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I.   INTRODUCTION

The opioid epidemic is one of the most serious and complex public health problems facing the United States, entailing devastating consequences extending into nearly every community. [1,2,3,4] More than 80,000 Americans died from opioid overdoses in 2021,[5] a staggeringly high toll, and only one measurement of a far-reaching crisis that requires innovative solutions. As a result of the continued consequences of the opioid crisis affecting our nation, the Secretary of Health and Human Services (HHS) has renewed the previous determination under section 319 of the Public Health Service Act that an opioid public health emergency exists nationwide.

Advancing efforts to mitigate the opioid crisis is one of the top priorities for the Food and Drug Administration (FDA) and the National Institutes of Health (NIH). Both agencies are taking steps to support the rapid development of more effective measures to prevent, diagnose, and treat opioid use disorder (OUD), as well as to mitigate other health concerns and dangers related to opioid use. As part of the commitment to addressing this national crisis, the FDA's Center for Devices and Radiological Health (CDRH) and NIH's National Institute on Drug Abuse (NIDA) are fostering the development of innovative medical devices to help individuals who use opioids, and to reduce the risk of opioid-related harm in the population.

It is essential to recognize that the depth, breadth, and complexity of the opioid crisis calls for a broad, multi-faceted, long-term effort to mitigate this public health crisis. Medical devices are an important piece of the puzzle, and medical devices may be of significant benefit to some people who use or are considering use of opioids in terms of lowering the risks to their health and mitigating harm. The majority of adults who meet the criteria for a substance use disorder began use in their teen and young adult years.[6,7] Given the many ways different groups of people have been negatively impacted by the opioid crisis, every contribution to softening that impact is valuable.

The FDA and NIH have taken numerous actions to encourage innovators in this field to develop safe and effective medical devices that meet the needs of patients. Many devices aimed at opioid use are under development by a variety of innovators, start-ups, small businesses, and other device manufacturers.

In keeping with efforts to promote this innovation, the FDA and NIH are holding two connected public workshops [8] on developing medical devices, including digital health technologies, aimed at diagnosing, monitoring, and risk prediction relating to opioid use and opioid use disorder. The

workshops are intended to provide stakeholders (including patients and their families or caregivers, device developers and clinicians) with several opportunities to:

- discuss challenges and opportunities relevant to device development, commercialization, and adoption
- examine the many considerations and challenges that arise throughout the total product life cycle (TPLC) of such devices; and
- explore monitoring, risk-prediction, and diagnostic use cases that can meet patients' needs, improve outcomes of people experiencing opioid use disorder, and better enable clinicians to help and protect patients.

The first workshop,[9] led by NIH, is dedicated to monitoring and diagnostic devices indicated for patients using opioids, while the second workshop,[10] led by FDA, is focused on devices intended to predict the risk of developing OUD or experiencing other opioid-related harms.

The workshops are consistent with the HHS Overdose Prevention Strategy,[11] as well as the FDA's Overdose Prevention Framework.[12] Specifically, FDA's Overdose Prevention Framework[13] identifies the following four priorities:

- Supporting primary prevention by eliminating unnecessary initial prescription drug exposure and inappropriate prolonged prescribing;
- Encouraging harm reduction through innovation and education;
- Advancing development of evidence-based treatments for substance use disorders;
- Protecting the public from unapproved, diverted, or counterfeit drugs presenting overdose risks.

II.   THE CURRENT LANDSCAPE OF DEVICES ADDRESSING OPIOID USE

A. Monitoring and Diagnostic Devices

Medical devices capable of monitoring particular parameters (for example, wearable digital sensors)[14] in patients may offer innovative solutions to patients who use opioids. For example, such devices could potentially catch early signs of respiratory depression, or decreased respiratory rate, which can be induced by opioids.[15] In severe cases, respiratory distress can lead to low oxygen saturation (hypoxia), high carbon dioxide values (hypercapnia), and decreased ventilatory response to hypoxia and hypercapnia.[16] Opioid-induced respiratory depression and resulting complete respiratory arrest are the major causes of mortality with opioid overdose.[17][18]

Safe and accurate monitoring devices could potentially be useful in healthcare facilities in monitoring patients to whom opioids have been administered, particularly in post-surgical situations. But they might prove especially helpful in monitoring opioid users in their homes, where most opioid overdoses take place,[19] and where problematic opioid use might go unnoticed.

Monitoring devices typically enlist some combination of electronic, mechanical, and biochemical sensors, in most cases in conjunction with software either built into the device or incorporated into a mobile or computer application.

Questions remain regarding which parameters to track. Blood oxygen saturation as non-invasively measured through the skin (pulse oximetry) and carbon dioxide measurement have been shown to correlate with respiratory depression diagnoses,[20] but there are a variety of other measurements ranging from respiratory rates to activity levels that might be enlisted to infer problems with opioid use. Most of these measurements can be performed by small wearable devices that upload data and provide alerts for use by clinicians and others remotely.[21,22] However, questions remain around these types of parameters, including what performance measures are meaningful in order to provide sufficient sensitivity while avoiding excessive false alarms.[23,24]

B. Predictive Risk Devices

Various types of data about individuals have been reported to be correlated with the likelihood that they will develop opioid use disorder or experience respiratory distress, an overdose, or other harm if exposed to opioids.[25] Knowledge of this risk could potentially inform clinicians' decisions about administering or prescribing opioids to a patient[26], and could potentially alert patients, caregivers and others to a need for increased monitoring and vigilance.

A wide range of different factors have been associated with the risk of opioid use disorder, respiratory depression, and overdoses. These include behavioral, demographic, and social factors, such as family history of substance misuse, age, and neighborhood.[27,28] Biological markers such as inflammation, endocrine levels,[29] urea concentrations[30] and various comorbidities such as pulmonary disease, renal disease and sleep apnea[31,32] have also been correlated with opioid risks. More recently, studies have identified metabolomic profiles[33] and genetic markers that may also be correlated with risk of developing OUD.[34, 35] There is currently a lack of consensus in the scientific community around the reliability of these markers,[36] but it is possible that their predictive ability may grow over time.

Gathering and assessing data on the risk for opioid use disorder and other harm has conventionally been accomplished through interviews and questionnaires[37] in the case of behavioral and environmental data, and through biomedical and diagnostic testing in the case of biomarkers and co-morbidities.[38] Medical devices may facilitate this process of generating a risk assessment. Software tools in particular may facilitate the required data gathering and analysis. In theory, wearable and other sensors could automatically draw some of the needed data by tracking behaviors and environmental conditions, and through biomeasurements. Artificial Intelligence and Machine Learning (AI/ML) has the potential to work in conjunction with these approaches to improve their accuracy and sensitivity, especially as data sets expand and include a larger number of variables. At the present time, researchers in the field have published conflicting findings and views about the reliability of AI/ML-based predictive tools and their

susceptibility to bias and discrimination,[39,40,41,42] but enhancing the reliability of such tools remains an area of research and a focus of development efforts.

Genetic predictive tests that look for particular variations in genes correlated with opioid risks are one area of research and development. But it is important to note that some scientists express ethical concerns[43,44] about employing genetic tests in this complex and sensitive area. In addition, challenges exist around conduct of clinical validation studies for these tests.[45] These concerns and challenges raise questions about how devices based on genetic testing can be ethically deployed, and how reliable their results should be considered.

C. Digital Health Technology Enabled Capabilities

Some digital health technologies may provide useful diagnostic and/or monitoring capabilities related to opioid use. Following are some examples of these types of technologies.

mHealth Apps. Some mobile apps may have the capability to provide monitoring, evaluation, diagnosis and treatment related to certain health and behavioral-health risks and conditions, including but not limited to heart disease, diabetes, obesity, and anxiety. Some mHealth Apps likewise may have the potential to address opioid use and OUD, whether patient-facing or clinician-facing.[46,47]

AI/ML-based tools. AI/ML approaches could be applied to opioid use and opioid use disorder to help identify possible impending or ongoing health crises, find patients who may potentially be at higher genetic or behavioral risk, and identify those patients who may potentially be at more immediate need of intervention. Such AI/ML-based technologies are generally trained using patient data, which is often available through electronic medical record databases.[48, 49]

It is important to avoid possible algorithmic bias for these AI/ML based technologies. Challenges surrounding possible bias in AI/ML-based technologies are discussed in section IIIE (of this document) *Challenges and Opportunities for Emerging Technologies*.

Wearable or smartphone respiratory rate and activity trackers. Fitness trackers and similar wearables that provide information about pulse, respiration, blood oxygenation, and body movement could potentially be developed and used to detect signs of possible respiratory depression[50] or even a possible overdose[51]. Sensor data could be analyzed, and the results could be used to issue alerts, or potentially to help clinicians reach diagnoses and gain insights into patient risks, behaviors, and health.[52]

Self-contained sampling and testing devices. Devices capable of automatically withdrawing tiny samples of a person's tissue or fluid, typically from the outer skin, might potentially be made small enough to be worn or carried by people who use opioids. Any such devices might also contain chip-based electrochemistry needed to analyze the sample, or store the samples for analysis elsewhere. The results from such a device could potentially yield relatively fast and frequent information, leading to insights into how opioids may be affecting a patient.[53]

Augmented reality and virtual reality. Virtual reality (VR) technologies may provide diagnostic or monitoring capabilities by presenting the user with immersive visualizations and soundscapes, providing tactile feedback, and recording user reactions with cameras, microphones and motion sensors. Such capabilities may also be incorporated in augmented reality (AR) technologies, which may be less cumbersome and may have the potential to be worn for longer periods of time, including during routine activities. These technologies are an active area of research, as demonstrated by the ongoing[54] and published research in this field.[55]

III. CHALLENGES AND OPPORTUNITIES FOR EMERGING TECHNOLOGIES

Because the opioid crisis is a large and multi-faceted problem, it is unlikely that a single device or technology could have a comprehensive impact on the crisis. Rather, many devices with a range of technologies, indications, and intended patient populations are likely to provide the most significant public health impact. The better targeted a device is at the specific needs of a particular patient population, the more likely it is to achieve its intended purpose. Thus, understanding different patient populations and their different needs may be helpful, if not essential, to developing successful devices.

A. Different Patient Populations

One of the most important aspects of the opioid crisis is that it is not a one-dimensional problem. Rather, it is composed of very different challenges involving groups of patients who are in very different situations. Although many patients who are treated with or otherwise use opioids may not neatly fit into any categories, or may fit into more than one, or may fit into different categories at different times, it can still be helpful to consider three broad patient populations: Acute use of opioids, chronic use of opioids, and opioid use disorder.

i. Acute use of opioids

A time range to define acute (or short-term) opioid use is not established at this time. However, acute patterns of opioid prescribing are generally considered to be less than 90 days.[56] The Centers for Disease Control and Prevention (CDC) reports that there were more than 140 million prescriptions written for opioids in 2020 in the United States.[57] In 2017, the last year for which data are available, the average number of days per prescription was 18 days.[58] Opioid analgesics are generally prescribed for pain.[59] Pain is a common symptom experienced with many health conditions; according to one study as many as 42% of emergency department patients report pain as a main complaint.[60]

ii. Chronic use of opioids

The CDC defines long-term opioid therapy as "use of opioids on most days for more than 3 months," and cites 2005 data estimating that 3%-4% of the U.S. adult population was using opioids on a long-term basis.[61] There are differing definitions about what constitutes "long-term" or "chronic" opioid use, and a lack of current data that clearly indicates how many people use

opioids on a long-term basis according to any of these definitions. But there are data that provide at least a rough picture of relatively current long-term opioid use in the U.S. About 55 million people in the U.S.—roughly a fifth of the adult population—report experiencing chronic pain.[62] According to one poll reported in 2018, almost one-third of Americans reported receiving a prescription for opioids in the past two years.[63] About 7% of opioid prescriptions are for longer than one month. One in seven people who either refill an opioid prescription or receive a second opioid prescription in a given year are taking opioids a year later.[64] Approximately half of people who receive repeated prescriptions for opioids are being treated for back pain.[65]

iii.   Opioid Use Disorder

Opioid Use Disorder (OUD) is a formal diagnosis involving specific criteria. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5, defines opioid use disorder as a problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following criteria, occurring within a 12-month period.[66]

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of an opioid.

    NOTE: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.

11. Withdrawal, as manifested by either of the following:
    a. The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal, pp. 547 to 548).
    b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

> **NOTE:** This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

More generally, opioid use disorder may be roughly described as "the chronic use of opioids that causes clinically significant distress or impairment."[67] In 2020, 2.7 million people in the U.S. were reported to fit the criteria for opioid use disorder.[68]

It is important to note that opioid use disorder is sometimes erroneously conflated with opioid "misuse," which is roughly defined as use outside of a prescription or through an inappropriately obtained prescription. In 2020, it was reported that among people aged 12 or older in 2020, 3.4% (or 9.5 million people) misused opioids in the years 2019-2020, more than triple the number of people diagnosed with opioid use disorder.[69]

B. Different Needs in Different Patient Populations and the Individuals Surrounding Them

Different patient groups have different needs. Possible examples to consider include:

i. *Needs of acute patients*

Tests that can help predict vulnerability to opioid use disorder may be of possible benefit for people who are potential users of opioids or may be using opioids for acute conditions such as following surgery. For example, assessment of that risk could potentially play into decisions about whether to prescribe opioids at all, or, if prescribed, into decisions about duration, frequency and dosage. Because acute prescription use can lead to misuse and opioid use disorder, devices that can monitor for excessive or other non-prescribed usage could potentially be helpful in alerting patients, family members and caregivers, and clinicians to possible problems associated with opioid use.

ii. *Needs of chronic patients*

Monitoring for respiratory depression or other potential indicators of overdose risk could be of possible benefit to patients who use opioids regularly. Monitoring for frequency, duration, or intensity of opioid use could also be of possible benefit to patients who undergo efforts to moderate or discontinue the use of opioids, or who may be at risk for opioid use disorder. Appropriately validated opioid use disorder-risk-prediction tests could potentially be helpful before a patient is placed on long-term opioid therapy.

iii. *Needs of Opioid Use Disorder patients*

Opioid use disorder patients could potentially derive special benefit from respiratory-depression monitoring, and other monitoring that could alert to a potential impending overdose. Monitoring for opioid usage could potentially be supportive of efforts to limit or stop the use of opioids.

iv. Needs of adolescent opioid users

Adolescence is a critical stage of development during which physical, intellectual, emotional, and psychological changes occur.[70] Adolescents merit special consideration when it comes to opioid risks, as well as to the potential benefits and challenges of medical devices aimed at the problem. In 2018, nearly 3% of U.S. adolescents aged 12 to 17 reported having misused opioids in the past year, and early use of opioids—whether prescribed or otherwise—is associated with higher likelihood of misuse later.[71,72]

There is little data to indicate how medical devices might be utilized in this population in terms of reducing risks of use, misuse, opioid use disorder, and overdoses. Given the unique developmental and behavioral considerations for adolescents,[49] it is likely that acceptance, compliance, and outcomes related to these devices will differ in some ways for adolescents from those of adult populations. Understanding the distinct cognitive and social factors relevant to adolescents may provide opportunities to tailor these devices in unique ways to adolescents in order to achieve higher acceptance and improve outcomes.

v. Needs of family members, loved ones, caregivers and healthcare providers

The impact of the opioid epidemic ripples well beyond those who use opioids. It has also created a crisis for their families and others who are close to them or depend on them, especially children.[73, 74] Clinicians often struggle to balance the needs of patients who are in pain with the growing pressure on them to reduce opioid prescriptions.[75,76]

C. Clinical Study Design and Conduct

Researchers surveying opioid studies have noted the lack of consensus and standardization in how these studies define and measure problematic opioid use and the outcomes of interventions.[77,78] Biomarkers as well as [Clinical Outcome Assessments (COAs)](79) present an opportunity for tracking and/or quantifying the degree of opioid use and opioid use disorder related signs and symptoms, as well as the impact of medical devices and other interventions on patients' lives.

Although use of biomarkers and COAs may present a potential opportunity to improve the quality and interpretation of studies, there are currently no biomarkers that are widely accepted for these purposes, and some study findings suggest that such markers may be less useful than patient-reported outcomes (PROs) in assessing treatment success.[80] There are also study challenges related to the fact that opioid use disorder and other opioid-related problems often overlap with other health conditions, potentially making it difficult for researchers to tease them apart.

PROs are one type of COA. COAs describe or reflect how an individual feels, functions, or survives,[81] and can be reported by the person themselves, a healthcare provider, or a non-clinical observer such as a parent; or a COA can be assessed through performance of an activity or task. COAs can be valuable evidence for benefit-risk assessment, including

assessing concepts of interest related to effectiveness and safety of a medical device; medical-device labeling, and clinical-trial eligibility.[82,83] They may also be useful for healthcare providers and payors.[84]

In the context of opioid use and opioid use disorder, COAs were discussed during a public meeting on April 17, 2018, held by FDA on Patient-Focused Drug Development for Opioid Use Disorder related to the following:

- Effects of using opioids, such as confusion, constipation, or other symptoms;
- Effects of opioid withdrawal, such as nausea, diarrhea, or other symptoms;
- Effects of opioid "cravings;"
- Impacts on ability to function in personal or professional life;
- Emotional or social effects; and
- Other potential effects.[85]

As scientific understanding and more precise tools for measuring different aspects of opioid use in different patient groups evolve, studies utilizing these new or updated tools may be in a better position to reflect or predict real-world outcomes in these groups. More reliable and relevant study data on opioid use may facilitate the development and acceptance of medical devices aimed at mitigating opioid-use-related problems. However, even with the emergence of more reliable study results, it will be important for innovators and other stakeholders to keep in mind that findings may not apply to all patient groups.

In clinical trials of devices with opioid-related indications, as with all types of medical devices, the diversity of the subjects participating in the trials is an important consideration. The FDA remains committed to increasing enrollment of diverse populations in medical product development and continues to engage with federal partners, medical product manufacturers, healthcare professionals and health advocates to reach this important goal.[86] For example, FDA's draft guidance document entitled "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials" proposes that sponsors of medical products develop and submit a Race and Ethnicity Diversity Plan to the FDA early in clinical development, based on a framework outlined in the referenced guidance.[87] In addition, FDA has issued two final guidance documents entitled "Evaluation of Sex-Specific Data in Medical Device Clinical Studies"[88] and "Evaluation and Reporting of Age-, Race- and Ethnicity-Specific Data in Medical Device Clinical Studies"[89] providing recommendations on the importance of studying diverse populations as well as analyzing and reporting that data in medical device clinical studies. More information on clinical trial diversity is available at Clinical Trial Diversity | FDA.[90]

To further innovation efforts relating to clinical studies in devices impacting opioid use, the FDA intends to publish a draft guidance with further clinical considerations for the development of devices intended to treat OUD. [91]

D. Concerns about Privacy and Stigma

The privacy of personal healthcare information is legally protected and is a high priority to many people. Those who use opioids may consider information related to that use exceptionally private, given the fact that employers, law-enforcement personnel, and even friends and family, among others, might react negatively when learning of opioid use. Studies have suggested this opioid-use-associated stigma and its impact on opioid users can vary in nature and intensity but can in many cases be quite strong and impactful.[92] For example, in one study, potential users of an opioid-related medical device cited privacy as one of the top factors impacting their willingness to accept the device.[93]

In addition, there are concerns that medical devices aimed at opioid use might threaten to compromise privacy and place device users at higher risk of exposure to stigma. For example, monitoring devices—especially those designed to be worn continuously on the wrist or elsewhere—may be readily visible, recognizable or readable to others.[94]

Another example is the possibility that the opioid-use-related data generated by devices gets into the wrong hands.[95] Protecting against that risk calls for cybersecurity measures throughout the entire web of people, devices and software that might touch that data, including but not limited to the device itself, the networks over which connected devices transmit data, phone apps that track and display the data, the cloud-based or other remote databases that gather and store the data, remote software that analyzes the data, and clinicians and technicians who might be able to access the data.

Even when all these potential vulnerabilities are adequately addressed on a technical and practical level, users may still harbor privacy concerns about these devices, which could impede the devices' acceptance and ultimately usage.

E. Sources of Potential Bias

One challenge to opioid-related medical-device development is unintended and/or unwarranted bias, which exists in several aspects of medical device development.

Healthcare-based bias that negatively impacts opioid users is a subset of opioid-use stigma and can be significant. In one study, over two-thirds of primary-care physicians indicated their unwillingness to accept a person being treated with medication for opioid use disorder as a neighbor or as someone marrying into their family.[96] It is not hard to imagine that treatment via a medical device could fare little better in overcoming that bias. Such bias could be a possible barrier to the willingness of clinicians to prescribe devices and could impact the willingness of opioid users to seek and use these devices.

Further, studies have documented biases in healthcare with regard to pain assessment and treatment.[97,98] For example, one study found that White medical students and residents tended to rate the pain of Black personss as less severe than that of White personss who presented with identical complaints, impacting assessment and treatment decisions.[99] Another study reported that women were perceived to have more pain than men, and that there was a

tendency by both men and women to underestimate pain in others, but that men showed a greater degree of underestimation.[100] Such biases may affect clinical decisions about opioid-related devices as well.

Unintended bias impacting certain segments of the patient population can be present in a medical device, especially for devices using software algorithms trained on data sets that were generated in environments where these biases exist. It can also be present in non-device software used in healthcare. Research has identified that unintended biases can exist in algorithms used to assess risk in patients with complex needs,[101, 102] which can determine how much attention and care different patients receive. One study reported that the number of Black persons flagged by these algorithms for extra care was less than half what it would have been without racial bias.[103] These unintended biases could potentially translate to reduced access to opioid-use-related devices based on race. Unintended bias rooted in the characteristics of the measurement and other technologies chosen and used in devices themselves can also negatively impact care.[104] A prominent example, as well as one that may be especially relevant to opioid-related monitoring devices, is that the light-based sensors intended to track the wearer's pulse are often significantly less accurate with dark skin than with light skin.[105]

While the results can appear quite accurate, they may also reflect bias due to a lack of diversity in the patient population from which the training data was derived; or bias due to the way patient data may be skewed by other social determinants of health as well as bias in healthcare quality and delivery.[106,107] The FDA has instituted efforts to continue to support innovative work in the regulation of these AI/ML related medical devices, including to minimize the negative impact of unintended bias. For example, a public workshop "Transparency of AI/ML Enabled Medical Devices"[108] was held by FDA on October 14, 2021. Preceding this workshop, FDA held a patient engagement advisory committee meeting entitled "Artificial Intelligence and Machine Learning in Medical Devices."[109] Highlighted in section V.C (of this document) – *Regulatory resources specific to digital health* are related digital health regulatory resources (AI and ML Software as a Medical Device Action Plan[110] and Good Machine Learning Practice for Medical Device Development: Guiding Principles[111]) that discuss related topics around bias and transparency (in AI/ML) that device innovators may find helpful for software-based and other digital health technologies related to monitoring, diagnostics, and predictive devices for opioid use and opioid use disorder.

Addressing these issues early in algorithm development is important because, once these unintended biases become embedded in AI/ML algorithms, they may be difficult to identify and correct for AI/ML algorithms with insufficient transparency.[112,113] The above described topics around bias impacting medical device development for devices relating to opioid use likely also translate to design and conduct of clinical studies, as discussed in section III.C – *Clinical study design and conduct*.

F. Disparities in Access

The FDA and NIH are committed to supporting solutions that are accessible across different patient populations. The public health would not be well-served by attempting to address the

opioid crisis through medical devices if some of the most vulnerable patient populations lacked access to them.

Ensuring equitable access to beneficial devices will require efforts on several fronts. One of the most impactful efforts will be that of managing the costs of these devices, both in terms of payor coverage and potential patient out-of-pocket costs. In addition, many of these devices will work in conjunction with a smartphone, and smartphone access may not be available across all groups of patients who use opioids. In one 2019 study of opioid users, only 38% of users owned a cellphone with Internet access.[114]

Another accessibility challenge will be access to providers who can prescribe and supply the medical device. Healthcare access varies widely among people who use opioids, suggesting that developers may need to be prepared to work with various organizations to help ensure that their devices reach the people who can most benefit from them.

G. User and Clinical Buy-in

In addition to concerns about privacy and challenges to access, many users may hesitate to embrace opioid-related medical devices for other reasons. One study of people who use opioids found that three-quarters of them said they would be willing to wear a medical device to detect and reverse opioid overdose, assuming adequate privacy and comfort.[115] But much more study and experience will be needed to gauge the scope and nature of this challenge, and to come up with approaches to overcoming it. Certainly, it will be helpful for developers to give close attention to making devices as friendly, unimposing, and helpful as possible.

Clinicians, too, may be resistant to embracing these devices, even aside from potential bias against patients who use opioids. While not limited to devices related to opioid use, a new type of device requires investing time in learning about indications, risks and benefits, as well as how to use the data it may provide. Clinicians are in general pressed for time during clinical visits, and any new technology that may involve modifying or interrupting existing workflows might be challenging to integrate.

For example, devices that issue respiratory depression, potential overdose, or other opioid-use-associated alerts may leave clinicians wondering if they will be called upon to take responsibility for addressing the alerts or to deal with patients or caregivers who are worried about an alert. The ability and willingness of innovators to anticipate and address these and other potential added responsibilities could have a significant impact on acceptance.

IV. NIH EFFORTS RELATED TO DEVICES FOR OPIOID USE

NIDA has been a leader in leveraging the power of small-business innovation to develop new tools and technologies for preventing, diagnosing, and treating drug-related problems and for advancing research. For example, through significant investment in its Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs, NIDA has supported the development of FDA-regulated therapeutic and diagnostic devices.[116]

NIDA also has funding opportunities relating to development of FDA-regulated devices for opioid use. Below is a summary of some of the relevant programs.

- Small Business Innovation Research (SBIR) and Technology Transfer (STTR) Programs

As the U.S. government's lead agency for advancing the science on drug use and addiction with the goal of improving public health, NIDA annually provides more than $45 million in awards to entrepreneurs, startups and small businesses through the [Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs](#).[117]

- Blueprint MedTech Initiative

Innovators developing groundbreaking medical device technologies face a number of challenges along the translational path from bench to bedside. The Blueprint MedTech program is an NIH incubator that aims to address such challenges and support the innovators by accelerating the development of cutting-edge medical devices to diagnose and/or treat disorders of the nervous system.

The overarching goal of the Blueprint MedTech program is to accelerate patient access to groundbreaking, safe, and effective medical devices. The program will provide support to sufficiently develop and de-risk technologies to the point where additional investments are warranted from industry partners, investors, and government.[118]

V.   FDA REGULATION OF MEDICAL DEVICES

The FDA also recognizes that there is an overarching need for rapid development of innovative devices that are safe and effective to help mitigate the devastating impact of the opioid crisis. This section provides information regarding the most common premarket authorization pathways, and a high-level overview of FDA programs that promote timely patient access to innovative devices.

A. Medical Device Marketing Authorization

Generally, a medical device intended for use in the diagnosis, cure, mitigation, treatment, or prevention of opioid use or OUD would require marketing authorization from the FDA prior to distribution in the U.S. Three common risk-based pathways for obtaining FDA marketing authorization are provided below with links to resources relevant to each:

- [Premarket Approval (PMA) | FDA](#)[119]
- [De Novo Classification Request | FDA](#)[120]
- [Premarket Notification 510(k) | FDA](#)[121]

B. Highlights of FDA Programs Supporting Device Innovation

The FDA is committed to facilitating efforts to mitigate the opioid crisis and considers it a priority.[122] The FDA believes activities that help accelerate patient access to innovative safe and effective medical devices[123] are important in addressing the opioid crisis. To that end, the FDA is interested in working with innovators to bring new devices to market that help address different components of the crisis through an efficient regulatory process.

FDA has implemented programs aimed at promoting timely patient access to innovative devices, and is working to provide early regulatory assistance to innovators and small businesses.[124]

> *i.   Q-Submission Program*

The FDA encourages innovators in this space to take advantage of the Q-Submission Program to receive feedback from the Agency during the planning stages of device development and validation. For example, as part of FDA's Q-Submission Program,[125] CDRH offers the option either to have an informational meeting with the FDA as part of ongoing device development, or to meet as part of a pre-submission to get FDA's feedback as innovators prepare their applications.[126]

> *ii.   Breakthrough Devices*

The Breakthrough Devices Program is intended to provide patients and healthcare providers with timely access to certain medical devices by speeding the development, assessment, and review of devices, while preserving the statutory standards for PMA, 510(k), and De Novo marketing authorization, consistent with the FDA's mission to protect and promote public health. This program is voluntary for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. Devices related to opioid use and OUD may be candidates for the Breakthrough Devices Program.[127] Opioid-related monitoring, diagnostic or predictive devices that apply for and are granted breakthrough device designation may be well positioned to engage in timely and collaborative interactions with FDA to reach a mutual understanding of development, data collection and review expectations.

> *iii.   Real-World Evidence*

Real-world data (RWD) and real-world evidence (RWE) are playing an increasing role in healthcare decisions.[128] The FDA has issued a guidance document entitled "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" to outline CDRH's current thinking regarding the use of RWE in regulatory decision making.[129] Specifically, the guidance seeks to clarify how the FDA evaluates RWD to determine whether they are sufficient for generating the types of RWE that can be used in FDA regulatory decision-making for medical devices.

iv.   FDA Innovation Challenge: Devices to Prevent and Treat Opioid Use Disorder

As part of efforts to address the opioid crisis, the [FDA launched an innovation challenge](#) in 2018 to spur the development of medical devices, including diagnostic tests and digital health technologies, to help combat the opioid crisis and achieve the goal of preventing and treating opioid use disorder.[130]

v.   Early Payor Feedback Program & Payor Communication Task Force

CDRH established the [Payor Communication Task Force](#) to facilitate communication between device manufacturers and payors to potentially shorten the time between FDA marketing authorization and coverage decisions. The [Early Payor Feedback Program](#) allows innovators to engage with payors while they are planning their pivotal clinical trials.[131]

C. Regulatory Resources Specific to Digital Health

Following are highlights of the regulatory resources that device innovators may find helpful as they consider product roadmaps for software-based and other digital health technologies related to monitoring, diagnostics, and predictive devices for opioid use and OUD. Additional FDA guidance documents related to digital health products are available at [Guidances with Digital Health Content](#).[132]

- [Policy for Device Software Functions and Mobile Medical Applications](#)

This guidance document, entitled ["Policy for Device Software Functions and Mobile Medical Applications,"](#)[133] is intended to inform manufacturers, distributors, and other entities about how the FDA intends to apply its regulatory authorities to select software functions intended for use on mobile platforms or on general-purpose computing platforms. Given the rapid expansion and broad applicability of software functions deployed on mobile or other general-purpose computing platforms, FDA has issued this guidance document to clarify the subset of software functions to which FDA intends to apply its authority.

- [Software as a Medical Device (SAMD): Clinical Evaluation](#)

This guidance document, entitled ["Software as a Medical Device (SAMD): Clinical Evaluation,"](#)[134] adopts the internationally converged principles agreed upon by the International Medical Device Regulatory Forum (IMDRF) on this topic. Additional related information about the IMDRF and FDA adoption of these principles is available at [Software as a Medical Device (SAMD): Clinical Evaluation | FDA](#).[86]

- [Artificial Intelligence and Machine Learning (AI/ML) Software as a Medical Device Action Plan](#)

The FDA developed the ["Artificial Intelligence and Machine Learning (AI/ML) Software as a Medical Device Action Plan"](#)[135] in 2021 in direct response to stakeholder feedback received from

a discussion paper issued by FDA in 2019, entitled "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML) -Based Software as a Medical Device (SaMD)."[136] As part of the AI/ML Action Plan, the FDA is highlighting its intention to develop an update to the proposed regulatory framework presented in the discussion paper. This Action Plan builds on the FDA's commitment to support innovative work in the regulation of medical device software and other digital health technologies.

The related [patient engagement advisory committee meeting "Artificial Intelligence (AI) and Machine Learning (ML) in Medical Devices"](#) proceedings[137] as well as AI/ML action plan[138] includes discussion around transparency and bias.

- [Good Machine Learning Practice for Medical Device Development: Guiding Principles](#)[139]

The FDA, [Health Canada](#), and the [United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA)](#) jointly identified 10 guiding principles that can inform the development of Good Machine Learning Practice (GMLP). These guiding principles are intended to help promote safe, effective, and high-quality medical devices that use AI/ML.

VI. SUMMARY

The field of opioid-related monitoring, diagnostic and predictive medical devices is still a developing one. Early efforts are already showing promise, and research and development is active and productive. NIH and FDA remain committed to accelerating this work and facilitating the movement of promising approaches for diverse impacted populations all the way through marketing authorization.

While such progress, when compared to the scale of the opioid crisis, may seem modest, there is good reason to hope that its success will soon be measurable in improved outcomes for a subset of opioid users and other patients. In that way, the U.S. can advance step by step toward a broader, multi-pronged solution to what is a large and multi-faceted problem.

The opioid crisis is a complex problem, and no one action or one organization will solve the crisis. However, taken together, these actions by the FDA and NIH in partnership with patients, clinicians, consumer advocates other governmental agencies, and many other stakeholders— can move us in the right direction. We welcome the opportunity to work in partnership to strengthen our response.

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