is even looked at retrospectively, is so compelling that it can still support a regulatory decision. But to Ben’s point when you already know the data that's in front of you and you say now this is how I'm going to look for a regulatory submission - that has a strongly negative impact on the sort of strength and credibility of those data. It can at times be overcome with such compelling information that we still can rely upon it. But good clinical trial design, good data analysis design - is to plan

what you're going to do before you have knowledge what those data say. And so the more you can do that, the greater reliance we can have on those data.

(Kim): Excellent. Thank you.

Coordinator: Thank you. The next question we have comes from Heather. Your line is open.

(Heather): Thank you. So thinking about new and novel types of data from different data sources, it would be really helpful for me if you could lay out some of your thinking around the types of documentation or policies and processes you would want to see in place under in particular under the sections for reliability of the data for new digital health applications, wearable and other tools that could be collecting real world data to support evaluations. Thank you.

(Ben Eloff) Hi this is (Ben Eloff again. The processes for doing these evaluations again are rapidly evolving and there are several working groups within the agency and in the (Nest) partnership that are approaching out to evaluate what documentation specifically to collect and so on. The general principles and high level principles we lay out in the guidance but as was mentioned in the earlier slides, we don't have a score sheet or a check list or anything like that at this point that can be used for full validation of any given data source or sources. We are hoping that through the NEST partnership and working with a variety of data sources and users of those data we can come up with some scenarios that can be reused more generalizably in the future, but the science is not at that point yet.

(Heather): Thank you and I have one more follow-up if you don't mind. It's actually about linkages between different data sources. In some ways it's written to look at a single source of real world data for an evaluation and it might be too

early days to talk about it, but it would be helpful if you guys had thoughts about data linkages between different real world data sources and what types of validation processes you ideally would like to see.

(Ben Eloff): We do. We actually have a number of examples and quite a bit of experience in the use of the linked datasets from a variety of different clinical areas and types of data. Within these specific sources, we continue to abide by scientific principles. The linkage between different data sources has been well described in the academic literature and methodology and we would rely upon that methodology as described and validation studies for the specific endpoints of interest so that we could rely upon them.

(Owen Faris): This is (Owen). I just wanted to add a little bit to (Ben)'s good comments that we've been sort of peripherally in our presentation today in answering the questions today talked about NEST, the National Evaluation System for Health Technologies. Maybe it's appropriate to just give a more direct shout out to what's happening there because NEST is really the bringing together of essentially all of the stakeholders in this space. So we're talking about FDA of course, but also manufacturers, patient groups, providers - sort of all the folks that are in this space of generating, colleting, interpreting, using real world evidence and trying to figure out best practices. Setting up ways to link data, developing both methods but also sources of data so that if I am a stakeholder and I have a question, eventually NEST will be able to help me figure out what data are available that can help me answer that question and so it is a very exciting time for real world evidence in that the National Evaluation System for Health Technology is just really getting off the ground this year. The director of NEST was named and the Board of Directors to support NEST was named. There is money allocated for the next five years to support NEST going forward and I think this is just going to be generating a lot of really useful resources and thinking in this area on the very kinds of

questions that you're asking: How do we do this? How do we do this well? What data are available to me? How can I rely upon it? These are the kind of questions that we'll be answering jointly as an ecosystem over the coming years and it's moving really quickly and its' been really in my mind very impressive thus far in terms of what they've done just over the past few months that they've been in existence.

Alex Hu: This is (Alex Hu) speaking. So, regarding the data assurance, besides the real world evidence guidance, there are also many published recommendations by, for example, Agency of Healthcare Research and Quality, Patient-Centered Outcome Research Institution, National Medical Device Registry Task Force, so on and so forth. In drafting these recommendations, FDA has been highly involved and these publications are laid out on the page 16 of the guidance. Please take a look.

(Kim): Thank you.

Coordinator: The next question is from (Napoleon). Your line is open.

(Napoleon): Thank you. Has, can, or will the real world evidence methodology be applied to combination products across the divisions of FDA. How is that working at NEST? Thank you.

(Owen Faris): So, this is (Owen). So, this guidance does apply to combination products and we are very interested across the agency in using real world evidence. There are a lot of activities and a lot of recent publications and outreach on using real world evidence across the agency for any kind of medical product. Obviously, combination products have particular challenges and unique questions and again our sort of standard answer is please come talk with us if

you have an idea for a combination product for which you wanted to use or develop real world evidence source, but absolutely that's on the table to do.

(Napoleon): As a follow-up the Parental Drug Association is meeting shortly again on combination products and I would hope that we can encourage them to be involved because they have a very board view. So thank you.

Irene Aihie: We'll take our next question.

Coordinator: Yes ma'am. The next question is from (Sonya) your line is open.

(Sonya) Hi thank for you the webinar. My first question is about informed consent. Is informed consent required for real world data collection? And the second one is there a difference between real world data collection and retrospective data collection? If yes, what's the can you elaborate on the difference?

(Owen Faris): So I may have to ask you to repeat the second part of your question. The first part around informed consent is a really complicated question and specifically has so many factors that it was really difficult for it to be included in the scope of this kind since there are many factors that play into whether or not informed consent is required. How are the data being used? Whether the data are identifiable. There are many other factors so there are situations where real world data are used in regulatory submissions that did not require informed consent. There are situations where it is used in which it did require conform consent. We specifically did not take that on in this guidance but we're happy to talk to you on a case-by-case basis.

Would you mind repeating the second part of your question?

(Sonya): My second question yes, I do believe that whatever type of data we're going to collect we need the pre-plan what we're going to do but my question is if there is any difference between real world data and retrospective data. If he asked can you elaborate on them?

(Owen Faris): The difference between real world data and retrospective data?

(Sonya): Yes.

(Owen Faris): So real world data can be retrospective data. There can also be a plan to collect real world data prospectively. The question is, are you collecting it in a way that's influencing care such that you protocolizing it then it becomes a little less real world or do you have a plan for collecting it going forward in a way that is really just seeing what is happening in the real world.

These are the kinds of questions that we start to get into when we think about whether this is an investigation that might require an IDE or whether it is really an observation of what's happening in the real world. It can be prospective. There could be a plan to do this prospectively. As (Ben) alluded to in one of the earlier answers, it can also be a plan to analyze data that already exists. So there could be data that has been collected in say electronic health care system or in a registry and you develop a plan for how you are going to analyze those data. As we've been discussing, that data will be much stronger and will be given much more creditability if the plan is developed before the data are known. But it could still be retrospective.

(Sonya): Thank you.

Coordinator: Thank you. The next question is from (Ronald) your line is open.

(Ronald): Yes, thank you. I don't know something about how real world data could be used in DeNovo submissions specifically. Can you comment on how the guidance addresses that point?

Josh Chetta: Hi this is (Josh). So, the guidance doesn't explicitly address that question but it does make clear that these types of data - real world evidence may be considered valid scientific evidence to support any regulatory decision for any device type. So certainly we would be open to evaluating real world data or real world evidence in De Novo submissions. Again we would encourage you to probably contact us via the pre-submission process before you plan to submit that De Novo application, but there's nothing that prohibits the use of those types of data in a De Novo

(Ronald): Thank you.

Coordinator: Thank you. The next question is from (David) your line is open.

(David): Yes, hello. I have a question from the IRB perspective. You know it was greatly helpful that you put in the criteria for if the study affects clinical care then you'll probably need an IDE and if it doesn't you probably won't need an IDE. My question has to do with those studies that don't need an IDE. Does FDA have an expectation that those will be non-significant risk studies under abbreviated IDE requirements or exempt studies when they're on label or are they not clinical investigations at all? I'm just thinking of the IRB recordkeeping process. Thank you.

(Owen Faris): Great question. Complicated answer. This is (Owen) again. This is again one of the questions that we decided we couldn't do justice to at this time to put it in the scope of this guidance. There is a lot of work in this space right now to figure out exactly the answers to the questions that you're

contemplating right now. So, I'm not sure that I can give you a specific answer right now. It would be very helpful to sit down with you and talk with you about a particular example if you have a particular question outside of this discussion here today. I would say the kinds of questions you're asking are very relevant today and are being contemplated and discussed inside the agency and outside the agency as well.

(David): Thank you.

Coordinator: Thank you. The next question is from (Ed), your line is open. Please strike your mute button your line is open.

(Ed): Was that a test maybe?

Coordinator: Go ahead.

(Ed): Okay. Thank you. Nice job on the guidance folks and appreciate the informative and helpful webinar. I know you probably have limitations on what you can say specifically but do you have any general comments you can make about cases in which efforts to use real world data have not been acceptable as real world evidence?

Alex Hu: There were cases using real world evidence from outside of the U.S. that lead to major deficiencies in some of the clinical areas. This is very in detail and probably beyond the scope of this webinar training for the guidance. And if you have detailed questions, please send us an email.

(Owen Faris): Hi this is (Owen). I will chime in a little bit and I think (Ben)'s going to chime in after me. I think the kinds of questions - I'll answer your question generally in how it applies more broadly than just real world evidence. We

have questions every day that come from the agency back to sponsors about the quality of the data that are provided whether they're from real world evidence sources or whether they're from a clinical trial and regardless of where they're conducted, we have times when the quality of those data aren't enough to get us over the bar and so you know you might think of some of the kinds of questions that might arise with real world data. We've already talked about the pre-specification of your data analysis plan relative to knowledge of the data. That's sort of the obvious one where we would have questions about that.

We might have questions about missing data, data completeness in terms of timelines for when those data were collected and were they collected on all of the patients or a significant portion of the patients. Those sorts of questions are the kinds of things that we will be digging into when data comes in and it really also depends on the kind of question that's put in front of us to ask. But if we're talking about considering marketing application for a new device or an expanded use of a device, we will be digging into many elements of the data quality and depending on how that datasets constructed - depending on how relevant that real world evidence source is to the question at hand, there may be questions about when you ask the question versus knowledge of the data, missing data, completeness of the data, all those sorts of pieces. And frankly, is this patient population? does it represent the patient population? The broad patient population that may be in the same new indication, but these are questions that come up not just in real world evidence, they come up broadly and really any kind of submission where data are provided to support a regulatory question.

(Ben Eloff): Hi and this is (Ben Eloff) and I'm going to approach this from a slightly different angle than (Owen) just did. Thinking about the acceptance of real world data as real world evidence is not a binary process. It would be

extremely rare for data presented to FDA to have no value whatsoever in a given regulatory decision. So it may be that data is presented that does not suffice as the entirety of the data necessary to support a given decision but to supplement somewhere else for that decision. But to have a source where you say flat out no, this has no value would be extremely, extremely and vanishingly rare.

(Ed): Okay. Thanks. Thanks, gentlemen.

Coordinator: Thank you and the final question is from Gina, your line is open.

(Gina): Hello thank you (Irene), (Josh), (Alex), panelist, the wonderful webinar today. My question is regarding the use of real world evidence in the 510K paradigm for class 2 devices. I know this is something that we're really excited for. The potential application of this to the 510K paradigm. So if you say that I'm a manufacturer of a class 2 510K cleared legally marketed device and I wanted to make a modification to that device. Let's say it's a labeling change or one that does not change the indications for use, it doesn't change the fundamental scientific technology. If I wanted to use real world data that had been collected using my legally marketed device, the unchanged device, my primary predicate device, it's my understanding it would have to be a traditional 510K if the real world evidence would be needed to answer patient safety and effectiveness questions relating to the particular change. In the view of the panel, if the real world evidence was not really used to answer any safety or effectiveness question, but say use as a validation to ensure the modified device still needs the user requirements, is the special 510K pathway still feasible for real world evidence supported modifications? I understand you may not be willing to (unintelligible). Sure.

Josh Chetta: This is (Josh). Thanks for that question. It's complicated and I think we're running out of time. To answer your question, you'd want to look at what the parameters of the special 510K are. the changes - how significant they were and whether the data provided to support that change would be applicable to the device depending the change. If it's a labeling change, you may be changing the intended use so there's a lot of questions to unpack there. We don't quite have time to go into all those. Again, the same answer you've gotten a number of times. Contact us with a pre-submission to talk about the particulars of the submission.

(Gina): Thank you.

Coordinator: Thank you. I'll turn the conference back to Ms. Aihie.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions. Today's presentation and transcripts will be made available on the CDRH webpage at www.fda.gov/training/cdrhlearn by Wednesday October 18th. If you have additional questions about today's presentation, please use the contact information provided at the end of this live presentation. As always we appreciate your feedback.

Following the conclusion of today's webinar, please complete a short 13 question survey about your FDA CDRH webinar experience. The survey can be found at www.fda.gov/cdrhwebinar immediately following the conclusion of today's live webinar.

Again, thank you for participating. This concludes today's webinar.

Coordinator: Thank you and this does conclude today's conference. All parties may disconnect.

END