Identifying and Selecting Sites for Psychedelic Clinical Trials

A Call for a More Inclusive Approach

Introduction

Selecting the best investigators and sites to conduct clinical trials is an operational challenge that is well understood and managed by Contract Research Organizations (CROs) in most therapeutic areas. However, research into psychedelics is one clear exception as the number of clinics with the necessary credentials and experience is small while the number of clinical studies is increasing. The situation calls for a specialized site selection approach and very specific CRO knowledge.

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Over the past two decades, interest in exploring therapeutic effects of psychedelics has resurged in the US after being sidelined in the 1970's following the enactment of the Controlled Substances Act (CSA). And in the last six years in particular, researchers have opened scores of trials globally to test the potential of psychedelics as treatments for substance use disorders, pain, depression, end-of-life anxiety, post-traumatic stress disorder (PTSD) and, degenerative diseases, and others.[1]

Those spearheading this field of research face many obstacles, including cultural bias and regulatory prohibitions. The US Drug Enforcement Agency (DEA) has classified psychedelics as Schedule 1 substances, meaning that they've been deemed to have "no currently accepted medical use and a high potential for abuse."[2] They are thus subject to strict control mechanisms in how they are stored, handled, and administered. These controls, of course, extend to clinical trial sites, exacerbating the diffifficulties in identifying sites that are trained, equipped, and registered to participate in studies of psychedelics.

Here, we explain what to look for in selecting sites and cover the pros and cons of the various options for identifying and qualifying clinical sites for a psychedelic study.

An Upward Trend

Research into the therapeutic benefits of psychedelics began in the 1940's[3] and reached its peak in the 1960's and 1970's. With the enactment of the CSA in 1970, most such substances were classified as "drugs of abuse with no recognized medical value,"[4] and their manufacture, distribution, and administration became strictly controlled. Research interest therefore waned.

In recent years, however, the field has experienced a resurgence. A systematic search of the clinicaltrials.gov database has revealed that as of 2022, 105 clinical trials were registered to study psychedelics[5], including ketamine, lysergic acid diethylamide (LSD), MDMA, DMT, and psilocybin.

The Controlled Substances Act [7]

The goal of the CSA is to maintain a "closed system of distribution" for controlled substances by requiring those handling them to possess a Controlled Substance Registration Certificate from the DEA. Any use of a Schedule 1 substance must be associated with a clinical protocol, so every new protocol must be submitted to the DEA as an amendment to the initial application, whether or not it involves the same substance for which a registration certificate was previously granted.

Practitioners dispensing a controlled substance to a patient or research subject must abide by special control mechanisms. Researchers must be "properly registered and qualified." Furthermore, "all individuals and firms that are registered are required to maintain complete and accurate inventories, and records of all transactions involving controlled substances, as well as security for the storage of controlled substances."

Ideal Investigator/Site Characteristics

In both regulatory and practical terms, the ideal sites for conducting trials with psychedelics in the US, will have:

- An active DEA Registration for Schedule I Controlled Substances for the proposed principal investigator (PI) at the current site. The DEA has published a Researcher's Manual to help researchers understand how to comply with the Federal Controlled Substances Act at https://www.deadiversion.usdoj.gov/GDP/(DEA-DC-057) (EO-DEA217)_Researchers_Manual_Final_signed.pdf
- Operational experience with clinical research in Schedule I controlled substances. While experience with the specific study drug is ideal, experience with any Schedule I substance offers strong advantages to be considered during site selection.
- Clinical experience with the unique challenges in psychedelic research. This includes knowledge of how to establish an appropriate "set and setting" for conducting psychedelic research studies and experience in managing expectancy bias and any disappointment that arises. "Functional unblinding" naturally occurs when participants can tell that they've been given a placebo.
- Clinical experience with the indication and participant population.
- A minimum of two clinicians who have been trained, or are qualified to be trained, as facilitators who can guide the participant through the experience. Typically one of the two session facilitators must be Clinical Psychologists or Psychiatrists and/ or an appropriately trained medical doctor. Prior experience with psychedelic drug administration is extremely valuable.
- A Lead Rater with experience administering the Patient and Clinician Reported Outcome Assessments for the study.
- The appropriate facilities. The site should meet DEA physical standards for safeguarding these substances (DEA conducts site audits) and should be conducive to protecting the participant during a mind-altering/mystical/hallucinogenic experience. For example, sites should be outfitted with quiet, comfortable treatment rooms. Usually, these have a non-clinical décor.

While we focus on US-specific regulatory considerations in this white paper, many of the above characteristics apply to sites for studies conducted globally.

Sites with and without experience in psychedelics: The Pros and Cons

Does the candidate site meet all ideal site characteristics?

Yes

Advantages

- DEA license already in place AND the site has knowledge/experience with the registration process
- Experience with the unique study design elements in psychedelic research
- Awareness of challenges such as functional unblinding, expectancy bias, set and setting, role of psychotherapy

Disadvantages

- Relatively limited number of sites/ PIs that fit this description
- Competition for sites is high

No

Advantages

- Lower competition for sites
- Opportunity to build strong, lasting relationships between Sponsor and site

Disadvantages

- Higher upfront costs which could extend from training to outfitting the physical environment at sites or more site oversight
- Longer start-up timeline due to timeline for DEA Registration
- More intensive training required

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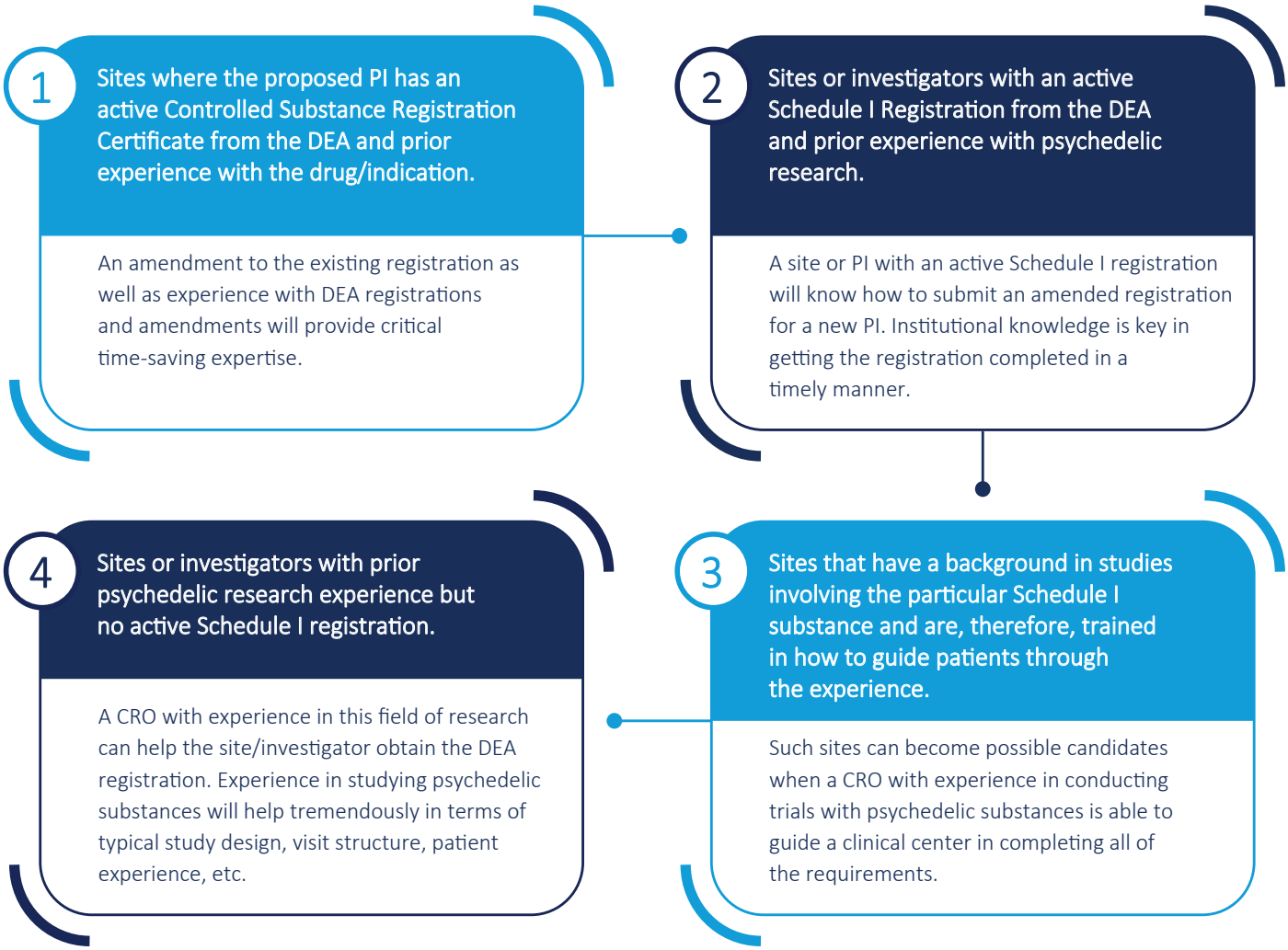
A Hierarchy of Preference

The competition for the relatively small number of sites that meet the above criteria means that Sponsors should not assume that they can achieve their recruitment goals by working only with those sites. As such, Sponsors may have to expand their search to include sites that may not meet all of the ideal site characteristics outlined above. As a CRO with experience managing site selection for psychedelic clinical trials, we find that not every site characteristic should be considered equally.

To evaluate the strength of a potential site without all of the ideal characteristics, Sponsors should consider sites according to this hierarchy:



In addition to working through a pool of possible sites in this order, Sponsors should also consider:

- The geographic distribution of sites. Ideally they are not all in one area so that participants are more demographically representative.
- State-specific requirements that may impact site feasibility. For example, California requires that proposed research studies using Schedule 1 substances to be reviewed and approved by the Research Advisory Panel of California (RAP-C)).

Advice for Sponsors

There is no “wrong” approach, as there are advantages to working with experienced sites as well as with sites that have no no experience in psychedelic trials. Often, practically speaking, the solution will be to pursue a hybrid approach that supplements a pool of sites that are characterized as “ideal” with those that the Sponsor/CRO must develop.

Don’t automatically discount the value of developing sites to become registered with the DEA. Such an investment can pay long-term dividends and prepare the site for future study participation.

One of the biggest disadvantages of expanding site selection to consider sites that are not yet registered is the impact on the study timeline. An experienced CRO will have a full understanding of the registration/training process and of the proper sequence of events so that some work streams can be conducted in parallel to save time.

The first critical step in site selection is actually CRO selection. The “right” CRO has experience in meeting all of the challenges of site selection to optimize the likelihood of success. A best practice is to conduct a feasibility assessment with potential sites and to request copies of any registrations to confirm the accuracy of what sites report.

Consult with experts as early as possible in the trial planning process. Involving an experienced CRO in study design and protocol development can directly serve the interests of site selection.

Conclusion

It is clear from the growing interest in studying the possible therapeutic effects of Schedule 1 substances that in the US, the demand for sites and investigators possessing all of the ideal characteristics exceeds the clinical community's current capacity. Sponsors entering this unique space might need to broaden their site/investigator search criteria and invest in sites that exhibit the potential to serve as leading sites in time.

While many of the regulatory considerations outlined in this white paper will vary, a CRO with a background in conducting Schedule 1 substance trials can advise you on the best site selection strategy, given the pros and cons of the various approaches – especially as they relate to the trial timeline. Because research into psychedelics is a highly specialized field subject to DEA regulation, opting to develop sites for their long-term potential is best undertaken with the help of a CRO that has demonstrated expertise in this area and understands what is required clinically, operationally, and legally.

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