

**Clinical Considerations for Studies of Devices Intended to Treat Opioid Use Disorder - Draft Guidance  
September 14, 2023**

**Moderator: CDR Kim Piermatteo**

**CDR Kim Piermatteo:** Hello everyone and welcome. Thanks for joining us for today's CDRH webinar. This is Commander Kim Piermatteo of the United States Public Health Service and I serve as the Education Program Administrator in the Division of Industry and Consumer Education in CDRH's Office of Communication and Education. I'll be your moderator for today's webinar.

Our topic today is the draft guidance titled "Clinical Considerations for Medical Device Premarket Submissions Targeting Opioid Use Disorder," issued on July 28, 2023. This draft guidance provides recommendations for the design of pivotal clinical studies for devices intended to treat Opioid Use Disorder, or OUD, and used to support marketing submissions. OUD device studies designed using the recommendations set out in this guidance may advance the treatment of OUD by providing scientific evidence that aids FDA in determining whether there is a reasonable assurance that a device intended to treat OUD is safe and effective.

We are holding this webinar to discuss the purpose and scope of the draft guidance, as well as discuss the challenges in designing studies of devices intended to treat OUD and discuss the important design features to consider for OUD device studies. We will also answer questions you might have about this draft guidance.

Before we begin, I'd like to provide two quick reminders for the webinar. First, please make sure you've joined us through the Zoom app, and not through a web browser, to avoid any technical issues. And second, the intended audience for this webinar is industry. Members of media are encouraged to consult with the FDA's Office of Media Affairs for any questions they might have.

I now have the pleasure of introducing our presenter for today's webinar. Sergio de del Castillo, Associate Director for Policy within the Office of Neurological and Physical Medicine Devices, which is also referred to as the Office of Health Technology number 5, or OHT5, in CDRH's Office of Product Evaluation and Quality, or OPEQ. We'll begin with a presentation from Sergio and then field your questions about today's topic.

Thank you all again for joining us. I'll now turn it over to Sergio to start today's presentation.

**Sergio de del Castillo:** Thank you, Kim. A warm welcome to everyone joining us today. Today, we will provide an overview of the draft guidance entitled, "Clinical Considerations for Studies of Devices Intended to Treat Opioid Use Disorder." The link to this guidance is provided in the slide.

After today's webinar, you should be able to describe the challenges in designing pivotal opioid use disorder device studies. Opioid use disorder is commonly referenced by the acronym OUD. You should also be able to identify the purpose of the draft guidance, as well as what is and is not within the scope of the document. Finally, you should be able to list the important features to consider for the design of pivotal clinical studies of devices intended to treat OUD. As a shorthand, we will refer to such studies as OUD device studies in this guidance.

Let's begin by talking about the opioid crisis and the complexities of opioid use disorder.

The opioid epidemic has been a major public health crisis in the United States. Millions of people have been affected by OUD, and thousands have died from opioid overdoses. The Department of Health and Human Services, in accordance with section 319 of the Public Health Service Act, determined on October 26, 2017, that a public health emergency exists nationwide. This public health emergency has been subsequently renewed repeatedly, most recently on March 31<sup>st</sup> of this year.

There is a clear need to support treatment of people with OUD and a desire to develop new non-pharmaceutical treatment options. FDA's OHT5 has been contacted by many device manufacturers seeking input on how to generate evidence in support of marketing applications for devices intended to treat OUD.

The draft guidance, which is intended to help sponsors design clinical studies to evaluate these devices, furthers the FDA's overdose prevention framework goal of advancing evidence-based treatment for those with substance use disorders. This guidance supports innovative approaches for evaluating medical devices that can help combat this national crisis and give patients new tools to treat opioid use disorder, with the assurance that the solutions we will need be driven by robust data.

Opioid use disorder is a complex, multi-faceted condition that is not well understood and can be difficult to treat. There are several factors that can contribute to the development of OUD, including but not limited to genetics, environment, and trauma. Opioids are highly addictive, with documented negative effects on physical, emotional, social, and cognitive functions.

OUD is a stigmatized disorder. People with OUD often feel ashamed or embarrassed about their condition, and they may be reluctant to seek treatment. This can make it difficult to get accurate data about the prevalence of OUD and the effectiveness of treatments.

OUD is also a chronic condition. People may relapse multiple times before they are able to achieve long-term recovery. This can make it difficult to design studies that can accurately measure the effectiveness and durability of treatments. These factors, among others, present significant challenges in designing pivotal OUD device studies.

Despite these challenges, FDA believes it is imperative to work with our stakeholders to develop recommendations that are applicable to the design and development of pivotal OUD device studies and support innovative options to combat the opioid overdose crisis. Promoting device innovation to assist in the treatment of individuals with OUD is vital to our ongoing public health response.

We'll now turn our attention to the content of the draft guidance, starting with the purpose and scope of the document. This draft guidance applies to pivotal clinical studies of safety and effectiveness for devices intended to treat OUD, the results of which are intended to be used to support submissions for marketing authorization-- for example, 510(k)s, De Novo classification requests, and Premarket Approval, or PMA, applications. While the focus of this guidance is for pivotal OUD device studies, our recommendations may also be applicable to other types of studies intended to generate valid scientific evidence that may be used in providing a reasonable assurance of safety and effectiveness.

This draft guidance applies only to devices intended explicitly to treat OUD. Early feasibility studies and other preliminary studies are outside the scope of this guidance. In addition, several types of devices

and intended uses are outside the scope of this document, including diagnostic tests for the detection of opioid use, devices intended to diagnose or to help determine the risk of developing OUD, devices intended to treat pain, and combination products-- for example, drug-device combinations.

I'll now walk through our current recommendations for pivotal OUD device studies, as outlined in the draft guidance.

As described previously, OUD treatment trials present many confounding factors that may complicate the assessment of safety and effectiveness. For this reason, we identify several overarching recommendations for the design of pivotal OUD device studies to mitigate uncertainty and potential bias. Where possible, pivotal OUD device studies should be well controlled and designed to generate valid scientific evidence that demonstrates clinically significant results in accordance with 21 CFR 860.7, determination of safety and effectiveness, and our guidance document entitled, "Design Considerations for Pivotal Clinical Investigations for Medical Devices."

While the recommendations in this draft guidance are founded on fundamental clinical trial design characteristics, FDA acknowledges the challenges in the field of OUD treatment, which may necessitate consideration of alternative methodologies and designs to demonstrate a reasonable assurance of safety and effectiveness of devices intended to treat OUD.

In addition, our recommendations for pivotal OUD device studies may change as the research community obtains more information about the disorder and experience with different study designs. Above all, we endeavor to provide the most current and applicable feedback to support successful marketing authorizations of devices intended to treat OUD. We strongly encourage device manufacturers to collaborate with us through the Q-Submission process to discuss the proposed clinical study plan or protocol.

The draft guidance provides a framework and recommendations for designing pivotal OUD device studies. Today's webinar will identify the key points to consider in each of the categories identified here.

We'll begin with an overview of the patient population and treatment assignment.

Study participants should be clearly defined and representative of the demographics of people diagnosed with OUD, including age, race, and sex. This helps to ensure that the study population and study results are applicable to people in the United States and to bolster certainty that the effectiveness of the device is relevant and meaningful to participants and prescribers of the subject device.

We also want to ensure that the evidence generated in pivotal OUD device studies provides confidence that the subject device itself is, in fact, providing a clinically meaningful benefit. For this reason, we recommend a sham control to avoid the introduction of bias.

Even so, FDA recognizes that designing an effective sham control may be challenging. We recommend using the Q-Submission program to discuss alternative approaches to minimize bias in this regard.

Pivotal OUD device studies must contend with the potential for inaccurate participant reports of drug use, in part due to stigma associated with OUD. To minimize uncertainty and bias, one should record all baseline medications, including those used for treating OUD, prior to treatment with the investigational

device. Each drug used by a participant should be recorded, including the dose, duration, and timing, as well as any changes in such drugs during the duration of the study. Although there are several methods for ensuring adherence to treatment medications, we recommend these be assessed with participant diaries, pill counts, and random or regularly scheduled toxicology drug screening for prescribed and non-prescribed drug use.

Appropriate monitoring of prescribed and nonprescribed drugs is another method for contending with inaccurate reports of drug use. This also provides a greater certainty in the clinical meaning of any demonstrated benefit of the investigational device. Pivotal OUD device studies should measure opioid usage with both participants' self-reports and objective verification measures.

Typical objective measures include random and scheduled urine tests using validated toxicology assays at times consistent with relevant drug pharmacokinetics. Other drug screening options include measuring drug levels in blood or saliva. As we continue to see innovation in validated drug detection technologies, these too may be appropriate in certain circumstances. Generally, positive toxicology results using quantitative methods should take precedence over self-reported qualitative data.

Because of the high rate of relapse as well as the long-term treatment and recovery of participants diagnosed with OUD, the duration of the clinical study is vitally important. We recommend pivotal OUD device studies be designed with a minimum treatment duration of six months. Further, because of the importance of a relatively longer study duration, the protocol should include a detailed description of the effective procedures for retaining study participants, risk-based ongoing data management, and procedures for obtaining primary outcome information that is missing while still available. This is related to and overlaps with the next category of recommendations.

The importance of maximizing participant retention and minimizing missing data cannot be overstated. Missing data have been major contributors to OUD study failure and introduce a high degree of uncertainty in study results. It is essential to incorporate pre-specified methods and procedures in the clinical study protocol and statistical analysis plan to not only address missing data, but also to detect and correct missing data early when it may still be retrievable and reliable.

We acknowledge that even when pre-specified, such methods may introduce uncertainty, and each case of missing data may require a different solution. Again, we strongly encourage device manufacturers to collaborate with us through the Q-Submission process to discuss these methods prior to initiating a clinical study.

The final set of recommendations outlined in the guidance covers clinical outcomes. To support a future marketing submission, clinical outcomes have to be chosen very carefully to generate valid scientific evidence and demonstrate clinically significant benefits. For the purposes of this guidance, we define a clinically significant benefit as an improvement in how a study participant feels, functions, or survives. This could include, for example, a reduction in hospitalizations or improvements in daily life, including the ability to resume work, school, and other activities.

The primary clinical outcomes are the main measures of effectiveness for a pivotal OUD device study. Importantly, the primary outcomes should align with and be directly relevant to the target population, the proposed indications for use, and the clinical objectives of the investigational device. Secondary

outcomes are additional measures that can help to confirm or explain the observed effect of the device, but generally cannot be used alone to provide reasonable assurance of safety and effectiveness.

We would like to point out that the recommendations in this section for OUD treatment trials are consistent with the guidance entitled "Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Treatment, Guidance for Industry," authored by the Center for Drug Evaluation and Research, also known as CDER, and published in October 2020.

We provide recommendations for several different types of primary and secondary clinical outcomes, shown in the slide here, that could be relevant for a pivotal OUD device study. We will not discuss these in detail today for the sake of time. However, there are a few important points we would like to emphasize.

First, as mentioned previously, sponsors should select study outcomes that are relevant to the target population, the proposed indications for use, and the clinical objectives of the investigational device. Second, the clinical outcomes identified in the guidance do not represent an exhaustive list of all conceivable outcome measures that can be considered for inclusion in a pivotal OUD device study. In this vein, there may be other outcome measures that would be appropriate to a specific study that are not identified in the guidance. Finally, we are not recommending that all pivotal OUD device studies include all the outcomes identified in this guidance.

Here are the guidance documents and other resources I mentioned earlier in the presentation, along with a full address that you can access after the presentation.

Although you can comment on any guidance at any time, to ensure that the FDA considers your comment on a draft guidance before it begins work on the final version of the guidance, submit either online or written comments on the draft guidance before the close date. Also, currently, this draft guidance is not for implementation.

On this slide, you will find the link to the docket and where you can provide comments to the guidance. Comments should be submitted by October 26, 2023, to be considered before we begin work on the final guidance document.

To summarize, this draft guidance is intended to encourage the development of innovative options to combat the opioid epidemic by providing our current recommendations on the design of pivotal studies of devices that are intended to treat opioid use disorder. Our recommendations are intended to support device manufacturers in developing valid scientific evidence from well-controlled studies to demonstrate clinically meaningful benefits and to provide reasonable assurance of safety and effectiveness.

The complexity of opioid use disorder creates many challenges in designing pivotal OUD device studies. For these reasons, we strongly encourage collaboration through the Q-Submission process to discuss proposed study designs prior to study initiation and, where appropriate and justified, alternative designs and methods. We welcome all feedback and suggestions to be submitted to the docket for this draft guidance.

Thank you very much for joining today's webinar. I'll now turn the program back over to Kim.

**CDR Kim Piermatteo:** Thank you Sergio for that presentation. At this point, we are going to transition to our interactive question-and-answer segment of today's webinar, where you get to ask your questions to our panel. So I'd like to introduce our additional panelists who will be joining Sergio in answering your questions.

First is Dr. John Marler, Deputy Office Director of the Office of Health Technology number 5, specifically neurological and physical medicine devices within OPEQ. Next is Dr. Allen Chiu, Medical Officer within the Division of Health Technology 5B, specifically neuromodulation and rehabilitation devices in OHT5. And Megha Reddy, Regulatory Advisor on the Regulation, Policy, and Guidance staff within OPEQ. Thank you all for joining our panel.

Before we begin taking the questions, I'd like to go over how we are going to manage this segment. To ask a question, please select the raise hand icon, which should appear on the bottom of your Zoom screen. I'll announce your name and give you permission to talk.

When prompted, please select the blue button to unmute your line, and then ask your question. After you ask your question, please lower your hand. And if you have another question, please raise your hand again to get back into the queue, and I'll call on you as time permits.

Additionally, within this segment, please remember to limit yourself to asking one question only, and try to keep it as short as possible. And also, we appreciate that you may have a very specific question involving your device or scenario, but please note that we might not be able to answer such specific questions, but we'll try to frame a broader response based on what's proposed in the guidance.

And lastly, just remember, this is your chance to better understand and get clarity on what we intend in the draft guidance. So we ask you to try to frame your questions with this in mind as well.

Now as we wait to receive some of your questions, I'd like to welcome our newest panelists with some questions we have gotten over the last few weeks about the draft guidance.

So for our first question, I'll be directing that to John. John, the question is, a company is preparing an IDE application for a pivotal OUD device study. Are they required to include a control group? For business reasons, they had intended this to be a single-arm study.

**John Marler:** Well, you know there are a lot of factors that are much more important or much more-- occur a lot more with opiate use disorder that introduce higher uncertainty and bias into the benefit-risk assessment of devices intended to treat OUD. These factors include, but are not limited to, the subjective outcomes that are used, the placebo effects, and the concomitant treatments prevalent in OUD studies.

Although they're not required, we do strongly recommend that pivotal OUD device studies be well controlled and designed to generate valid scientific evidence, evidence that demonstrates that there are clinically significant results with minimal uncertainty that the device is the cause of the results and not another factor, such as bias, placebo effects, and other factors.

**CDR Kim Piermatteo:** Thanks, John. Now for our next question, I'll be directing that to Allen. Allen, the question is, a company is intending to conduct a pilot study prior to initiating a pivotal trial. Should they follow the recommendations in this guidance?

**Allen Chiu:** So this guidance is primarily written to address the clinical considerations and possible outcomes for pivotal studies. So they're not directly-- the recommendations in this guidance are not directly applicable to feasibility studies or pilot studies.

However, considering the purpose of a pilot trial and that its primary purpose is to assess whether the study design, the methods, and procedures are workable, and whether they will gather the preliminary data that is useful for a future pivotal study, it's not to say that the suggestions and the outcomes are not applicable. You may be wise to actually consider some of the outcomes being discussed when designing and conducting a pilot or feasibility study. However, I advise sponsors to utilize the Q-Submission process for more feedback if that's specifically what they're interested in.

**CDR Kim Piermatteo:** Great. Thanks Allen for that response. Now for our next question, I'll be coming to Megha. Megha, the question is, when will the final guidance be available?

**Megha Reddy:** So let me start by providing some details about the guidance development process in general. FDA is required to follow good guidance practices in accordance with 21 CFR 10.115. So once the draft guidance is published and the comment period is closed, we'll consider all the comments that we've received and will prepare a final version of that guidance that incorporates any suggested changes, as appropriate.

Once this is completed, FDA will publish a notice to the Federal Register announcing that the final guidance is available. And we will post the guidance document to the FDA website. While we endeavor to publish final guidance documents as quickly as possible, I am not able to provide an exact date for publication of the final guidance at this time. This is due to various factors that include, but are not limited to, the number of comments that we've received, as well as the available resources.

**CDR Kim Piermatteo:** Thanks, Megha. Alright, at this time, we'll now take our first live question. That question is coming from Daisy. Daisy, I've unmuted your line. Please unmute yourself and ask your question.

Daisy, are you able to unmute your line?

Alright, we're going to go ahead and go down. We're going to go to our next caller, which is Allison. Allison, I have given you permission. Please unmute your line and ask your question.

**Allison Komiyama:** Hi, can you hear me?

**CDR Kim Piermatteo:** Yes, we can.

**Allison Komiyama:** Hi, this is Allison Komiyama. Thanks for setting up this webinar today and also for the guidance document. I had a quick question about pediatric populations, because I noticed that there is no mention of that, even though there is a section about considerations for the populations that are being studied.

I know opioid use disorder is really-- and how it's defined in the DSM-5, it's more as a desire to obtain and take opioids despite social and professional consequences. Does FDA see this draft guidance as applicable to pediatric patients, those maybe neonates that are born with opioid withdrawal symptoms? Is this guidance applicable to them as well? Or is that something that I should put into a comment to the draft?

**CDR Kim Piermatteo:** Thanks, Allison. Sergio, would you like to provide a response?

**Sergio de del Castillo:** Sure. Thanks for the question, Allison. Certainly, I think when we developed the guidance, we developed it with no specific indication or population in mind. So it's really broad. And I do think there are certainly elements of it that could be applied to a study for pediatric populations.

However, we did not specifically include any comments that were specific to that point. So we would encourage you to include comments to the document.

**Allison Komiyama:** Awesome. Thank you.

**CDR Kim Piermatteo:** Thank you, Allison, for the question, and thank you, Sergio, for the response. Alright, our next question is coming from Tasha. Tasha, I have unmuted your line. Please unmute yourself and ask your question.

**Tasha Bond:** Thank you very much. Can I first thank the FDA, both for putting the time into the draft guidance and for the webinar. I appreciate the recognition from the FDA team on the challenges of a placebo arm in these trials and also fully acknowledge the necessity and value of having those control arms in order to fully study placebo effects and confounding effects in this complex population.

I'm wondering if the FDA has any more concrete guidance or examples of where creative study design or non-traditional control arms might be appropriate or where such studies have been successful in the past, rather than simply acknowledging that this is difficult and relying on industry to come up with solutions to a hitherto very tough nut to crack.

**CDR Kim Piermatteo:** Thanks, Tasha. I'm going to turn that back over to Sergio again.

**Sergio de del Castillo:** Yeah, thanks for the great question, Tasha. Unfortunately, we do not have any such examples that we could share with you today. And indeed, we are very interested in obtaining feedback from industry and other interested parties on examples of where we could consider a more creative or alternative approach.

**Tasha Bond:** OK, thank you.

**CDR Kim Piermatteo:** Thank you, Tasha. Thank you, Sergio. Alright, our next question is coming from Navid. Navid, I've unmuted your line. Please unmute yourself and ask your question.

**Navid Khodaparast:** Hi, there. Can you hear me?

**CDR Kim Piermatteo:** Yes, we can.

**Navid Khodaparast:** Great, hi. Hi, everyone. Navid Khodaparast. And thank you to FDA for running this webinar. It's been very informative.

My question is regarding cravings in relation to opioid use disorder. From my understanding, there have been some comments from the FDA that there aren't really any appropriate opioid craving scales available that could be used as a primary endpoint for pivotal trials. So I'd love to see if there's any commentary or if the draft guidance will be able to provide any directions towards the cravings aspects of opioid use disorder. Thank you.

**CDR Kim Piermatteo:** Thank you, Navid. I'm going again to turn it back over to Sergio.

**Sergio de del Castillo:** Yeah, thank you for the question. And I will also ask John and Allen to provide any additional details if they think that's necessary. Again, we appreciate the challenge there and recognize that there aren't specific measures that are validated to study cravings in the context of a pivotal OUD device study.

Again, we would also be very interested in getting feedback in this regard on how to approach that. But at this time, we don't have any additional recommendations.

**John Marler:** I guess I'd like to add that there's a weak connection between the existence of cravings or the perception of cravings and actually how the patient's able to function in life. So if reducing the cravings could be shown to either treat the OUD in terms of improving their return to function in life, that might be a consideration about the outcome measure that would not be cravings itself, but some measure of the effect on the patient's daily experience in life, their occupational, social, and physical function.

**Navid Khodaparast:** So with regards to cravings and, really, any other patient-reported outcome, which is an entire category of outcomes, I think the real issue with these types of outcomes is that the magnitude of change on these outcomes that represents a clinical benefit is oftentimes an uncertainty when making a benefit-risk determination. And it's a significant uncertainty.

The effect that these secondary outcomes have on the primary disease process, I think, is where we have a difficult time drawing a direct correlate. So oftentimes, we recommend that use of these types of secondary outcomes can be informative in the trial. However, we usually recommend that the primary outcome measure be a measure of behavioral change, such as a change in drug use pattern that has a more clear and sort of historically consistent definition of what a clinically meaningful benefit is on that particular outcome.

**CDR Kim Piermatteo:** Thank you, Navid. Sergio and John, I don't know if you have anything else you want to add, before we move on.

**Sergio de del Castillo:** No additional details for me.

**John Marler:** And none for me.

**CDR Kim Piermatteo:** OK. Thank you, Navid. Alright, our next question is coming from Madris. Madris, I've unmuted your line. Please unmute yourself and ask your question.

**Madris Kinard:** Hi, this is Madris Kinard. The question I have is just a quick statement before it that CDRH recently unredacted the age, sex, and demographic information for all adverse event reports. So these would be like the MAUDE reports, if you're familiar with that. And now that this is publicly available, will requirements exist to evaluate predicates that are being used with this new pediatric data that we'll have available, or even race or sex data that we haven't had available in the public for the last 25 years?

**CDR Kim Piermatteo:** Thank you, Madris. Sergio, I'm going to come to you again for a response.

**Sergio de del Castillo:** Sure. Great question. I don't think that we've contemplated to that level of detail in the guidance because it's also not specific to a 510(k) pathway and evaluation of predicate devices for the purposes of demonstrating substantial equivalence. I think that's something, again, that we would like to hear more about from our industry representatives as comments to the docket for the draft guidance.

**Madris Kinard:** Thank you.

**CDR Kim Piermatteo:** Thanks Sergio. Thanks Madris. Alright, Megha, I'm going to come back to you with some questions that we have received. This is a two-part question. The first part of the question is, how do I find and read all the comments submitted by others for the draft guidance? Additionally, is there a preferred method or format for submitting comments?

**Megha Reddy:** Sure. So let me address the first part of that question first. So while everyone can comment on the draft guidance, not every comment is made publicly available to read. So you'd only be able to access the comments that were posted to regulations.gov. And the way to do this would be when you are viewing the docket details page from the Browse All Comments tab, you'll be able to access a consolidated list of all of the comments that are in the docket.

And then the second question about the preferred method or format, we do recommend a tabular format when possible, because this facilitates our analysis and the compilation of all of the comments that are received. So, for example, in its simplest form, the table would include three columns, one column identifying the relevant line number or section number of the draft guidance, a second column that includes the specific comments and explanation of your comments, and then the third column, if applicable, a column identifying proposed new or edited language for our consideration.

**CDR Kim Piermatteo:** Thanks, Megha. That's actually very helpful information.

Sergio, I would like to ask you a question that we received. Specifically, the stakeholder's asking, we are developing a diagnostic to detect the presence of opioids in blood. Should we follow the recommendations in this guidance?

**Sergio de del Castillo:** Yeah, as we mentioned earlier, diagnostic devices are outside the scope of the draft guidance document at this time. So we would recommend that you reach out to the relevant office and division for feedback, for example, through the Q-Sub process.

**CDR Kim Piermatteo:** Thanks, Sergio. Another one for you, Sergio, is, we have a 510(k) cleared TENS device indicated for pain relief and are interested in studying the device for reducing a patient's need for opioid medications. Which recommendations in the guidance are applicable to this scenario?

**Sergio de del Castillo:** So we're certainly aware that there is interest in obtaining marketing authorization for devices that could reduce or even eliminate opioid usage. However, also as explained in the guidance, devices that are primarily intended to treat pain, even with those claims, are outside the scope of this guidance document. In particular for this particular situation, we strongly recommend that you work with us through the Q-Submission process so we can provide the most meaningful feedback in generating the evidence that would be needed to support those claims.

**CDR Kim Piermatteo:** Great. Thanks Sergio. Alright, at this time, I do not see any more raised hands. So I'm going to make a callout. If anyone attending today has a question they would like to ask our panel, I encourage you to raise your hand.

While we wait for some more hands to be raised, Sergio, I did want to ask you another question. This one specifically says, some of the recommended primary outcomes do not seem to apply to the device we are developing. Are we obligated to include all of them?

Oh, Sergio, you're still muted if you're talking.

**Sergio de del Castillo:** Sorry, you'd think I would have had that down by now. Sorry.

**CDR Kim Piermatteo:** No worries.

**Sergio de del Castillo:** So the short answer is, no, not obligated to include all of them. What we have been trying to message during the presentation and in the guidance is that we're not recommending that all the outcomes that are currently identified in the document be included in all pivotal OUD device studies. You should select study outcomes that are relevant to your device in consideration of the target population, the proposed indications, and the clinical objectives of the investigational device.

Also, the outcomes that are identified in the guidance do not represent an exhaustive list of all conceivable outcome measures that could be considered for inclusion in such a study. So we would encourage you, again, to work with us, particularly if you want to recommend an alternative design or certain study outcomes through the Q-Submission process.

**CDR Kim Piermatteo:** Thanks, Sergio. And I think this kind of aligns with another question about, am I required to adhere to all the recommendations in this guidance? Did you want to follow up with that one?

**Sergio de del Castillo:** Sure. So similarly, there are many-- there are several different outcome measures that could be considered. But certainly, not any one is going to be exactly appropriate for every single device type and every single device study. So you should be considering, again, what are the specific elements of your device in terms of the indications for use in the patient population. And then from there, develop the appropriate recommendations from the guidance that would be applicable to your particular submission.

**CDR Kim Piermatteo:** Great. Thanks, Sergio. Alright, I'm going to make one last callout if anyone has any questions. But I do want to come back to Megha real quick. So if a stakeholder has comments, and they miss the 90-day comment period, will their comments be considered in the final guidance? I just wanted to clarify that.

**Megha Reddy:** Sure. So stakeholders can comment on guidance documents at any time. But if they would like their comments acted upon by the Agency immediately or before this guidance is finalized, we recommend that those comments get in before the deadline, by October 26. But comments that are submitted at any time, we will still review them, but they may not be included until the document is next revised or updated.

**CDR Kim Piermatteo:** Great. Thanks Megha. That's very helpful. Alright, at this time, we do not see any more raised hands. So we're going to move on.

Sergio, thank you so much for your presentation. And I want to thank everyone for an engaging question-and-answer segment and our panelists. But at this time, I'd like to turn it back over to Sergio for his final thoughts for today. Sergio?

**Sergio de del Castillo:** Thank you, Kim. And once again, I want to thank everyone for taking the time to join us today and asking all their wonderful questions. As we've said before, the draft guidance we put forward is intended to encourage the development of new and innovative options to combat the opioid epidemic. And we're doing so by putting forward our current recommendations for the design of pivotal studies of devices that are intended to treat OUD.

Recommendations are intended to support device manufacturers in developing valid scientific evidence from well-controlled studies to demonstrate clinically meaningful benefits and to provide reasonable assurance of safety and effectiveness. The complexity of OUD creates many challenges, as you know, in designing such studies.

And for these reasons, we strongly recommend collaboration with us through the Q-Submission process so we have an opportunity to discuss your proposed study designs prior to study initiation and certainly, where appropriate and justified, alternative designs and methods. Again, we welcome all feedback and suggestions to be submitted to the document-- docket for this draft guidance document. Thank you.

**CDR Kim Piermatteo:** Thank you, Sergio. Thank you for those final thoughts. And again, thank you for your presentation. Again, I'd just like to thank John, Allen, and Megha for joining our panel and assisting in answering our questions today.

For your information, printable slides of today's presentation are currently available on CDRH Learn at the link provided on this slide under the section titled Specialty Technical Topics and the subsection Neurological Devices. A recording of today's webinar and transcript will be posted to CDRH Learn under this same section and subsection in the next few weeks. A screenshot of where you can find these webinar materials has been provided on this slide.

If you have any additional questions about today's webinar, feel free to reach out to us in DICE at [DICE@fda.hhs.gov](mailto:DICE@fda.hhs.gov). And we hope you're able to join us for a future CDRH webinar. You can find a listing of upcoming webinars via the bottom link on this slide at [www.fda.gov/CDRHwebinar](http://www.fda.gov/CDRHwebinar).

This concludes our webinar today and thank you all again for joining us.

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