Psychedelic Research in Human Subjects Studies: Emerging Science, Evolving Ethics, and What Massachusetts Researchers Should Know

By AnneMarie Mal

Interest in psychedelic-assisted therapies has expanded dramatically over the past several years, with studies investigating psilocybin, MDMA, LSD, and other psychedelic compounds. These therapies and compounds have been used for conditions including treatment-resistant depression, post-traumatic stress disorder (PTSD), substance use disorders, anxiety associated with serious illness, and obsessive-compulsive disorder. While the scientific literature continues to grow, so too do the ethical and regulatory considerations surrounding this unique area of human subjects research.

For investigators and Institutional Review Boards (IRBs), psychedelic research presents challenges that extend beyond traditional clinical trial oversight. Recent guidance from the FDA, discussions led by the Office for Human Research Protections (OHRP), and proposed legislation in Massachusetts all signal that this field is rapidly evolving.

A Growing Body of Clinical Evidence

Several high-quality clinical trials have demonstrated promising results for psychedelic-assisted therapy when conducted within carefully controlled clinical settings. One of the most widely cited studies from Johns Hopkins Medicine found that psilocybin-assisted therapy produced sustained improvements in many participants with major depressive disorder, with benefits lasting up to one year after treatment. While these findings are encouraging, researchers emphasize that psychedelic therapies remain investigational and should only be administered within regulated clinical environments until sufficient evidence supports broader clinical use.

At the federal level, the FDA continues to evaluate psychedelic compounds through the traditional drug development pathway. No classic psychedelic has yet received FDA approval for routine clinical use, making IRB oversight particularly important for protecting research participants.

FDA Guidance Signals Continued Growth

Recognizing the increasing number of psychedelic clinical trials, the FDA recently released its first draft guidance specifically addressing psychedelic drug development. The guidance provides recommendations for investigators designing clinical trials and highlights several unique considerations, including:

- Appropriate participant selection and psychiatric screening
- Enhanced informed consent processes
- Psychological support before, during, and after drug administration

- Safety monitoring during acute psychedelic experiences
- Long-term follow-up to evaluate delayed adverse events
- Standardization of therapist training and intervention protocols

The guidance also acknowledges that the therapeutic effect of psychedelics may be inseparable from the structured psychological support provided during treatment, creating additional complexities for study design and interpretation.

Ethical Considerations Beyond Traditional Clinical Trials

Psychedelic research raises ethical questions that differ from many other biomedical studies because these compounds intentionally alter consciousness, perception, and emotional processing.

Recent analyses from OHRP and bioethics researchers identify several areas requiring careful consideration:

Enhanced informed consent. Participants should understand not only potential physical risks but also the possibility of profound emotional experiences, temporary loss of normal perception, distressing psychological reactions, and the uncertainty regarding long-term effects.

Participant vulnerability. Many psychedelic trials enroll individuals with depression, PTSD, trauma histories, or terminal illness. These populations may be especially vulnerable to therapeutic misconception—the mistaken belief that research participation is intended primarily to provide individualized treatment rather than generate scientific knowledge.

Expectancy effects. Public enthusiasm and widespread media coverage may influence participant expectations, making it more difficult to distinguish true treatment effects from placebo or expectancy responses.

Boundary management. Because psychedelic-assisted therapy often involves lengthy preparation sessions, extended treatment visits, and integration therapy, maintaining appropriate professional boundaries between participants and therapists requires ongoing attention.

Long-term follow-up. Investigators should consider mechanisms for monitoring participants after study completion, particularly if psychological effects continue beyond the active treatment period.

These themes were central topics during OHRP's 2023 Exploratory Workshop on Ethical and Practical Considerations of Psychedelic Research, which emphasized that existing human subjects protections remain applicable but may require heightened attention when reviewing psychedelic protocols.

Safety Considerations

Human hallucinogen research has historically demonstrated that risks can be significantly reduced through careful protocol design. Best practices consistently include:

- Comprehensive psychiatric and medical screening
- Exclusion of participants with conditions associated with elevated psychiatric risk

- Continuous monitoring during dosing sessions
- Immediate access to qualified medical personnel
- Structured psychological preparation and post-session integration
- Clearly defined stopping rules and adverse event reporting procedures

For IRBs, reviewing investigator qualifications, therapist training, emergency procedures, and participant support plans becomes particularly important during protocol review.

Massachusetts: Legislative Momentum Continues

Although Massachusetts has not legalized psychedelic therapy, legislative interest continues to grow.

Representative Steven Owens introduced **H.2506**, which proposed targeted decriminalization of psilocybin for certain qualifying medical conditions. During the current legislative session, that proposal was incorporated into a new committee bill, **H.4986**, which would establish a five-site nonprofit therapeutic psilocybin pilot program across Massachusetts. Under the proposal, the Department of Public Health would develop regulations governing licensed therapeutic centers, facilitator qualifications, and operational standards. As of this writing, H.4986 has been reported favorably by the Joint Committee on Public Health and referred to the Joint Committee on Health Care Financing; it has **not** yet been enacted into law.

Importantly, these legislative proposals do **not** change the requirements governing human subjects research. Clinical investigations involving psychedelic compounds remain subject to applicable federal regulations, FDA requirements (when applicable), IRB review, and institutional oversight.

What This Means for Researchers and IRBs

As interest in psychedelic research continues to expand, investigators should anticipate increased scrutiny in several areas:

- Scientific justification for participant selection
- Risk minimization strategies
- Investigator and therapist qualifications
- Enhanced informed consent language
- Safety monitoring plans
- Emergency response procedures
- Data and Safety Monitoring Board (DSMB) oversight when appropriate
- Long-term participant follow-up

IRBs should similarly expect protocols that require multidisciplinary expertise, including psychiatry, psychology, pharmacology, and ethics.

Looking Ahead

Psychedelic research represents one of the fastest-growing areas of clinical investigation. While preliminary evidence suggests meaningful therapeutic potential for certain conditions, many

questions remain regarding long-term safety, effectiveness, equitable access, and implementation.

For HRPPs and IRBs, the challenge is balancing scientific innovation with participant protection. Existing federal regulations already provide a strong ethical framework, but psychedelic research highlights the importance of thoughtful protocol review, robust informed consent, careful safety monitoring, and continued attention to participant welfare throughout the research process.

As regulatory guidance evolves and state legislation continues to develop, investigators and IRBs should remain informed of both federal expectations and emerging state policy to ensure that research advances responsibly while maintaining the highest standards of human subjects protection.

Resources

Federal Guidance & Regulatory Resources

- FDA – Psychedelic Drugs: Considerations for Clinical Investigations (Guidance)
- FDA News Release – FDA Issues First Draft Guidance on Clinical Trials with Psychedelic Drugs
- FDA – Psychedelic Drugs Resource Center
- FDA Workshop – Advancing Psychedelic Clinical Study Design (January 2024)

OHRP / HHS Ethics Resources

- HHS – Exploring the Ethical and Practical Considerations of Psychedelics Research
- NIH VideoCast – OHRP Exploratory Workshop (2023)
- The New Amsterdam Psychedelic Law Blog – OHRP Workshop Presentation Summary

Research Ethics & Safety

- Ethical Issues and Recommendations in Psychedelic Research and Practice: A Scoping Review (PMC)
- Human Hallucinogen Research: Guidelines for Safety (PMC)

Clinical Research

- Johns Hopkins Medicine – Psilocybin Treatment for Major Depression Effective for Up to a Year for Most Patients
- Johns Hopkins Center for Psychedelic and Consciousness Research

Massachusetts Policy & Legislation

- Boston University – Supporting Possession and Regulated Use of Psychedelic Therapy
- Marijuana Moment – Massachusetts Lawmakers Approve Bills to Create Psychedelic Therapy Pilot Programs

- Massachusetts Legislature – H.4986: An Act Relative to Therapeutic Psilocybin Treatment Centers (Psychedelic Therapy Pilot Program)
- Massachusetts Legislature – H.2506: An Act Relative to Targeted Decriminalization of Psilocybin