Contains Nonbinding Recommendations

Draft – Not for Implementation

Clinical Considerations for Studies of Devices Intended to Treat Opioid Use Disorder

---

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on July 28, 2023.

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact the Office of Health Technology 5 (OHT5), Neurological and Physical Medicine Devices, Division 5B at 240-402-3039.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

Additional Copies

Additional copies are available from the Internet. You may also send an email request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please include the document number GUI00019017 and complete title of the guidance in the request.

Table of Contents

Clinical Considerations for Studies of Devices Intended to Treat Opioid Use Disorder

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

The opioid overdose crisis is a serious and complex challenge [1] facing the United States. The Agency has already taken significant steps to decrease unnecessary exposure to opioids, prevent new cases of opioid use disorder (OUD) and support the treatment of people with OUD.[2] The Center for Devices and Radiological Health (CDRH) is committed to helping to end this national crisis.[3]

This guidance provides recommendations for the design of pivotal clinical studies[4] for devices intended to treat OUD (hereafter "OUD device studies") and used to support marketing

[1] As a result of the consequences of the opioid crisis affecting the United States, on October 26, 2017, the Department of Health and Human Services, pursuant to section 319 of the Public Health Service Act, determined that a public health emergency exists nationwide. This determination has subsequently been renewed repeatedly, most recently on March 31, 2023. https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.

[2] This timeline provides selected FDA activities and significant events related to addressing substance use and overdose prevention: https://www.fda.gov/drugs/information-drug-class/timeline-selected-fda-activities-and-significant-events-addressing-substance-use-and-overdose.

[3] For example, on May 13, 2018, CDRH launched an innovation challenge for the development of devices intended to prevent and treat OUD. See FDA Innovation Challenge: Devices to Prevent and Treat Opioid Use Disorder. https://www.fda.gov/about-fda/cdrh-innovation/fda-innovation-challenge-devices-prevent-and-treat-opioid-use-disorder

[4] 21 CFR 812.3(h) defines "investigation" to mean "a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device." For the purposes of this guidance, the terms *study*,

submissions. These recommendations are applicable to the design and development of clinical studies to provide a reasonable assurance of safety and effectiveness for a device intended to treat OUD. The recommendations in this guidance may also be useful for the evaluation of other types of valid scientific evidence demonstrating clinically significant results that may be used to provide a reasonable assurance of safety and effectiveness. 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. These recommendations may change as more information becomes available, and the research community gains experience with different designs in relation to OUD device studies.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5-TR) defines OUD as a "problematic pattern of opioid use leading to clinically significant impairment or distress," as manifested by at least two factors identified in the DSM-5-TR, "occurring within a 12-month period." OUD causes significant long-term impairment of physical, emotional, social, or cognitive function.[5] The disorder can arise as an unintended consequence of misuse of prescription opioid pain medications, or the use of illicit drugs.

Because of the complexity of OUD, there are many challenges in designing OUD device studies. These challenges include inaccurate participant reports of drug use, high rates of missing data, the confounding effects of concomitant drug treatments, and the need to demonstrate the durability of the device's treatment effect, which can necessitate prolonged observation. To help spur innovative options to combat the opioid overdose crisis and treat OUD, this guidance provides recommendations on the design of pivotal OUD device studies. Through these recommendations, FDA intends to aid sponsors in developing OUD device studies that provide scientific evidence used to determine whether there is a reasonable assurance of safety and effectiveness for treating OUD.

III. Scope

clinical study, *trial*, and *investigation* are used interchangeably. A medical device pivotal study is a definitive study in which evidence is gathered to support the safety and effectiveness evaluation of the medical device for its intended use. For more information on pivotal clinical studies, please see FDA guidance Design Considerations for Pivotal Clinical Investigations for Medical Devices, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-pivotal-clinical-investigations-medical-devices.

[5] Specific criteria are in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5-TR), F11.10 through F11.21.

This guidance applies to pivotal clinical studies of safety and effectiveness for devices intended to treat OUD and that are used to support marketing submissions. The principles discussed in this guidance are intended to assist sponsors and investigators designing studies that can provide a reasonable assurance of safety and effectiveness for a device intended to treat OUD. This guidance recommends well-controlled studies for pivotal OUD device studies, but recommendations within this guidance may 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. Early feasibility studies and other preliminary studies are outside the scope of this guidance.[6]

The following products are outside the scope of this guidance:

- 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.[7]

IV. Clinical Study Design

This section of the guidance outlines recommended study design features for pivotal OUD device studies.[8] Because of the large uncertainty due to subjective outcomes, placebo effects, concomitant treatments, and potential bias, among other factors, pivotal OUD device studies should be well-controlled and designed to generate valid scientific evidence that demonstrates clinically significant results. In particular, pivotal OUD device studies used to support marketing submissions should have a well-defined study population, appropriately monitor drug use, control for bias, and include an appropriate follow-up period, study participant retention plans, and data analysis plan. The study population should represent the diversity prevalent among individuals with OUD. For more information about well-controlled clinical studies, see 21 CFR 860.7(f) and FDA's guidance document: Design Considerations for Pivotal Clinical Investigations for Medical Devices.

CDRH acknowledges the challenges in study methodology in the field of OUD treatment and encourages sponsors to develop alternative methodologies to overcome these challenges while still producing valid scientific evidence that can be used to support a marketing submission. In certain circumstances, FDA is open to alternative approaches to demonstrate a reasonable assurance of safety and effectiveness of devices intended to treat OUD. FDA recommends that sponsors use the Q-Submission process to discuss such approaches prior to study initiation. For

[6] For more information on early feasibility studies and other exploratory studies, please see FDA guidance documents, Design Considerations for Pivotal Clinical Investigations for Medical Devices, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-pivotal-clinical-investigations-medical-devices and Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-device-exemptions-ides-early-feasibility-medical-device-clinical-studies-including.

[7] For more information about combination products, please see available resources at https://www.fda.gov/combination-products.

[8] For further information on the determination of safety and effectiveness, see 21 CFR 860.7.

details on the Q-Submission Program, please refer to FDA's guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program".[9]

A. Patient Population and Assignment to Treatment and Control Groups

When designing a pivotal OUD device study, CDRH encourages sponsors to define the population the device is intended to treat by defining specific inclusion and exclusion criteria that readily translate to clinical practice. FDA believes that clearly defining the study population in practical terms will allow eventual prescribers to be confident that the evidence of effectiveness established in the OUD device studies is relevant to the patients for whom they prescribe or recommend the device. In other words, prescribers can be confident the patients for whom they prescribe the device are like those in the study population. [10]

None of the participants, treating investigators, or evaluators should be aware of a participant's treatment assignment. A demonstration of a reasonable assurance of effectiveness generally relies on a comparison of the device to a control in a way such that study results can lead to a valid conclusion that any difference between the treatment and control is caused by the device. For devices, participants in the control group are treated with a sham control to avoid the introduction of biases. A sham control is a treatment or procedure that is performed as a control and is similar to, but omits therapeutic elements of, the treatment or procedure under investigation. Effective controls are particularly important in pivotal OUD device studies. CDRH recognizes that designing effective sham controls to limit bias may be difficult. We recommend using the Q-submission Program to discuss alternative approaches to provide unbiased outcomes.

B. Recording Medication Use

Pivotal OUD device studies should record all baseline medications including those used for treating OUD prior to initiating treatment intervention with an investigational device. Investigators should record each drug, the dose, the duration of use, changes in dose, and starting or stopping a drug after participation in the study begins. Adherence to OUD and other SUD treatment medications may be assessed with participant diaries, using pill counts, and random or regularly scheduled toxicology drug screening for prescribed and non-prescribed drug use, among other methods.

C. Monitoring Prescribed and Non-prescribed Drug Use

Appropriate monitoring of prescribed and non-prescribed drugs is integral to a pivotal OUD device study design. Without appropriate drug screening measures or objective methods of verifying opioid use, the clinical meaning of any demonstrated benefit of the device is unclear. False or inaccurate results can occur in self-reported outcome measures of opioid use. For this reason, pivotal OUD device studies should measure opioid usage with both participant self-

[9] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

[10] CDRH encourages sponsors to include in studies of devices intended to treat OUD a diverse population that is representative of the United States population living with OUD.

reports and objective verification measures. Testing for non-prescribed drugs may be useful in some studies.

Typical objective measures to corroborate participant self-reports are 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, and the use of validated drug detection technologies as they become available. A positive toxicology result that is confirmed by a quantitative reference method (e.g., liquid chromatography with tandem mass spectrometry) should take precedence over self-reported abstinence since the last negative result.

D. Appropriate Study Length and Evaluation

The duration of a clinical study is important to consider. CDRH recommends that OUD device studies have a length that is clinically significant and well justified. Pivotal OUD device studies with a minimum treatment duration of 6 months are recommended. Appropriate study duration is necessary because OUD is a condition with a high rate of relapse, and brief intervals of modification of drug use are unlikely to confer significant clinical benefit. It is essential that, for an indication for OUD treatment, investigators consider the durability of the effects of the device and acknowledge any uncertainty about the benefits and risks. Because of the importance of a long study duration, the protocol should include a detailed description of effective procedures for retaining study participants, risk-based ongoing data management, and procedures for obtaining primary outcome information that is missing while it is still available to be retrieved as further discussed in sections IV.E and IV.F.

E. Participant Retention and Preventing Missing Data

During the design of a pivotal OUD device study, considerable effort should be made to maximize participant retention and reduce missing data by ensuring adherence to treatment plans and follow-up schedules. This aspect of research in pivotal OUD device studies may necessitate new methods. If participants do not adhere to the treatment and follow-up plan, the primary outcome may not be obtainable, which would weaken the credibility of the intention to treat analysis. Because the methods of retention may affect the study outcomes, FDA recommends ensuring adequate blinding of the treatment assignment to minimize decisions to drop out. High rates of missing data have been major contributors to OUD study failure. Therefore, protocols should anticipate this problem and provide procedures to prevent it.

Sponsors should acknowledge that missing data typically does not occur at random and use conservative estimates for missing data when analyzing study results. If the proportion of missing data is not much less than the difference in response rates, there will be significant uncertainty in the study results. Methods to account for missing data should be prespecified in full detail in the statistical analysis plan before the study starts. Even if prespecified, these methods are accompanied by a large amount of uncertainty when missing data exceeds more than a few percent. The protocol should ensure that investigators have the resources and a powerful strategy to detect and correct missing data while allowing flexibility and adaptive procedures to reduce loss of critical data. Each case of missing data may require a different solution. Data management should be proactive in early detection of critical missing data at a

time when it may still be retrievable and reliable. It is also helpful to minimize the amount of data to be collected to reduce the workload on investigators so they can concentrate on the most critical data.

Missing data can include adverse events. Access to clinic, hospital, and pharmacy records can provide more accurate information than participant reports. Adverse life changes are also potential adverse events that should be assessed and recorded.

F. Clinical Outcomes

Clinical outcomes that provide valid scientific evidence of clinically significant benefits provided by the device are essential to support OUD treatment indications.[11] For the purposes of this guidance, FDA considers a clinically significant benefit to be an improvement in how a study participant feels, functions, or survives, such as a reduction in hospitalizations, or improvements in daily life including the ability to resume work, school, and other activities.[12] When choosing primary outcomes for pivotal OUD device studies, sponsors should identify the clinical objectives of the device for the target patient population and align the objectives with the desired indications for use, a relevant definition of a clinically significant benefit, and the choice of effectiveness outcomes. FDA recommends the inclusion of secondary outcomes that measure different manifestations of OUD to support the robustness of any evidence of demonstrated clinically significant difference in the primary outcome. The presentation of a consistent and clinically significant difference across an array of outcomes can contribute to the evidence needed to support a marketing submission.

Secondary outcomes are intended to support the primary outcome and generally cannot stand alone. To the extent possible, secondary outcomes should be limited in number and should be minimally burdensome to participants and investigators to enhance retention and prevent missing data. See section IV.E on missing data. If the primary outcome measure shows how a participant feels, functions, or survives, well-chosen secondary outcomes can provide evidence that confirms or explains the observed effect.

FDA recommends that sponsors select study outcomes that are relevant to the population, the indication, and the clinical situation. The outcomes discussed below are recommended primary or secondary outcomes that can be considered for use in a pivotal OUD device study. The list provided below is not exhaustive. FDA does not recommend choosing all the listed outcome measures for any given study and recognizes that there may be other outcomes that would be appropriate to a specific study that are not listed below.

[11] To provide consistency across OUD treatment trials, the recommendations in this section are consistent with the guidance entitled "Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Treatment Guidance for Industry," U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) October 2020, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/opioid-use-disorder-endpoints-demonstrating-effectiveness-drugs-treatment-guidance-industry.

[12] Alan E. Kazdin, The Meanings and Measurement of Clinical Significance. Journal of Consulting and Clinical Psychology, June 1999, Volume 67, No. 3, pages 332-339.

(1) Change in Drug Use Pattern[13]

FDA generally accepts a positive change in drug use patterns as a surrogate for the benefits of abstaining from drug taking or for the presumed benefits of reducing drug taking. A reduction in drug-taking behavior has been used as a surrogate outcome for the benefit of abstinence[14] or presumed benefit of reducing drug taking in many investigations, including those used to evaluate drug products for the treatment of OUD.

If using "change in drug use pattern" as an outcome, FDA recommends that sponsors compare percentages of responders rather than group means. For example, a responder could be defined as a participant who reduces the use of opioids to an amount associated with a clinically significant benefit. In general, the threshold may vary according to study design. Thresholds may not be transferable from study to study because of differences in the populations, treatments, risks, benefits, uncertainties in study results, and methods of analysis. FDA recommends a sponsor provide a rationale for how their response threshold will improve the lives of those with OUD. For example, studies of devices for use with prescribed medication-assisted treatments for OUD should demonstrate clinically significant improvement compared to a group not receiving active device treatment and receiving the same protocol-defined medication-assisted treatment.

Sponsors should consider the treatment goals of their device when defining a responder. Abstinence can be used to define a treatment responder. To demonstrate a complete abstinence response, pivotal OUD device studies should be designed with frequent measurements of drug use to reduce uncertainty about the true magnitude of the treatment effect.

Drug use changes short of abstinence may be considered when evaluating clinically meaningful responses to OUD treatment. When proposing other drug use patterns to define a clinically meaningful response, sponsors should explain how the change in drug use pattern will be measured and verified objectively and submit valid scientific evidence showing that such a reduction in drug use is clinically significant, with evidence of improvements in physical, social, cognitive, and emotional function in their lives.

(2) Change in OUD Disease Status Using DSM-5-TR Diagnostic Criteria

Diagnostic criteria for OUD encompass drug use and its effect on health and well-being. For devices intended to treat OUD, an appropriate outcome may be a clinically significant change in

[13] "Drug use pattern" refers to the frequency, timing, quantity, and intensity (uses per day or amount per use) of problematic drug use by an individual patient. From a practical standpoint, several of these parameters are infeasible to measure, and the most commonly used parameter is days of use. The phrase "change in drug use pattern" is used to emphasize that individual patient responses are of interest. See page 4 of "Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Treatment Guidance for Industry," U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) October 2020, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/opioid-use-disorder-endpoints-demonstrating-effectiveness-drugs-treatment-guidance-industry.

[14] "Abstinence" refers to zero days of use within an assessment window. The more general phrase "reduction in drug use" is subject to many interpretations, including reduction of group means on quantity or frequency of problematic drug use with no single individual having an improvement in their OUD. See id.

disease severity related to the clinical diagnosis of OUD. We recommend that, if all study participants meet the DSM-5-TR criteria for moderate-severe OUD at baseline,[15] sponsors could use the proportion of participants meeting DSM-5-TR criteria for remission of OUD at the end of the study as a primary or secondary effectiveness outcome. When designing a study to determine safety and effectiveness, a sponsor should ensure the clinical diagnosis method or scale is appropriate to support the proposed indication. In a pivotal OUD device study, the clinical evidence should demonstrate a clinically significant change in disease status or duration of OUD.

(3) Reduction in Adverse Outcomes of OUD

FDA encourages sponsors to design clinical studies that evaluate the reduction of clinically significant adverse outcomes related to OUD. Examples of clinically significant adverse outcomes related to OUD include:

- The need for emergency intervention;
- Hepatitis C virus infection or reinfection; and
- Mortality (overall mortality or overdose-induced mortality).

Use of other adverse outcomes may be appropriate when there is clear clinical significance associated with a reduction in that adverse outcome as it relates to the treatment of OUD. However, not all adverse outcomes are inherently clinically significant for treating OUD. Sponsors can propose other adverse outcomes than those listed, and can study several outcomes in the same study, selecting one as the primary outcome, and selecting one or more as secondary outcomes or a composite of adverse outcomes. Consideration for the sample size and study duration can be informed by the rate of adverse outcomes of interest in the population being studied.

(4) Patient-Reported Outcome Instruments

Patient-reported outcome (PRO) instruments with established clinical significance may provide information to help evaluate how a patient feels or functions. When designing a study using PRO instruments, sponsors should consider the magnitude and duration of change in the PRO that represents a clinically significant benefit. Sponsors can develop PRO instruments to evaluate concerning symptoms and experiences associated with OUD that effect how a patient feels or functions in daily life. When selecting or developing a PRO instrument, sponsors should follow principles outlined in the FDA guidances, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims"[16] and "Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation."[17]

[15] Specific criteria are in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5-TR), F11.10 through F11.21.

[16] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims.

[17] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-selecting-developing-modifying-and-adapting-patient-reported-outcome-instruments-use.

(5) Other Outcome Measures

FDA encourages sponsors to consider other outcome measures that might help demonstrate the clinical benefit of devices intended to treat OUD. For example, a reduction in hospitalizations for OUD or improvements in a participant's ability to resume work, school or other positive social activity. If available, such data may be significant to both participants and clinicians and are highly valuable because they represent the benefits that are significant to participants, their families and caregivers; namely evidence of a real, durable improvement in how the participant functions in daily life. A complementary clinician's assessment corresponding to each patient-reported outcome during the study can provide additional information that is helpful when making a benefit-risk determination. Additional outcomes measuring treatment retention and measures of participant satisfaction with treatment accompanied by evidence of a clinically significant improvement in function in daily life caused by the device, may be included as supportive secondary outcome measures.