

# Ethical Issues in Research Involving Participants With Opioid Use Disorder

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## Abstract

In the current epidemic of opioid use disorders, there is both a scientific and ethical imperative to develop effective medical and behavioral treatments for opioid addiction. Research in subject populations with active and ongoing drug addictions bring unique ethical considerations and challenges. Sponsors, researchers, and institutional review board (IRB) members should be familiar with these unique ethical and medical issues as they design, review, and conduct research planned for this population. Issues include those of informed consent and decision-making capacity of research participants, compensation for participation and concerns about undue inducement, forces that threaten the voluntary nature of research participation including the scarcity of available drug treatment programs, and ensuring that participants are aware of and understand risks that may continue after research participation such as increased risk of overdose after research-mandated drug abstinence. This manuscript discusses the current thinking on these issues.

## Keywords

research ethics, informed consent, vulnerable populations, compensation, drug addiction

## Introduction

Given the current opioid crisis and its impact on individuals and greater society, there is both a scientific and ethical imperative to develop effective medical and behavioral treatments for opioid dependence. Sponsors, researchers, and institutional review board (IRB) members should be familiar with the unique ethical issues that are relevant to conducting research with this population. There are no specific ethical guidelines for conducting research with individuals who abuse opioids, beyond those regulations, guidelines, and standards that apply broadly to human research. There is, however, a robust literature addressing ethical issues relevant to conducting substance abuse research. This includes a growing evidence base on best practices and data from empirical studies assessing the views and behavior of individuals with substance abuse disorders. In this narrative review, we summarize and integrate the current literature and thinking with regard to the multiple ethical complications that may arise specifically in research involving individuals with opioid use disorder (OUD), and suggest best practices for when these complications are encountered. We intend for this review to serve as a resource for IRBs, sponsors, researchers and study teams as they design, oversee, and conduct clinical trials involving participants with OUD.

While previous authors suggest reasons to consider that additional factors that are considered to denote vulnerability may be relevant to individuals who use and/or are addicted to drugs, including opioids, IRBs—and other parties—may

judge the potential risks and benefits of research based on certain assumptions<sup>1</sup> about addiction and persons with addiction rather than on empirical evidence.<sup>2,3</sup> Therefore, we aim to provide data from relevant empirical studies wherever possible. Topics covered include potential participants' capacity to provide informed consent to research; guidelines for paying individuals who abuse drugs to participate in research; unique threats to voluntariness that may arise in the context of research with individuals who abuse opioids, namely, limited access to treatment options; and other aspects of individuals with OUD or research on OUD that require special ethical consideration. This article does not contain any studies with human or animal subjects performed by any of the authors.

## The Opioid Epidemic

Opioid addiction is epidemic in the United States, with the number of new addictions continuing to increase. One analysis by a major insurance carrier estimated that the number of

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covered individuals with diagnosed addictions to opioid products, both prescribed and illicit, increased 493% between 2010 and 2016.<sup>4</sup>

The “gold standard” of treatment for opioid addiction is generally considered to be medication-assisted treatment (MAT), which is a combination of behavioral therapy and medication such as methadone or buprenorphine. One study found that adding Suboxone® (buprenorphine plus naloxone) could double the likelihood that a patient would be drug-free 18 months after treatment.<sup>5</sup> In Europe and Canada, several countries have instituted programs for heroin-assisted treatment (HAT), in which pharmacologic heroin is administered as part of treatment for patients who have not responded to methadone or other opioid replacement therapies.<sup>6</sup> Despite the progress in treatments for the management of opioid addiction over the last few decades, treatment failure rates are high, with 60% to 80% of individuals unable to achieve abstinence at the end of the first year after treatment.<sup>7</sup> And with the increasing number of opioid-addicted people requiring treatments, significantly more research is needed into ways to prevent, manage, and cure these addictions.

A number of experimental therapies are being examined for their ability to treat opioid addictions, with a recent search of the clinicaltrials.gov registry indicating 44 studies currently enrolling or preparing to enroll new participants.<sup>8</sup> Interventions being tested in these studies included deep brain stimulation of the nucleus accumbens, acupuncture to facilitate opioid weaning, extended release and implantable formulations of currently used medications such as naloxone, and peer-delivered behavioral interventions. Populations to be recruited for these studies included individuals being released from prison systems who need to be connected to postprison health care, opioid-addicted women in the immediate postpartum setting, and drug users being treated for infectious endocarditis (as a result of using infected needles). Experts have also indicated that more research is necessary in the treatment of overdoses (including public health efforts to broaden the number of persons equipped to treat overdose quickly).

It is also important to recognize that the prevalence of psychiatric comorbidities with opioid addictions is extremely high, complicating both treatment for the addiction and treatment for the psychiatric illness. Studies have reported a prevalence of psychiatric diagnosis in 47% of opioid-addicted patients seeking treatment, primarily personality disorders and depressive disorders,<sup>9</sup> and multiple studies have found that persons with substance abuse disorders were twice as likely as the general population to suffer from mental illness, and conversely, that persons with mental illness were twice as likely to have substance abuse disorders.

### *Informed Consent and Decision-Making Capacity*

For informed consent for research to be valid, potential participants must be competent to make decisions for themselves. Researchers must also provide key information in language that

is understandable, and potential participants must understand that information and choose to participate voluntarily.<sup>10</sup> The decision-making capacity (DMC) of individuals who abuse opioids has been called into question based on both the short-term effects of intoxication and withdrawal and the potential cognitive consequences of long-term drug use.

As noted above, studies have shown high rates of comorbid psychiatric disorders among substance abusers. However, empirical data suggest that to assume that all opioid addicts lack DMC or are even similarly vulnerable is to ignore the diversity of this population.<sup>11</sup> It should never be *assumed* that individuals cannot provide individual informed consent to participate in research by virtue of the fact that they abuse opioids.<sup>12</sup> Routine assessment of DMC may be reasonable for research that poses greater than minimal risk, but this should be independent of the population.<sup>13</sup> Even in research that poses minimal risk, there are good reasons to be prepared to *consider* assessing DMC of individual participants who show signs that they may lack DMC. Standardized tools to assess DMC are available.<sup>14</sup>

Individuals should never be invited to participate in research studies when they are intoxicated, high, or experiencing severe withdrawal. It is recommended that individuals being invited to participate in research should be actively screened for withdrawal symptoms during the informed consent process.<sup>15</sup> If an individual is determined to be in withdrawal, then researchers should wait to continue the informed consent process until withdrawal symptoms have been managed.<sup>11,16</sup> In the case that an experimental treatment must be started during intoxication or withdrawal, when the potential subject is unable to provide consent themselves, it may be possible to obtain consent from a legally authorized representative to begin the study, and then to obtain consent from the subject once they regain decision-making capacity.

Beyond the requirement that a research participant possess DMC, in order for informed consent to be valid, an individual must comprehend what it is they are agreeing to do. Comprehension is independent of decision-making capacity, and a large body of research suggests that across many kinds of studies, only about half of all research participants adequately understand the goals of a given research proposal, and even fewer understand concepts associated with randomization, risks, the voluntary nature of participation, or the ability to withdraw participation at any time.<sup>17,18</sup> Given this evidence that informed consent is challenging, and because of the unique risks present in opioid addiction treatment research (eg, increased risk of unintended overdose after a period of abstinence), there are good reasons to assess *participant understanding* when research poses greater than minimal risk. This is especially important given the overall low rates of general and health literacy in the United States<sup>19</sup> and differences in the way people from different subgroups assess information presented during the informed consent process.<sup>20</sup>

### *Financial Compensation and Concerns About Undue Inducement*

It is standard practice to pay research participants reasonable amounts of money (cash or equivalent) as compensation for their time and effort. However, concerns have been raised about the potential for payment to “unduly influence” individuals into research participation. Such concerns assume that payment affects a participant’s ability to weigh risks and benefits of a research study.

This results in inconsistent decisions by IRBs, indicating a need for empirical data and clearer ethical guidelines on research payment. Recent thinking in this area indicates that much of the concern about subject payment is unnecessary; undue inducement would mean that someone is persuaded to undertake unreasonable risks because of the promise of payment, but if the research has been approved by an IRB that has assessed the risks and finds them reasonable in relation to the potential benefits, then no amount of payment can make the risks unreasonable.<sup>21</sup> The debate over research payment has been particularly contentious in substance abuse research because of concerns that addicts will spend any money they have to buy drugs.<sup>22</sup> Such an argument may be based on a disease model of addiction, which assumes that the addict has no control over his or her behavior.<sup>23</sup> Or, the argument may just be a moral one—while recognizing that the addict may have the right to use any money they earn from research to buy drugs, the IRB may decline to approve payment for research to prevent or discourage them from doing so, to avoid feeling that they are in effect contributing to someone’s use of drugs. A variety of types of payment can be used in research including cash, check, gift cards or vouchers for specific vendors (such as grocery stores), food, or other small token items (eg, pens). It has been commonly advocated by IRBs that gift cards are “safer” for individuals who abuse drugs than cash or checks<sup>24,25</sup>; however, there is no evidence to support such a view.

The reasons that people choose to participate in research (or not) are quite complex. Research has shown that financial gain is only one of many reasons that an individual might choose to participate in research; others include hope for some direct benefit (eg, ending drug dependency), boredom, altruism, and curiosity.<sup>26–28</sup> Payment in and of itself is not ethically problematic, even in cases where an individual may choose to participate “just for the money.” Payment and voluntariness are not mutually exclusive; as Fry et al remind us, “All decisions, even voluntary ones, are motivated by something.”<sup>21</sup>

There is a growing body of empirical research on the effects of payment on research participants in terms of their decision to participate, their feelings of inducement, and in the case of individuals who use/abuse drugs, their post-research drug use.<sup>21</sup> Research that has focused on individuals who use/abuse drugs suggests several things that are contrary to the attitudes demonstrated and decisions made about paying research participants by IRBs. Most notably, paying individuals who use/

abuse drugs (even in cash) does not appear to increase their drug use. In fact, one recent study of nontreatment seeking opioid-dependent individuals found that participation in an opioid administration study did not increase subsequent heroin use, decreased substance use in the short term, and even resulted in some individuals seeking treatment.<sup>29</sup> In two other controlled studies that randomized participants in outpatient substance abuse treatment programs to different payment types and amounts, Festinger and colleagues found that neither the type of payment (cash or gift certificate) nor the amount (between \$10 and \$160) increased rates of drug use or affected participant perceptions of coercion 6 months after the study ended.<sup>22,23</sup> In fact, out of more than 750 participants in 2 studies, only 1 reported purchasing illicit drugs with incentive money.

When conducting research with a hard to reach population, incentive payments may be required in order to recruit a sufficient number of participants as well as to offset the costs of participation. Payment amounts should not be unjustifiably high, but rather should reflect the time and effort required of participants. Few guidelines exist to determine appropriate payment amounts—although some research has been done to identify standard practices<sup>30</sup>—and local customs vary widely. Ultimately, what is most important from an ethical standpoint is that risks are minimized and communicated clearly during the informed consent process in order to support an individual participant’s decision making.

### *Other Threats to Voluntariness*

In terms of threats to voluntariness, more problematic than financial incentives are the lack of access to treatment options facing many individuals with opioid dependence<sup>12</sup> and the involvement of some individuals in the criminal justice system.<sup>31</sup> “(The) treatment of addiction involves the management of behavior that is considered criminal, that creates adverse consequences for both the individual and the rest of society, and is increasingly understood to be neurobiologically driven to some degree. When opioid dependent individuals seek treatment, they are often in desperate social, financial and health circumstances.”<sup>16</sup> Access to treatment depends on income, insurance status, geographic location (eg, urban vs rural), but overall there is a lack of access across the United States given the limited availability of effective treatments and the limited number of providers certified to prescribe medication-assisted treatment (MAT). In one study, 96% of states had rates of opioid addiction that were above their maximum capacity to provide MAT, and 38 states reporting that their treatment centers were already operating at or above 80% of maximum capacity.<sup>32</sup>

Involvement in the criminal justice system can take many forms in addition to imprisonment. Someone charged with a drug-related offense may be awaiting trial or on probation, they may be on parole, or they may be in a jail-diversion program and under the supervision of a judge.<sup>28</sup> Individuals

under court supervision may be required to undergo substance abuse treatment, for example, in order to reduce their sentence or restore custody of a child.<sup>28</sup> Given the high percentages of drug-addicted individuals who are involved in the criminal justice system, research should not exclude these individuals; otherwise, not only may samples not be representative but researchers may also struggle to enroll sufficient numbers of study participants.

Even for individuals not involved in the criminal justice system, finding treatment may be challenging. In some cases, research may offer the only (or easiest) treatment option they can access. Individuals may also be under pressure from family members or employers. Additionally, individuals who have failed traditional treatment options (and especially those who have failed multiple treatment options) may feel that they have no choice but to enter a research study; “Although such influences are arguably coercive, it is not clear that they are always ethically inappropriate or should preclude research participation.”<sup>28</sup>

### *Unique Risks That Arise in Research With Individuals With Opioid Use Disorder*

In the assessment of the relative risks and potential benefits of research studies involving populations with active opioid addictions, it may also be important for sponsors, researchers and IRBs to recognize that there may be additional medical and physical risks to be considered. Depending on the severity of the addiction and the availability to access medical care, conditions such as cancer, diabetes, and hypertension may be undiagnosed, unmanaged, or undermanaged. Potential subjects may have hepatitis C or HIV infections which may be undiagnosed. One study found a rate of all-cause mortality that was 10 times higher for people with active addictions than for the age- and sex-matched nonaddicted population.<sup>33</sup> In addition, the high rates of psychiatric comorbidities noted earlier must also be considered.

The study design may contribute additional risks as well. Designs that include wash-out periods, or restrict the use of comedications should be carefully considered; it may be appropriate to obtain agreement from the prescribing physician that any current medications can be stopped for the study, rather than just allowing the participant to agree to do so. Designs that restrict the use of other substances such as alcohol or nicotine may be difficult to adhere to in the outpatient setting, and may risk inducing symptoms of withdrawal from these substances in the inpatient setting, resulting in both safety issues for the participants and a confounding of adverse event data for the study.

After the study has been completed, if the design has involved a period of abstaining from drug use and that abstinence does not continue, it has been well documented that the tolerance to drug use is lower and the possibility of accidental overdose, even when using doses similar to those used prior to the period of abstinence, is significantly higher.<sup>34</sup> It is essential

to ensure that participants are aware of and comprehend these risks. If a participant wants to continue to abstain from drugs after the completion of a study period, valid aftercare referrals should be provided.

## **Conclusion**

As we seek solutions for the current opioid epidemic in the United States, and federal and private funding for research—particularly research on medication-assisted treatment—increases, sponsors, researchers, and IRB members will need to become familiar with the unique ethical considerations relevant to individuals with opioid use disorder. These stakeholders may also require some education regarding existing evidence that may contradict their currently held assumptions about individuals who are addicted to drugs and the best ways to implement ethical requirements for informed consent, balancing risk and benefits, and ensuring justice in participant selection and recruitment. This will require partnering with key stakeholders including individuals with OUD.

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