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Clinical Research with Controlled Substances

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Controlled substances like MDMA (ecstasy), cannabis (marijuana), cannabinoids and many others are gaining attention for treating pain, psychiatric and other conditions.[1,2] Clinical research on these substances is subject to additional federal and state laws and regulations to ensure they are not misused or diverted for illicit purposes. Careful consideration of the additional resources necessary to conduct such research is therefore critical.

Federal Regulations

Under the Controlled Substances Act, the U.S. Drug Enforcement Administration (DEA) classifies controlled substances into five schedules, ranging from Schedule I (e.g., marijuana, heroin, LSD, etc.), which represent substances that have no legally acceptable medical use in the U.S. and a high potential for abuse, down to Schedule V (e.g., cough medicine with Codeine), which are considered to have acceptable medical uses and less potential for abuse.[3] DEA regulations set forth requirements for registration, security controls, handling, documenting, reporting and disposing of controlled substances. Even if a researcher is already registered with the DEA for clinical practice or research activities with Schedule II-V substances, a separate registration is required for Schedule I substances when used in research.[4] The National Institute on Drug Addiction (NIDA) Drug Supply Program (or another DEA-registered manufacturer) provides certain controlled substances and research chemicals, for example, research-grade marijuana, for qualified research studies. The Controlled Substances Act also governs the import of controlled substances into the U.S.

Food and Drug Administration (FDA) regulations apply to controlled substances, like any other drug. In addition, the following rules apply:

> If an investigational new drug is a substance listed in any schedule of the Controlled Substances Act (21 U.S.C. 801; 21 CFR part 1308), records concerning shipment, delivery, receipt, and disposition of the drug, which are required to be kept under this part or other applicable parts of this chapter shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, be made available by the investigator or sponsor to whom the request is made, for inspection and copying. In addition, the sponsor and investigator shall assure that adequate precautions are taken, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution. (21 CFR 312.58(b) & 21 CFR 312.69)

In addition to HIPAA, 42 CFR 2a – Public Health – Protection of Identity – Research Subjects protects the identity of participants in studies of alcohol and other psychoactive drugs, including controlled substances, "by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals." This is the regulation that created the certificates of confidentiality that the National Institutes of Health (NIH) can issue. The HIPAA statute includes a provision that HIPAA rules "supersede any contrary provision of state law" except those that address controlled substances. (1178(a)(2)(A)(ii))

Furthermore, the violation of a state or federal law related to controlled substances can lead to exclusion from Medicare programs. 42 CFR 1001 – Program Integrity – Medicare and State Health Care Programs states: "The OIG may exclude an individual or entity convicted under Federal or State law of a misdemeanor relating to the unlawful manufacture, distribution, prescription or dispensing of a controlled substance, as defined under Federal or State law." (42 CFR 1001.401)

State Laws and Regulations

Regulations pertaining to controlled substances vary by state, so it is essential to consult individuals with the necessary expertise. State laws and regulations can include requirements for licenses or other authorizations, along with fees and renewal periods, prior to engaging in research. States might classify controlled substances into different schedules than the DEA does. States often have specific requirements for the security (e.g., the type of safe, vault or cabinet used to store main and working stock), management, recordkeeping, inventory, reporting, and disposal of controlled substances.

State licenses and registrations require that controlled substances be stored, handled and administered in the locations specified in the application. Federal and state entities typically inspect these locations before issuing a license or registration. Ambulatory care locations (i.e., where medical care is provided to outpatients) that are not connected to a pharmacy might require additional communications with federal and state offices to confirm that the rules will be followed correctly.

Additional Responsibilities, Risks and Costs

Research on controlled substances requires sites to carefully plan the operational details of a study:

- Who will need to be involved with the study?
- How will study participants be recruited to ensure that their interest in the study is legitimate?
- Where will the study product be ordered, received, stored and administered or dispensed?
- If the study product will be dispensed, how and where will unused supplies be retrieved from subjects?
- How will retrieved, unused and expired study product be disposed of at the end of the study?
- Who will transport the study product, and with what security precautions?
- Who will account for the study product, regularly monitor related activities, and with what process?
- How will participant privacy and confidentiality be maintained?
- Who will train study and support personnel in these processes?
- How much will it cost to conduct the study in compliance with all the additional regulatory requirements?

The additional complexity of clinical studies on controlled substances increases the study budget for personnel time, qualified study personnel, and possibly the acquisition of equipment like safes and secure transport containers. Tasks like transporting study product from the pharmacy that one person would normally perform might require two authorized individuals. After administration, subjects might need to be monitored for serious or

unexpected adverse events by study personnel with the necessary expertise and qualifications.

Standard operating procedures and documentation of study activities, already essential to any clinical study, are even more important for research on controlled substances, especially their receipt, handling and disposition. Risk management plans should address possible protocol deviations, such as loss of study drug or documentation errors. The institution might need to provide additional support, guidance and monitoring of the study, and develop new policies, processes and training programs.

Everyone involved in the study, including the study sponsor, institutional review board, pharmacy, research compliance office, facility administrator, research administration, environmental health and safety office, security department, and local state and DEA field office contacts will need to be consulted as to existing policies and procedures, briefed on the study plan, and kept informed, as needed, as the study proceeds.

Sites new to clinical research on controlled substances should obtain advice from someone with the requisite experience to guide the site through the process. Investigators involved in research on a controlled substance who also hold the Investigation New Drug (IND) application with the FDA will require additional training on the study sponsor's regulatory requirements.[5] For multi-center studies with international participating sites, sponsor-investigators also need to consider regional and local regulations on using controlled substances in research.

Conclusion

Clinical research on controlled substances provides a unique opportunity for researchers to enrich the body of knowledge for treatment of serious medical conditions. However, because of their possible diversion for illicit purposes and the consequent additional layers of regulation, such research is more complex, time-consuming, expensive and riskier for the investigator and site. Thorough preparation, training, documentation and communications will translate into more cost-effective and faster study start-up and conduct, and ensure that clinical trials are conducted in compliance with the additional regulatory requirements.

References

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3. DEA Controlled Substances Act, Schedules of Controlled Substances 21 CFR §§ 1308.11 – 1308.15 (www.dea.gov)
4. Title 21 CFR §§ 1300 – 1321
5. Title 21 CFR §§ 312.50-312.70 Subpart D Responsibilities of Sponsors and Investigators

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