WHITE PAPER

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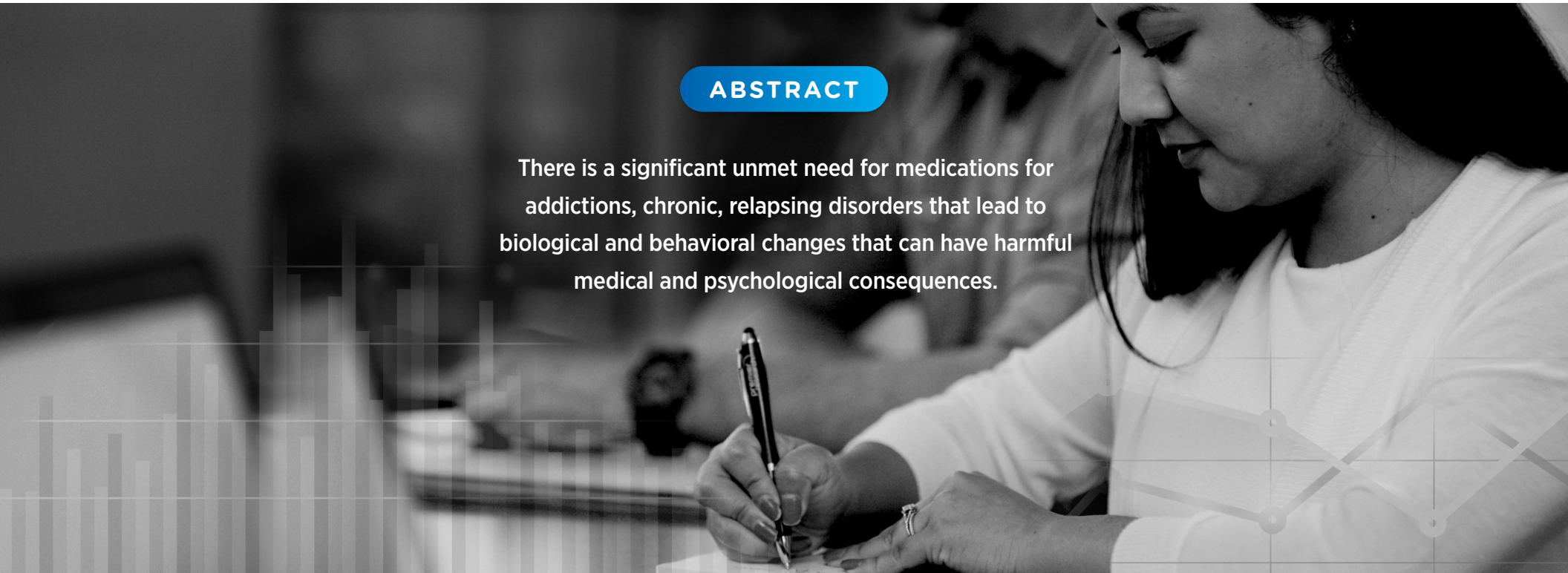
NEUROSCIENCE

Challenges in
Medication Development for Addictions



ABSTRACT

There is a significant unmet need for medications for addictions, chronic, relapsing disorders that lead to biological and behavioral changes that can have harmful medical and psychological consequences.

Introduction

Addictions are common, debilitating and costly disorders resulting in more than $740 billion a year in increased healthcare costs, crime, and lost productivity.[1] Multiple medications have been studied for the treatment of addictions, but only a few have been shown to be efficacious in well-controlled studies. To date, medications that have been approved by the U.S. Food and Drug Administration (FDA) target opioid, alcohol, and nicotine addiction, while no approved medications are available for cocaine, benzodiazepine, and other addictions. Further, even when an approved medication is available for treatment, only a fraction of patients receive medication-assisted therapies.

In this white paper, we present an overview of the medications that have been developed for addictive disorders, the study endpoints that have been used for market approval, and the challenges companies may face when developing medications for addictive disorders.

Background on addictions

Addiction is defined as a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful medical and psychological consequences.[2] The behavioral changes associated with addiction are also accompanied by changes in brain functioning, especially in the brain's natural inhibition and reward centers. In fact, brain imaging studies from people addicted to drugs show physical changes in areas of the brain that are critical for judgment, decision-making, learning, memory, and behavior control.

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Each year, illicit and prescription drugs and alcohol contribute to the death of more than 130,000 Americans, while tobacco is linked to nearly half a million deaths per year.[3,4,5]

The molecular mechanisms that lead to addiction are well understood. Nearly all addictive drugs directly or indirectly target the brain's reward pathways by flooding the circuit with dopamine. Overstimulation of these pathways produces the euphoric effects sought by people who abuse drugs and teaches them to repeat the behavior. Interruption of drug use is associated with withdrawal and craving, which are alleviated by using the drug again. This makes it difficult for those who are addicted to resist relapse, making addiction very similar to other chronic relapsing-remitting disorders.

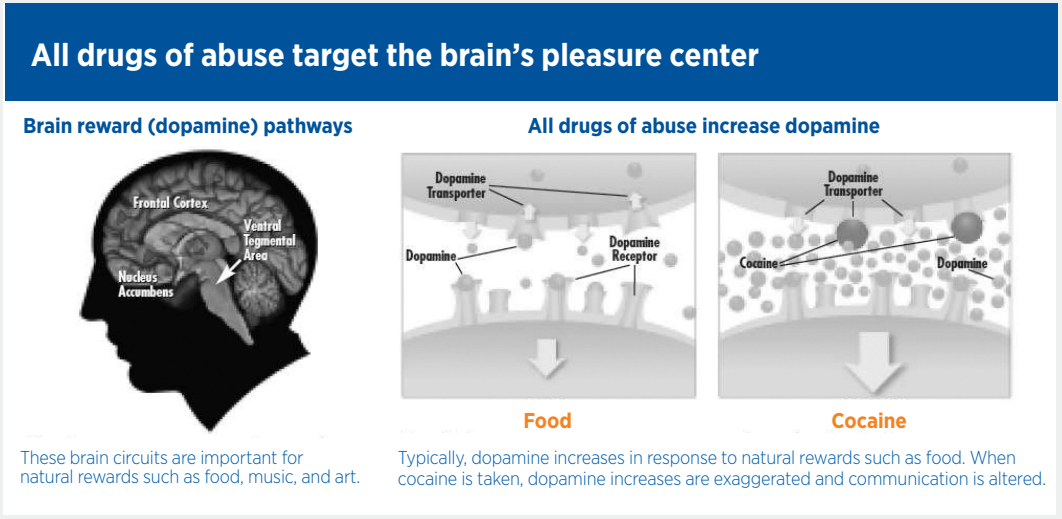

Figure 1. Pathophysiology of addiction[2]

While the pathophysiology of addiction is well understood, susceptibility to addiction is less well defined. What is known is that genetic heritability, personal choice, and environmental factors all play a role in the risk for addiction.

If left untreated, addiction can lead to negative outcomes, such as overdose, hepatitis C, human immunodeficiency virus (HIV) infection, or even death. Effective medical treatments are available for some types of addiction, which may help patients with addiction progress to lead meaningful, productive lives.

Scientific definition of addiction

Addiction is not considered a specific diagnosis in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Rather, DSM-5 uses the term "substance use disorder," which is defined as a problematic pattern of use of an intoxicating substance leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:[6]

Biological symptoms

+ Craving, or a strong desire or urge to use the substance
+ Tolerance, as defined by either
  - A need for markedly increased amounts of the substance to achieve intoxication or desired effect, or
  - A markedly diminished effect with continued use of the same amount of the substance
+ Withdrawal, as manifested by either
  - The characteristic withdrawal syndrome for that substance, as specified in the DSM-5 for each substance, or
  - The substance, or a closely related substance, is taken to relieve or avoid withdrawal symptoms

Behavioral symptoms

- The substance is often taken in larger amounts or over a longer period than was intended
- There is a persistent desire or unsuccessful effort to cut down or control use of the substance
- A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
- Recurrent use of the substance resulting in a failure to fulfill major role obligations at work, school, or home
- Continued use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use
- Important social, occupational, or recreational activities are given up or reduced because of use of the substance
- Use of the substance is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
- Recurrent use of the substance in situations in which it is physically hazardous

DSM-5 also provides guidance on classifying the severity of substance abuse disorder.

- Mild: 2-3 symptoms
- Moderate: 4-6 symptoms
- Severe: 6 or more symptoms

Epidemiology of addiction

Addictions are common in the U.S., as seen in Figure 2.

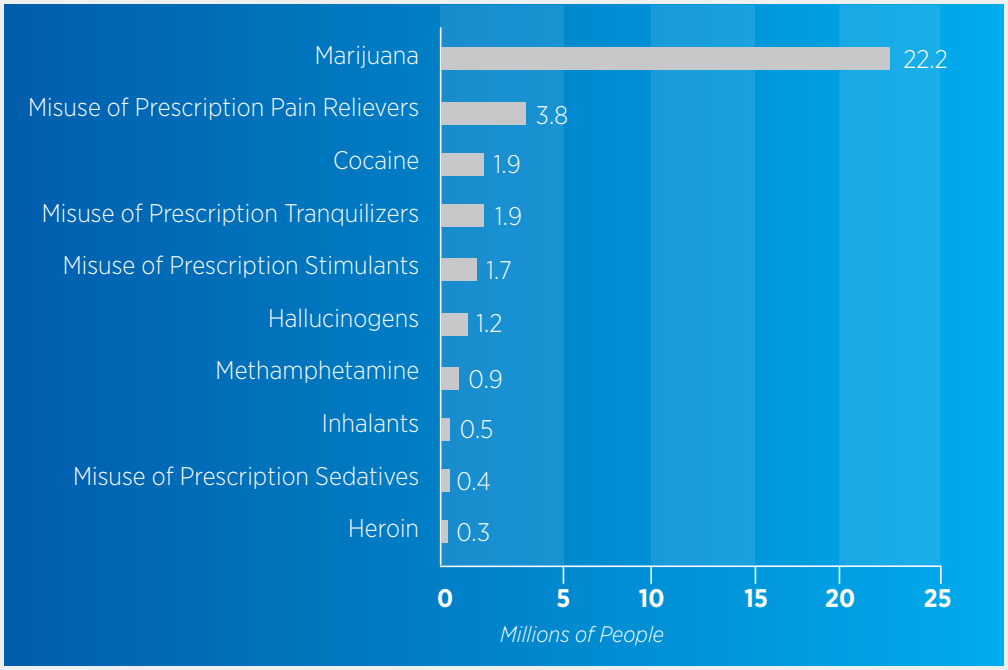

Figure 2. Prevalence of addiction in the U.S.[7]

Recent data show an increase in heroin addiction and heroin-related overdose death, which increased nearly six times in the period from 2002 to 2015 (see Figure 3). There has also been an increase in the number of deaths from prescription opioid pain relievers, with an estimated 183,000 deaths since 2000.[1]

Alcohol use disorder (AUD) is also common in the U.S., with an annual economic burden of approximately $223.5 billion. According to recent data, the lifetime prevalence of alcohol dependence in the U.S. is 29.1 percent, and 10 percent of children live with a parent who has AUD. An estimated 88,000 people die each year from alcohol-related causes, making alcohol-related death the third leading preventable cause of death in the U.S.[9]

Tobacco still results in the highest number of deaths among all addictions, but rates of smoking are slowly declining.[10] However, cannabis use rates have been increasing steadily since 2007.

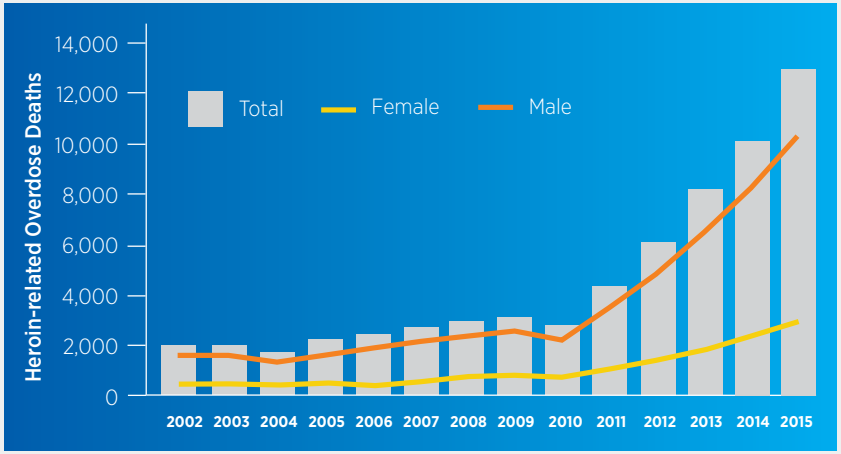

Figure 3. Heroin addiction and heroin-related overdose death[1]

Opioid Addiction	Alcoholism	Tobacco
+ Methadone	+ Naltrexone oral	+ Nicotine replacement
+ Buprenophine	+ Naltrexone depot IM	+ Varenicline
+ Naltrexone depot IM	+ Acamprosate	+ Bupropion
+ Naloxone (OD only)	+ Disulfiram	

Figure 4. FDA-approved medications to treat addictions

Tobacco still results in the highest number of deaths among all addictions, but rates of smoking are slowly declining.

Medications that have been developed for addictions

The FDA has approved a number of medications to treat opioid, alcohol, and tobacco addictions (see Figure 4).

The mechanism of action for these medications may be:

1. **Aversive**, e.g., disulfiram, which blocks the metabolism of alcohol and results in the accumulation of a toxic intermediary called acid aldehyde, which causes the user to feel sick
2. **Receptor agonism**, e.g., methadone, buprenorphine, nicotine replacement, and varenicline, which replace the addictive substance with a drug that is less harmful or less euphoric
3. **Other central nervous system (CNS) mechanisms**, such as gamma-aminobutyric acid (GABA) or dopamine receptor blockade, e.g., naltrexone, naloxone, acamprosate, and bupropion

To date, there are no approved medications for the following addictions:

+ Stimulant Use Disorder, which includes cocaine and methamphetamine abuse
+ Sedative/Anxiolytic/Hypnotic Use Disorder, which includes benzodiazepine abuse
+ Cannabis Use Disorder
+ Hallucinogen Use Disorder
+ Dual diagnosis, which includes a combination of mental illness and addiction

FDA-accepted study endpoints for addiction studies

The study endpoints that have been accepted by the FDA for addiction studies vary depending on the type of addiction:

+ **Opioid addiction**. Urine drug screening for opiates has been accepted as a valid endpoint for opioid addiction studies.[11]
+ **Smoking cessation**. For smoking cessation, based on a review of the approval package for varenicline, the FDA expects abstinence throughout treatment following a pharmacologically-justified grace period, with a primary endpoint of self-reported abstinence confirmed by exhaled carbon monoxide measurement.[12]
+ **Alcoholism**. According to the FDA guidance on developing drugs for the treatment of alcoholism, trials showing a difference in the proportion of patients who attain or sustain abstinence may support an indication of treatment for alcoholism. Further, the guidance indicates that analyses of existing data also support the use of another valid surrogate endpoint defined by a pattern of reduced drinking, described as 'no heavy drinking days.' Heavy drinking days are defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as days when the patient consumes more than four standard drinks (men) or more than three standard drinks (women).[13]

Challenges of developing medications for addictions

There are a variety of challenges associated with the development of medications for addictions.

Patient-related challenges

Addiction is associated with a social stigma, which may delay or deter a patient from seeking treatment or participating in research. Patients with addiction may also suffer from a lack of support, which can limit access to treatment. In addition, traditional treatment approaches for addiction often do not support the use of medications to maintain sobriety.

The inherent nature of addiction can also lead to patient-related challenges such as:

+ **Relapse and retention in treatment.** In a Swedish study of heroin dependence, patients were randomly assigned to daily buprenorphine or a tapered six-day regimen of buprenorphine followed by placebo. One-year retention in treatment was 75 percent in the daily buprenorphine group and zero percent in the placebo group, highlighting both the challenge of retaining patients in a clinical trial and the potential risk of relapse.[14]
+ **Polysubstance abuse.** Use of multiple substances is common. People who are addicted to alcohol, marijuana, cocaine, and prescription opiate painkillers are more likely to also be addicted to heroin (see Figure 5). Suppressing one addiction while leaving another untreated still leaves patients at risk for the medical and social consequences of addiction, and can impact clinical trial participation. One approach for addressing this challenge is to narrow the clinical trial population to patients with an addiction to only one substance.

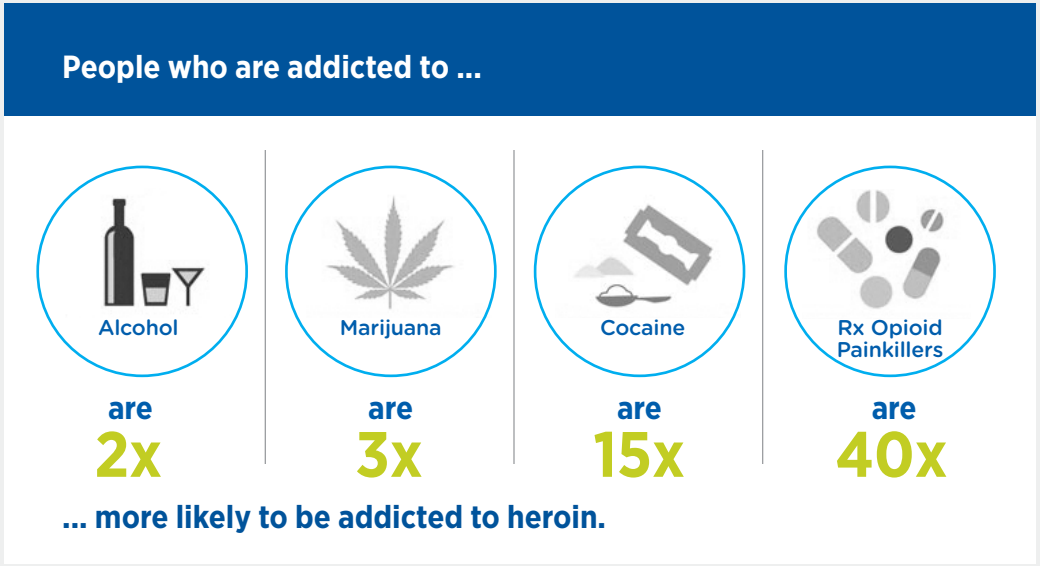

Figure 5. Risk of polysubstance abuse[15]

Regulatory challenges

For many forms of addiction treatment, there is no standard or defined regulatory pathway. For example, for cocaine and benzodiazepine dependence, regulatory authorities have not yet provided guidance regarding what level of reduction in use constitutes clinically meaningful change, or whether the trials should be designed to test if complete abstinence can be achieved. While there has traditionally been a lack of interest by large pharmaceutical companies in developing medications for addiction, recent years have seen an increased interest in this space.

Operational challenges

Operational challenges associated with the conduct of a clinical trial for an addiction medication include:

Detoxification before treatment. For many indications, detoxification is required before treatment. In some cases, a medication only works — or is more effective — when the patient has undergone detoxification. When recruiting clinical trial sites, sponsors should check that sites have the detoxification capability, or can work in collaboration with a detoxification facility.

Patient retention. As mentioned earlier, patient retention can be difficult and relapse is common. Frequent engagement in the form of phone calls and texts, as well as short duration between study visits, may help in addressing these challenges.

Patient-reported outcomes. Another challenge from an operational perspective is ensuring that clinical trial endpoints which rely on patient recollection of use, such as the timeline followback, are collected uniformly across the investigative sites. For these types of endpoints, training and certification of the principal investigators is very important.

Compliance with the study drug. Poor adherence to study medication can obscure results in any clinical trial, and it is unknown whether compliance is any more problematic in patients with addiction than in other populations. In a clinical trial of

vigabatrin for cocaine dependence, there were no significant differences observed between the vigabatrin group and the placebo group on the primary outcome measure of cocaine abstinence as assessed by self-reports and quantitative urine drug screens. However, post-hoc vigabatrin urine concentration levels suggested that approximately 40 to 60 percent of patients assigned to vigabatrin may not have been adherent, and this lack of adherence may have obscured any evidence of efficacy.[16] As with the challenge of patient retention, frequent reminders and short duration between study visits may be useful in improving compliance.

Scheduled study drug. The use of scheduled study drugs may limit the number of eligible clinical trial sites due to the requirement of certain licenses to prescribe scheduled drugs. It also increases the amount of paperwork and requires special storage. Providing assistance and guidance to obtain these licenses can help otherwise qualified sites to participate in clinical work.

Abuse liability and diversion of the study drug. If the study drug has abuse liability, the FDA has provided guidance on its handling. According to this guidance, sponsors should make every effort to do the following:[17]

+ Set criteria, collect data, and tabulate the abuse, misuse, noncompliance, and diversion cases across the studies and study sites with special attention to aberrant drug behaviors that may be indicative of drug abuse, misuse, and/or diversion
+ Provide complete information, including case report forms and final outcomes, on all instances of addiction, abuse, misuse, overdose, drug diversion/drug accountability, discrepancies in amount of the clinical supplies of the study drug, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons why subjects dropped out of the study. Implementing a study-wide Drug Diversion Plan that is signed by any site member that comes in contact with the study drug is a good way to mitigate this challenge.
+ Provide information on the risks of addiction, abuse, misuse, overdose, and drug diversion in the study populations

Conclusion

There is a significant unmet need in the area of medications for addictions, representing substantial opportunity for sponsors to bring more effective medications to market. Growing public awareness of the magnitude and impact of addiction, as well as recent advances in the development of medications for addiction, are making a difference for people who are struggling with substance abuse. With so much work still to be done, understanding the challenges of addiction clinical trials — and developing strategies to address them — will help sponsors increase their likelihood of success.

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Krista Armstrong has held leadership roles for Project Management and Operations delivery at Premier Research and now oversees the Neuroscience Business Unit. This Business Unit includes Premier's most experienced neuroscience clinical research professionals for psychiatric and neurological indications to ensure that the team provides sponsors with the best possible regulatory, scientific, medical, and operational delivery advice. Dr. Armstrong's primary therapeutic and operational expertise has had a specific emphasis on psychiatric indications such as ADHD, schizophrenia, mood disorders, ASD, eating disorders, substance use disorders, and PTSD as well as neurological conditions such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy, and stroke.

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