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Conducting Psychedelic Clinical Trials

FIVE LEGAL CONSIDERATIONS TO ENSURE COMPLIANCE AND SUCCESS

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Psychedelic drugs are currently the subject of multiple clinical trials and are making scientific news as potential life-changing therapies for disorders such as posttraumatic stress disorder (PTSD), major depressive disorder, obsessive compulsive disorder, short-lasting unilateral neuralgiform headache attacks (SUNHA), fibromyalgia, anxiety disorders, and behavioral conditions such as cocaine use, smoking cessation, and binge eating disorder.

Most psychedelic clinical trials differ from traditional pharmaceutical trials because there is a therapy component in addition to the administration of the medication. For example, in a traditional pharmaceutical clinical trial, the researcher administers an experimental drug meant to treat a physical ailment and monitors the subject. By contrast, psychedelic clinical trials administer the drug in a clinical setting and then conduct talk therapy (also known as integration sessions) with the subject. This novel modality of treatment—involving both a prescribing physician and a licensed therapist—could establish closer to a physician-patient relationship than traditional trials (although its classification is yet undecided by the legal system), making risk management and insurance coverage even more important. Below, I explore five legal considerations for entities wishing to conduct psychedelic clinical trials.

1. FDA approval of IND applications

The clinical trial process for Schedule I substances involves both DEA and FDA regulatory processes such as registrations, licenses, and inspections, as well as state and local laws where applicable. FDA's Manual of Policies and Procedures (MAPP) from the Center for Drug Evaluation and Research (CDER) establishes responsibilities and procedures for Controlled Substances

Staff within CDER to review research protocols sent by DEA.[1] The only time a Schedule 1 drug can be used legally is through research (DEA Form 225).

For clinical investigations, researchers are first required to submit an IND to FDA [referred to in the regulation as a "Notice of Claimed Investigational Exemption for New Drug (IND)." See 21 C.F.R. 1301.18(b).] In early preclinical development, the sponsor must focus on collecting data and information necessary to establish that the product (new drug) will not expose humans to unreasonable risks when used in limited, early-stage clinical studies. The IND application must contain information in three broad areas:

1. Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans.
2. Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product.
3. Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, the FDA has an opportunity to review the IND for safety to assure that research subject will not be subjected to unreasonable risk. This approval process may be tricky to navigate, and sponsors should consider consulting a regulatory specialist to avoid a clinical hold.

2. DEA registration

Federal law requires researchers conducting clinical trials with Schedule I drugs under an IND to have a DEA research registration. 21 CFR part 1301.18. All psychedelics being used in clinical trials are currently Schedule I drugs under the Controlled Substances Act (CSA). Whenever a sponsor of a clinical trial transfers controlled substances between locations in the United States, the receiving party must have a DEA Form 222 and order the substances via a registered form. The goal of the regulatory scheme is to create a "closed system" of distribution in which only authorized handlers may distribute controlled substances. Individuals or entities that work with controlled substances are required to register with DEA, which has created a dedicated web portal [2]for submitting an application through the agency to conduct a research on Schedule I substances. Researchers still need a research registration from DEA and FDA.

Only entities who actually handle the drug are required to be DEA registrants. See 21 C.F.R. § 1301.11. Registrants must maintain records of transactions involving controlled substances, establish security measures to prevent theft, and monitor for suspicious orders to prevent misuse and diversion. Thus,

the registration system aims to ensure that any controlled substance is always accounted for under the control of a DEA-registered person until it reaches a patient or is destroyed.

IND and IRB approved protocols are required to apply for the DEA license. If a site already has the requisite Schedule I licensure, the DEA review period typically takes 4-12 weeks. The site itself needs to be registered as well as the investigator for handling the substance. Schedule I licensing of a site may be difficult and subject to many delays. Physical inspections are mandatory. Clinical sites that do not yet have the requisite licensure can expect delays exceeding six to 12 months or longer. As such, it is advisable to seek the assistance of a regulatory professional with regard to DEA licensure.

3. Insurance

Insuring a biotechnology company is more expensive than insuring a traditional company, and this is especially so for those working with Schedule I drugs. This is because of the inherent risk associated with working with Schedule I drugs and the increased complexity of DEA compliance. Adequately insuring a psychedelic clinical trial, although expensive, is an indispensable layer of protection for the directors, officers, researchers, and subjects. If a clinical trial is not properly insured, one unprotected liability could use the entire funding of a clinical trial. Below are some of the types of insurance that are recommended for sites and clinicians running psychedelic-therapy trials.

Clinical Trial Insurance

Clinical trial insurance covers (1) personal damage due to physical injury or illness of subjects, (2) material damage to equipment, and (3) damage due to data breaches related to the clinical trial.[3] Although the United States does not require clinical trial insurance, many countries such as Canada and Mexico do. Despite the fact that it is not required in the United States, clinical trial insurance is tailored to cover common liability issues associated with clinical trials and is a good starting point when considering MDMA clinical trial insurance policies.

General/Commercial Liability Insurance

Most general liability insurance policies cover claims for bodily injury, even those that occurred as a result of emotional distress.[4] While malpractice insurance (discussed below) could cover some claims, general liability insurance casts a wider net in protecting companies from negligence claims.

While a clinical trial may have thorough reviews and safe policies, plaintiffs often sue the clinical trial researcher for employees' and others' negligence. This could be for anything from a subject falling in the parking lot on their way into the building to emotional distress from the trial. A commercial liability insurance policy acts as an invaluable safety net for negligence claims.

Malpractice Insurance

A plaintiff to a medical malpractice claim must prove (1) there was a physician/patient relationship, (2) the standard of care recognized by the medical community, (3) the physician's departure from that standard of care, and (4) that the departure caused the plaintiff's injury. For MDMA and other psychedelic-related clinical trials, it is unclear whether courts will find that the therapists and other researchers have a physician/patient relationship with the subject. The other issue is the applicable standard of care. The standard of care in clinical trials is constantly evolving and varies based on location. While clinical trials must balance efficiency with a high standard of care for subjects, clinical researchers must protect themselves from liability for medical malpractice suits. Although the applicable standards have not been set, a subject may eventually claim medical malpractice. Fighting that legal battle without a medical malpractice policy funding a legal defense would prove costly for researchers.

There are multiple types of medical malpractice insurance policies, and cost varies based on numerous factors; however, a typical policy will cover attorney fees, court costs, arbitration costs, settlement costs, punitive and compensatory damages, and medical damages.

Products Liability Insurance

For a products liability case, a plaintiff must prove (1) the product distributed caused the injury, (2) the defect existed at the time it left the manufacturer's possession/at the time of sale, and (3) the defect made the product unreasonably dangerous. It has been noted that "the biotechnology industry has been relatively safe from products liability lawsuits. As the number of human pharmaceuticals in distribution or in the pipeline for distribution to the public increases, however, it seems likely that products liability litigation may emerge."[5] In this case, the product would be the psychedelic drug. A products liability insurance policy can protect research trials by providing coverage against claims for any bodily injury or unlawful death caused by the drug itself.

Cyber/Data Breach Coverage

Cyber/data breach is a relatively new source of liability. As all medical facilities move toward storing data electronically, the facilities become vulnerable to hackers stealing patient data. The numbers speak for themselves: "[s]ince 2009, about 29 million patient health records have been compromised, with a shocking 138% increase [from] 2012 to 2013 alone. Accounting for this rapid increase in data breaches is the widespread adoption of electronic health records in order to reduce medical errors. Unlike its traditional paper-file counterpart, electronic records can be stored in massive quantities, millions of files on a single laptop hard drive."[6]

Hackers need but a small vulnerability to hack the entire system. Besides having a secure, encrypted data management system, clinical research trials of all types would benefit from having cyber/data

breach insurance. The cost and type of cyber/data breach coverage depends on the size of the operation and the nature of the policy.

Directors and Officers Insurance

Directors and Officers (D&O) insurance protects directors and officers against suits from employees, subjects, vendors, and more for costs such as attorneys' fees, settlements, judgments, etc. "[D&O] insurance can help your company if the directors and officers are accused of wrongdoings such as: causing a financial loss or bankruptcy, failure to comply with workplace laws, misrepresentation of company assets, theft of intellectual property, slander, libel and copyright infringement, mismanaged funds, and discrimination against an employee."[7]

"Lawsuits targeting directors and officers are becoming more common. Without D&O insurance, the company's assets and the personal assets of the directors and officers are at risk. In addition, [D&O] insurance protects the personal assets of spouses of a director or officer. These assets could also be at risk in a lawsuit."[8] Types and costs of insurance vary on circumstance. Securing D&O insurance is important not only for insuring current directors and officers, but offering protection for potential new directors and officers.

Commercial Property Insurance

"Commercial property insurance protects commercial property from such perils as fire, theft, and natural disaster."[9] Any psychedelic research trial should consider insuring the building, all equipment, company documents, inventory, signs, and any other tangible property on the premises.

Medical equipment of any type can be expensive. Insurance coverage can keep a headache from becoming a financial disaster in the event that a natural disaster or thief wreaks havoc on the research site.

EPLI Insurance

Employment practices liability insurance (EPLI) covers an employer from suits by employees. These claims include but are not limited to claims of discrimination, wrongful termination, negligent evaluation, wrongful infliction of emotional distress, and many other potential lawsuits.

While proper management, including hiring processes that prevent discrimination, clear and visible corporate policies, and appropriate and thorough documentation, is the best way to mitigate successful claims by employees, EPLI shields a company from potential lawsuits where supervising employees fail to follow protocol. Over the course of psychedelic research, management must constantly supervise employees and revise therapeutic practices. EPLI insurance is a key component to a risk management system to protect from wrongful evaluation and termination claims.

Umbrella Insurance

Umbrella insurance policies are your insurance policy's insurance policy. Most every insurance policy has a cap, whether it is $50,000 or $10,000,000 or somewhere in between. An insurance cap limits the amount of money that an insurance company will pay in defending a claim. Once that cap has been reached, plaintiffs can pursue a judgment against the company or the directors. For example, if a plaintiff gets a judgment against a company for $400,000, and the company only has general liability insurance for $100,000, the company and potentially the directors are on the hook for the remaining $300,000. The umbrella insurance provides funds for the excess amount that insurance will not cover.[10] Commercial umbrella insurance policies are available for $1 million to $15 million.

The purpose of clinical research trials is to test the safety and efficacy of a drug. Uncertainty is inherent with testing. While a general liability policy may cover what you can anticipate at the time an insurance policy is chosen, an umbrella policy protects your company from unforeseen liability.

4. Using digital health tech in your clinical trial (apps & devices)

Digital therapeutics, like most new telehealth programs, are racing to keep up with medical needs and concerns. The software programs used in digital therapeutics usually have underlying artificial intelligence capabilities to analyze big data sets and predict outcomes. Many clinical researchers are seeking to use digital health technologies in their trials to enable passive data collection which could ease data collection of certain biomarkers. Wearable devices can lessen the need for participants to travel to a physical site, which can enable organizations to recruit patients and diversify clinical trials participation and may boost participant retention because of better patient monitoring.

Many sponsors are choosing to use digital health technologies in their clinical trials. There are no federal privacy laws; however, there are at the state level. Some lawmakers are trying to rein in health data sharing. California State Assembly member Rebecca Bauer-Kahan introduced a bill in February that could redefine "medical information" in the state's medical privacy law to include data gathered by mental health apps. Among other things, this would prohibit the apps from using "a consumer's inferred or diagnosed mental health or substance use disorder" for purposes other than providing care. It is advisable that researchers choose vendors that have the appropriate certifications to ensure privacy and address cybersecurity issues and work with regulatory counsel to ensure compliance with evolving legal standards for digital health technologies.

5. Informed consent

Informed consent and preparation of the trial participants will become a key consideration for your clinical trial. It is the investigator's responsibility to protect rights, safety and welfare of subjects and

obtain informed consent of each subject. The consent form that will be used needs to be approved by the Institutional Review Board (IRB).

Good Clinical Practice mandates that the investigator obtains informed consent. Each subject must provide legally effective informed consent prior to participation in the study unless waived by the IRB or it is emergency research. Consent may not include exculpatory language by which subject appears to waive legal rights. It is more than a document; it is a process. It must not be coercive. The consent must be in a language understandable to the subject. The investigator cannot obtain the consent until the subject has been given an opportunity to discuss study with others before consenting. Additionally, the subject must be given an opportunity to have any questions answered prior to consenting. And the subject must be provided a copy of signed/dated consent form. The consent must notify that medical information collected during study may be disclosed to other entities including the sponsor, the IRB and the FDA. 21 CFR Part 50, et seq. A common FDA inspection finding includes failure to obtain and/or document the subject's consent and a finding of inadequate informed consent forms used.

Psychedelic-mediated therapy requires ongoing consent, especially when it comes to touch. Consent for touch should be obtained at intake and during the therapy sessions.[11] At intake, providers should discuss with the potential patients the purpose of therapeutic touch, at what points it could be used, and where on the body it will be used.[12] Providers should also assure patients that there will not be any sexual touch.[13] During the sessions, providers should once again ask for consent to touch, unless the patient is in imminent harm.[14] The MAPS manual for MDMA-assisted therapy only allows for two types of touch: nurturing touch and focused bodywork touch.[15] Nurturing touch involves actions such as holding the patient's hand or patting them in the back when they are agitated.[16] Focused bodywork touch involves the provider "offering resistance for the patient to push against."[17] Consent for touch is always important, but it is especially important when treating patients who suffer from PTSD due to sexual assault. [18] Due to its ongoing nature, consent should be at the forefront of providers' minds at every step of the process.

Conclusion

Psychedelics are once again the subject of much research and excitement over its potential use to treat debilitating conditions and behaviors. While the stigma around researching psychedelic substances may be waning, their use in clinical trials may be held to a higher level of scrutiny. With the myriad of regulations and laws for sponsors to navigate, it is advisable to seek ongoing advice from professionals to not only ensure compliance but smooth interactions with regulatory agencies in order to avoid clinical holds and prevent the shut down of an investigator site.

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[1] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp

[2] https://www.deadiversion.usdoj.gov/drugreg/index.html

[3] *Clinical Trial Insurance: Coverage, Claim & Exclusion*, paisabazaar (July 15, 2022).

[4] Allison Zamani, *Insurance Coverage for Practitioners of Ketamine-Assisted Psychotherapy*, Insurance Coverage Law Center (2022).

[5] Michael Traynor & Erin Wallace, *Clinical Trials: Emerging Issues Regarding Globalization of Pharmaceutical Research, Insurance, Informed Consent, Securities Litigation, And Public Policy*, SN014 ALI-ABA 73, 87 (2007).

[6] Jes Alexander, *Anatomy of a Data Breach--What Cyber Policies Should Cover*, 13 J. Tex. Ins. L. 5, 12–13 (2015).

[7] Jason Metz, *How to Get Directors and Officers Insurance*, Forbes Advisor (July 15, 2022).

[8] Metz, *supra*.

[9] Julia Kagan, *Commercial Property Insurance*, Investopedia (July 15, 2022).

[10] Lacy Lazarony, *How to Get Commercial Umbrella Insurance*, Forbes Advisor (July 15, 2022).

[11] Shannon C. Carlin et al., *MAPS MDMA-Assisted Therapy Code of Ethics*, MAPS (Apr. 22, 2019).

[12] Id.

[13] Id.

[14] Id.

[15] Michael C. Mithoefer, *A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder*, MAPS, 11 (Aug. 19, 2015).

[16] Bethany Lindsay, s*upra* at 5.

[17] Id.

[18] Id.