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present

Reimbursement Pathways for Psychedelic Therapies in Europe

A project funded by Norrsken Mind

Paving the Way for Psychedelic Medicine in European Healthcare

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floris@blossomact.com

martingisby@magnetaraccess.com

psychedelicsandreimbursement.com

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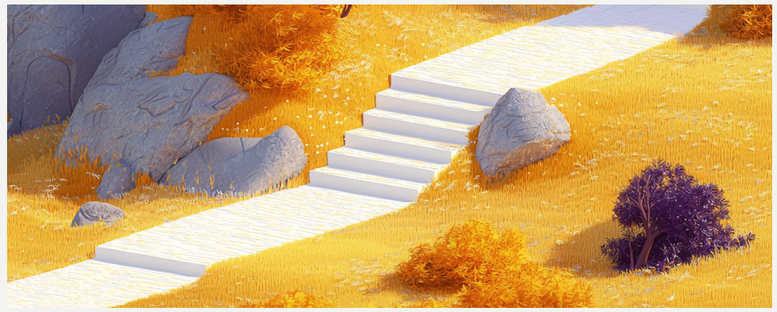


1.1 Overview of Psychedelic Therapies and Reimbursement Challenges

The Promise of Psychedelic Therapies

Mental health disorders impose a severe and growing societal and economic burden across Europe. Both national governments and the European Union (EU) now recognise that current treatments often fail to meet patients' needs. Treatment resistance is a significant challenge, with approximately 30-50% of patients across various mental health conditions showing limited or no response to conventional therapies. These 'treatment-resistant' patients face limited therapeutic options and incur the highest medical costs.

Psychedelic[1] therapies[2] have emerged as a promising option for conditions like depression, post-traumatic stress disorder (PTSD), and addictions. Although these interventions come with significant historical context and face multiple scientific and regulatory challenges, they represent the next wave of innovation in mental healthcare. Similar to previous therapeutic frontiers like cell and gene therapies, these interventions may also encounter significant reimbursement barriers.

For patients with 'treatment resistant' conditions, who represent approximately one-third of all cases, the current situation is particularly dire. The emergence of psychedelic therapies offers new hope, with research spanning academic, commercial, and non-profit initiatives. These novel approaches represent a potential paradigm shift in mental health treatment for those who have exhausted conventional treatment approaches. →

PTSD is one of the most promising fields for the application of psychedelic therapies. Phase III clinical trials of MDMA therapy have demonstrated remarkable efficacy, with 67% of participants no longer meeting PTSD diagnostic criteria after three sessions, compared to 32% in the placebo group (Mitchell et al., 2021; Mitchell et al., 2023).

For treatment-resistant depression (TRD), psilocybin therapy has shown considerable promise. A large-scale Phase IIb clinical trial across 22 sites in Europe and North America, involving 233 patients with TRD, demonstrated that a single 25mg dose of synthetic psilocybin, administered with psychological support in a controlled setting, led to a significantly greater reduction in depression symptoms at the three-week primary endpoint compared to the 1mg control group (Goodwin et al., 2022).

Ketamine-based therapies have already achieved regulatory recognition for depression, including TRD. In 2019, esketamine nasal spray received approval from the FDA and EMA, representing the first psychedelic treatment to gain widespread regulatory acceptance (EMA, 2019; FDA, 2019). The FDA later expanded its indication as a standalone treatment for TRD, eliminating the requirement for concurrent antidepressant medications (Johnson & Johnson, 2025). When evaluated in Germany's health technology assessment process, it received the second highest possible clinical benefit rating for TRD treatment, marking a significant milestone in the acceptance of novel psychiatric interventions (G-BA, 2023).

In addiction treatment, psychedelic therapies are showing promise across multiple substances. Early research in psilocybin therapy for smoking cessation showed 80% abstinence rates at six-month follow-up (Johnson et al., 2014), leading to expanded research, including a National Institute on Drug Abuse-sponsored double-blind trial of 66 patients with $1.5 million in funding (NIDA, 2023). For alcohol use disorder, both psilocybin and ketamine therapies have demonstrated encouraging results. Psilocybin therapy showed significant reductions in heavy drinking days (Bogenschutz et al., 2022), while ketamine therapy achieved a remarkable 86% abstinence rate over six months post-treatment (Grabski et al., 2022; Awakn, 2022). For opioid use disorder, NIDA has committed $15 million to investigate psilocybin's potential in reducing opioid cravings among patients on methadone maintenance therapy (B.More, 2024).

Regulatory approaches to psychedelic therapy have evolved significantly over time. Switzerland pioneered the medical use of LSD and MDMA through specialised clinics from 1988 to 1993. Since 2014, it has allowed restricted therapeutic access to multiple psychedelics (including LSD, MDMA, and psilocybin) through compassionate use programs (Liechti, 2019). Similar compassionate use frameworks in Canada provide controlled access to psilocybin and MDMA to patients with demonstrated unmet needs (Health Canada, 2023). More recently, Australia made a landmark decision to reschedule psilocybin and MDMA for therapeutic use under controlled circumstances, allowing psychiatrists to prescribe these treatments for specific mental health conditions (TGA, 2023).

In the United States, state-level initiatives have emerged on a different trajectory. Oregon and Colorado have established frameworks for regulated access to psilocybin services that operate separately from medical frameworks (Oregon Health Authority, n.d.; Colorado Department of Regulatory Agencies, n.d.). While groundbreaking, these state programs represent a distinct approach from the medical models seen in other countries.

These diverse regulatory approaches reflect different responses to mounting clinical evidence and urgent patient needs. Medical models like those in Switzerland, Canada, and Australia emphasise therapeutic frameworks with established clinical protocols and safety controls. Meanwhile, state-level U.S. initiatives offer insights into alternative regulatory structures. Together, these varied approaches provide valuable data and experience to inform future policy development in other jurisdictions. ■

[1] Psychedelics include classical psychedelics such as psilocybin (the active compound in "magic mushrooms"), LSD, DMT, atypical psychedelics like MDMA and ibogaine, and dissociative anaesthetics such as ketamine and its variant esketamine (approved for depression treatment as a nasal spray under the brand name Spravato). In this report, we focus primarily on emerging psychedelic compounds like psilocybin and MDMA, using ketamine-based treatments as a regulatory and market access reference point. While ketamine shares some mechanistic similarities with other psychedelics, it typically produces less pronounced alterations in consciousness and is generally classified separately in clinical and regulatory contexts.

[2] For brevity, we use the term 'psychedelic therapy' throughout this report. These interventions are more precisely described in the academic literature as 'psychedelic-assisted therapy' or 'psychedelic-assisted psychotherapy', emphasising the adjunctive role of the psychedelic compound within a broader therapeutic framework. Developers typically frame these interventions as 'psychedelic treatments' or 'psychedelic medicines'. We remain agnostic regarding optimal implementation models, and our terminology aims to capture the full spectrum of approaches—from pharmaceutical models prioritising the psychedelic compound to integrative therapeutic models where the drug serves as a catalyst within a comprehensive psychological treatment programme.

Current Reimbursement Landscape

In Europe, a new medicine must demonstrate safety and effectiveness through clinical trials. After regulatory approval by the European Medicines Agency (EMA) or national agencies, each country independently assesses whether the medicine should be included in its public healthcare system. Health technology assessment (HTA) bodies evaluate its benefits, risks, and costs compared to existing treatments before determining reimbursement coverage.

Despite encouraging clinical results, emerging psychedelic therapies will potentially face significant reimbursement obstacles that could create barriers to patient access. Reimbursement frameworks work best for simpler pharmaceutical prescribing models. They are often not optimised to evaluate and reimburse more complex treatment protocols, such as combining drug administration with supportive psychotherapeutic care. Implementation may also be challenging with respect to arranging local funding to establish a new care pathway.

The challenges facing psychedelic therapies mirror those encountered by advanced therapies such as cell and gene treatments, where significant improvements in efficacy and patient outcomes confronted substantial reimbursement barriers. These barriers included high upfront costs for therapy, limitations in HTA methodologies related to long-term outcomes analysis, and the need for new care pathways and local infrastructure.

The historical context of psychedelic compounds, drug scheduling controls, and implementation challenges within existing healthcare systems add further complexity. Additionally, there are practical and methodological challenges in meeting the gold standard for evidence reviews, particularly in conducting double-blinded randomised controlled trials (RCTs) due to the noticeable psychoactive effects and establishing comparisons against existing standards of care.

The cost burden of psychedelic therapies presents a significant access barrier. Current ketamine and esketamine treatments typically range from €3,000 to €12,000 per patient for a course of treatment lasting between 4 to 12 weeks, accounting for medication costs, clinical supervision, and clinician time. Future psychedelic treatment costs may reach even higher due to more intensive therapeutic protocols, drug costs (influenced by patents and market exclusivity), and dedicated treatment facilities. Without insurance coverage or reimbursement from national health systems, these costs will be prohibitive for most patients.

The current reimbursement landscape for novel mental health treatments varies significantly across Europe. While esketamine (Spravato) has achieved reimbursement in some countries, access to ketamine treatments often relies on out-of-pocket payment through private clinics, limiting availability to those with substantial financial resources. →

For emerging psychedelic therapies, healthcare payers are likely to express even greater hesitancy due to several factors:

1. **Regulatory Complexity:** International conventions classifying substances like psilocybin and MDMA as Schedule I drugs complicate their medical adoption and integration into healthcare systems.

2. **Evidence Requirements:** Despite promising clinical results, traditional HTA frameworks and payer expectations for comparative data and evidence packages may not align well with the unique characteristics of psychedelic therapies.

3. **Health System Integration Challenges:** The perceived need for specialised settings, trained therapists, and multi-hour dosing sessions poses logistical and financial challenges that current reimbursement systems would find difficult to handle.

The absence of clear regulatory, reimbursement, and access pathways for emerging psychedelic therapies creates significant uncertainty for multiple stakeholders. Healthcare providers may hesitate to invest in training and infrastructure without assured compensation pathways. Similarly, developers and investors face challenges in planning appropriate clinical studies that will satisfy both regulatory and reimbursement requirements while building necessary health system infrastructure. The experience with ketamine and esketamine integration demonstrates that these challenges are real and suggests that the barriers for emerging psychedelics may be even more substantial without proactive planning and stakeholder engagement. ■

Purpose of the Report

This report addresses challenges to reimbursement and access of psychedelic therapies in Europe. By exploring how these treatments can integrate into European healthcare systems, the report aims to bridge the gap between clinical results and patient access. Through analysis of the current landscape, the report identifies barriers to reimbursement and proposes solutions within existing frameworks.

Key objectives include:

1. **Mapping the Reimbursement Landscape:** Providing a clear and detailed overview of current reimbursement pathways and insurance coverage across Europe, focusing on Germany, the Netherlands, the United Kingdom, and the Czech Republic. This involves identifying gaps specific to psychedelic therapies and understanding how existing reimbursement and insurance models can accommodate or hinder their integration.

2. **Stakeholder Engagement:** Summarising insights from engaging with payers, regulatory bodies, drug developers, healthcare professionals, and patient advocacy groups. The report captures the multifaceted challenges and opportunities associated with reimbursing psychedelic therapies by incorporating diverse perspectives.

3. **Identifying Challenges and Solutions:** The report highlights the barriers to reimbursement, including regulatory uncertainties, clinical evidence requirements, economic considerations, and infrastructural needs. It proposes practical recommendations for integration, such as potential reimbursement models, policy reforms, and strategies for demonstrating value to payers.

4. **Facilitating Access:** Offering strategies to make psychedelic therapies accessible within existing healthcare frameworks. This includes outlining steps for integrating these therapies into standard care, addressing infrastructural and training requirements, and ensuring that reimbursement mechanisms support equitable patient access.

1.2 Key Findings

Potential Barriers to Reimbursement

- **Evidence Assessment Challenges:** HTA bodies and payers may struggle to evaluate psychedelic therapy trials due to methodological complexities like blinding issues and limited comparative data. These unique trials create tension between meeting regulatory requirements and generating evidence expected for reimbursement decisions.

- **Regulatory and Policy Hurdles:** The pathway for psychedelic therapies faces multiple regulatory challenges throughout development, approval, and reimbursement: EMA authorisation, national drug control requirements, and country-specific healthcare system approvals. This multi-layered regulatory framework creates complex barriers to widespread adoption.

- **Infrastructure Limitations:** Successful implementation requires appropriately configured therapeutic spaces and trained professionals, but healthcare systems face significant workforce shortages, particularly in mental healthcare. This challenge is compounded by limited psychotherapy coverage in public healthcare systems and existing barriers such as long waiting times, additional fees, and session restrictions.

- **Economic and Cost Considerations:** High upfront costs pose a significant barrier, even for products without psychotherapeutic care components, due to patented compound pricing, specialised staffing requirements, and monitoring needs. This cost challenge is particularly stark given the relatively low cost of many standard treatments, which often include generic drugs.

- **Stigma and Ethical Concerns:** Historical attitudes and ethical considerations shape how healthcare providers, policymakers, and the public view psychedelic treatments, which can delay acceptance and funding.

Differences Across Countries

- **Germany:** Reimbursement in Germany can be almost immediate after regulatory approval, but Germany's rigorous HTA processes require high-quality clinical evidence and comparison to the existing standard of care for the benefit assessment. Navigating HTA evaluations to secure a favourable reimbursed price requires proactive engagement and alignment on clinical studies with the GBA.

- **The Netherlands:** The country's liberal regulatory approach and insurers' open approach to different funding models make it more favourable for pilot programs and real-world evidence collection. Still, reimbursement for novel therapies faces scrutiny for economic value and scalability at the national HTA and insurer levels.

- **United Kingdom:** The UK has progressive initiatives like the Innovative Licensing and Access Pathway (ILAP) which aims to support high-value therapies to the market. However, integration into the NHS for innovative therapies requires demonstrating clinical effectiveness and cost-effectiveness at the national HTA level and navigating complex local funding and access decision-making.

- **Czech Republic:** With established ketamine clinics and an active approach to novel mental health treatments, the Czech Republic is exploring regulatory pathways and clinical trials for psychedelic therapies. Whereas the country offers an advanced ecosystem for development, its innovative insurer landscape is beginning to work with clinics on reimbursement models, though broader infrastructure for widespread implementation remains limited.

Stakeholder Insights

- **Developers:** Expressed need for clearer guidance on trial design requirements, more tailored HTA methodologies, and practical agreements regarding reimbursement arrangements and long-term follow-up data collection.

- **Payers:** Highlighted risk aversion, budget constraints, and the need for clear economic models demonstrating direct benefits—with potential consideration of indirect benefits—of psychedelic therapies.

- **Providers:** Pointed to workforce shortages and the lack of standardised training programs as barriers to scaling implementation.

- **Policymakers:** Acknowledged the need for updated regulatory frameworks and special access pathways to enable real-world data collection and phased rollouts.

- **Advocacy Groups:** Stressed the importance of public education campaigns and ethical guidelines to counter stigma and ensure equitable access.

1.3 Actionable Recommendations

Strengthen Clinical Evidence Generation

- **Comparator Trials:** Where feasible, prioritise head-to-head comparisons against standard treatments, particularly for countries like Germany, where such evidence is critical for favourable pricing and reimbursement decisions.
- **Innovative Trial Designs:** Where standard clinical trial approaches present specific challenges for psychedelic therapies, drug developers should consider adaptive protocols, active placebos, or hybrid (factorial) models that assess the relative contributions of drug and therapy components. Early engagement with regulators and Health Technology Assessment (HTA) bodies can ensure alignment with evidence expectations.
- **Long-Term Data Collection:** Incorporate extended follow-ups and real-world evidence pilots to address uncertainties about the durability of therapeutic effects and economic impact. Establish registries for post-market monitoring to support long-term evaluations.
- **Independent Research Initiatives:** Foster state-funded research programmes and multi-stakeholder collaborations beyond industry-sponsored trials to generate evidence. These studies can complement commercial development programmes and address broader public health questions.

Enhance Regulatory and Policy Pathways

- **Leverage Enhanced Regulatory Pathways:** Engage with regulators through available mechanisms such as the UK's ILAP and the EU's PRIME pathways to facilitate deeper collaboration and dialogue with regulatory and access stakeholders throughout development.
- **Special Access Programmes:** Introduce phased (pilot) rollout mechanisms and conditional approvals to enable earlier access while collecting real-world data to address uncertainties.
- **Standardised Guidelines for Controlled Substances:** Collaborate with policymakers to streamline frameworks for rescheduling and clarify requirements for psychedelic therapies.

Optimise HTA, Economic Modelling and Pricing Strategies

- **HTA Methodology:** There is a need for tailored HTA guidance and methodologies to guide both developers and assessors through acceptable evidence approaches on psychedelic-specific challenges such as blinding and bias, comparator choice, and drug plus psychotherapeutic considerations.
- **Comprehensive Economic Evaluations:** Develop cost-effectiveness models that demonstrate both direct and indirect benefits—such as improved productivity and reduced caregiver burden—to better demonstrate societal value to a broad set of stakeholders.
- **Flexible Pricing Approaches:** Propose outcome-based agreements, risk-sharing frameworks, and managed entry schemes to mitigate payer concerns about initial high costs and performance uncertainty.

Implement Flexible Reimbursement Approaches

- **Performance-Based Contracts:** Developers and payers should consider adopting reimbursement models tied to measurable patient outcomes to offset uncertainties about longer-term effectiveness.
- **Bundled Payments:** Where not currently in place, payers should consider developing integrated payment structures that can account for both drug and psychotherapeutic costs, streamlining billing and ensuring comprehensive coverage.
- **Longer Term Patient Management Payments:** Payment mechanisms covering six months plus of patient management should be considered to allow providers to make treatment choices free from short-term budget impact influence.

Build Implementation Infrastructure

- **Workforce Development:** Support the creation of standardised training programs and continuing education frameworks to build and maintain a qualified provider network.
- **Clinical Protocols and Guidelines:** Develop standardised treatment protocols covering patient screening, preparation sessions, medication administration, therapeutic support during sessions, integration, and follow-up care.
- **Dedicated Treatment Rooms:** Establish appropriate therapeutic environments within existing healthcare facilities or new spaces, ensuring settings are suitable for psychedelic sessions while meeting safety and regulatory requirements. Multi-stakeholder guidance is needed to define the essential characteristics of these therapeutic spaces.
- **Professional Training Standards:** Define requirements and establish consensus on core competencies for healthcare providers delivering psychedelic therapy.

Address Societal and Ethical Barriers

- **Equitable Access Policies:** Eliminate cost barriers to psychedelic therapies by mandating insurance reimbursement, providing government subsidies, and instituting income-adjusted sliding-scale fees—ensuring affordable treatment across all socioeconomic groups.
- **Educational Campaigns:** Advocacy groups should lead efforts to reduce stigma through public education, balanced media engagement, and patient testimonials.
- **Ethical Guidelines and Oversight:** Establish professional standards for informed consent, therapist training, and treatment monitoring for patient safety.

Foster Multi-Stakeholder Collaboration

- **Cross-Sector Platforms:** Establish new collaborative forums or leverage existing ones (such as the WHO/Europe Access to Novel Medicines Platform) where developers, payers, providers, and regulators can align on expectations and resolve bottlenecks.
- **Patient-Centric Design:** Integrate patient perspectives into trial designs, HTA evaluations, and public education efforts to maintain focus on outcomes that matter most to patients and societal health.
- **Data-Sharing Initiatives:** Establish shared databases and registries to pool clinical and economic data, accelerating learning and policy development across regions.

1.4 Conclusion

Psychedelic therapies present an opportunity to transform mental healthcare, providing hope for patients who have not responded to conventional treatments. With rising rates of depression, PTSD, addiction disorders, and other psychiatric conditions, there is an urgent need for innovative solutions.

The path to widespread access to these therapies is complex, particularly regarding reimbursement and market access. Current experiences with ketamine and esketamine demonstrate both the challenges and opportunities in securing coverage. Each European country presents unique evaluation and funding approaches, requiring tailored strategies. Evidence generation and analysis methods need adaptation, while infrastructure and workforce readiness uncertainties may negative influence access decisions. Without proactive solutions, Europe risks becoming less attractive for development programmes, ultimately limiting patient access to these potentially transformative treatments.

Success requires coordinated action across stakeholders. While modest adaptations to existing HTA processes—combined with stakeholder flexibility—could enable appropriate evaluation of these therapies, this demands early and sustained collaboration between developers, policymakers, payers, and providers. Key priorities include establishing clear evidence requirements, developing suitable reimbursement models, and creating practical delivery solutions. Most importantly, these discussions must begin well before regulatory approvals to ensure timely and equitable access.

The path forward demands bold action. Stakeholders must prioritise evidence generation, streamline regulatory processes, adapt HTA and reimbursement frameworks, and build the infrastructure to deliver these therapies safely and equitably. Through collaboration, psychedelic therapies can move from margins to mainstream, improving patient outcomes and advancing mental healthcare. ■

1.5 Funding

Norrsken Mind, a non-profit foundation dedicated to advancing psychedelic science in Europe, supported this report through a project grant.

Norrsken Mind funds high-quality research to investigate the therapeutic potential of psychedelics for mental health disorders, along with non-profit initiatives to lay the foundation for future integration of these treatments into healthcare. The foundation has previously supported pioneering research, including the first modern Swedish clinical trial of psilocybin-assisted therapy at Karolinska Institutet.

Beyond funding scientific research, Norrsken Mind promotes education, collaboration, and stakeholder engagement to create the necessary conditions for psychedelic treatments to be rigorously studied, responsibly implemented, and accessible to patients in need.[4] ■

[4] Learn more about Norrsken Mind in Appendix 14.8

1.6 Acknowledgements

We have many people to thank for supporting this report. We are indebted to the stakeholders who agreed to speak with us in formal and informal settings, ranging from emphatic patient advocates to forward-thinking drug developers to those with deep knowledge of the reimbursement landscape in Europe.

We are grateful to our collaborators, Viktor Chvátal and Sumudu Gouri Boyina from PsychedelicsEUROPE, Tadeusz Hawrot from PAREA, and Josh Hardman of Psychedelic Alpha, for their invaluable insights and support throughout this project. Their expertise and commitment to advancing the field have significantly enriched this report.[3]

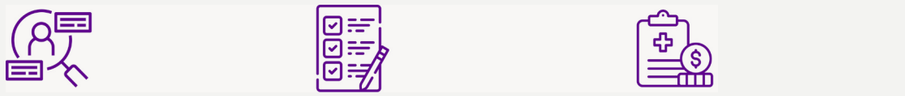
We sincerely thank Marcus Stråth and Emma Christersson from Norrsken Mind for their trust and unwavering support in making this report possible.

As a co-author, Martin has sought to apply an analytical mindset to the subject while drawing on his knowledge of market access from commercialisation of medicines in Europe. Co-author Floris brings a deep understanding of psychedelic research, established writing skills, and seeks to synthesise complex information into access insights for the reader.

Finally, we would like to acknowledge the countless individuals working tirelessly across Europe and globally to advance the field of psychedelic medicine. Their dedication to making these innovative treatments accessible to patients while maintaining the highest safety and efficacy standards continues to inspire our work. ■

[3] Explore the stakeholders we've consulted in Appendix 14.2.3

Visual Chapter Guide



Research → **Evaluation** → **Reimbursement**

2 Introduction to Psychedelics ... ... and Reimbursement

3 Understanding the Drug Development to Reimbursement Pathway

4 Clinical Development of Psychedelic Therapies

5 Payer and Health Technology Assessments

6 Reimbursement Landscape in Europe

7 Challenges and Barriers to Reimbursement

8 Solutions and Recommendations

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10 Summary of Potential Reimbursement and Access Pathways

11 Critical Observations from Collaborators

1.7 How to Read This Report

This report is designed to serve multiple stakeholders, from policymakers to healthcare providers to industry professionals. While we encourage reading the complete report for a comprehensive understanding, we recognise that different readers may have specific interests. Here's a guide to help you navigate the content based on your primary interests:

For a General Overview
- Chapter 2 provides a comprehensive introduction to psychedelics and reimbursement
- Chapter 11 offers our concluding thoughts and key takeaways

For Drug Developers and Clinical Researchers
- Chapter 3 outlines the complete pathway from drug development to reimbursement at a high level
- Chapter 4 details current clinical trials and development challenges
- Chapter 5 covers health technology assessment requirements crucial for development planning
- Chapter 7 highlights specific market access barriers that may be encountered
- Chapter 8 provides actionable solutions and recommendations for evidence generation
- Chapter 10 explores potential reimbursement pathways and alternative access strategies

For Policy Makers, Regulators and Payers
- Chapter 5 focuses on health technology assessment requirements and processes
- Chapter 6 examines the reimbursement landscape across European countries
- Chapter 8 outlines regulatory pathway modifications and policy reforms to consider
- Chapter 10 explores alternative access pathways and innovative payment models

For Healthcare Providers and Clinics
- Chapter 6 explains how reimbursement systems work in practice
- Chapter 8 provides guidance on infrastructure development and implementation approaches
- Chapter 9 addresses equity considerations and practical implementation
- Chapter 10 discusses various service delivery models

For Patient Advocates
- Chapter 7 maps out current barriers to access
- Chapter 9 focuses on ensuring equitable access and ethical considerations
- Chapter 10 explores alternative pathways to treatment access

Reference Materials
- Chapter 12 provides a glossary of terms and concepts
- Chapter 13 lists all sources used in the report
- Chapter 14 contains additional detailed information in the appendices

Each chapter is designed to be relatively self-contained, with key terms explained throughout. While chapters build upon each other, they can be read independently based on your interests and needs. The country-specific insights in Chapters 6 and 8 may be particularly valuable for stakeholders operating in Germany, the United Kingdom, the Netherlands, or the Czech Republic. ■

Scope of the Report

This report primarily focuses on emerging psychedelic therapies, particularly MDMA and psilocybin, whilst using ketamine and esketamine as instructive case studies for healthcare system integration. The current implementation of (es)ketamine therapies in European healthcare systems offers valuable precedents, despite these compounds differing from classical psychedelics in their mechanism of action, effect duration, and therapeutic protocols.

Esketamine (Spravato), having secured regulatory approval and reimbursement in several European countries, provides particularly relevant insights into system adaptation challenges and solutions.

This report examines critical barriers that could restrict access to upcoming psychedelic therapies in Europe. The anticipated high costs and unclear reimbursement pathways present significant challenges. Without coverage from national health systems or federal insurance, these treatments risk remaining inaccessible to many potential beneficiaries.

By providing clarity and actionable recommendations, this report aims to guide stakeholders—including drug developers, payers, and providers—through the complex reimbursement landscape.

Focus Countries

Germany: Known for its advanced healthcare system, Germany has well-defined HTA processes that play a crucial role in pricing and reimbursement decisions. These assessments impact beyond Germany, as this single-largest market often spearheads European implementation of novel medicines as an early launch market of choice for drug developers.

The Netherlands: Characterised by progressive policies and a demonstrated interest in integrating innovative therapies, the Netherlands offers a valuable case study in exploring pathways for novel treatment modalities. Examining the Dutch approach provides insights into potential opportunities for early adoption and case studies into implementing psychedelic therapies.

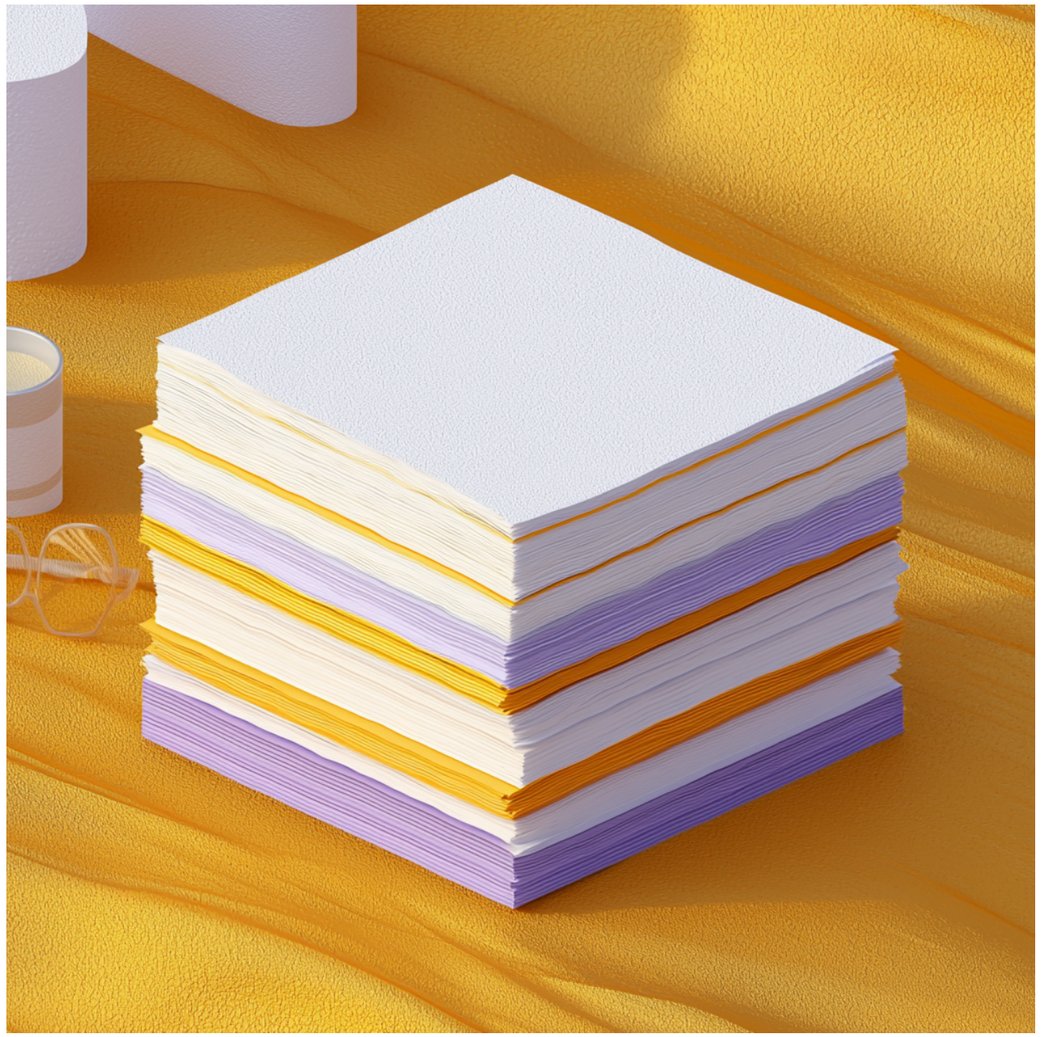
United Kingdom: A country with independent regulatory processes and an internationally recognised HTA body (NICE), the UK promotes itself as a market for innovative medicines with a dedicated innovation pathway but is also known to be a complex market for achieving market access. The report examines these established frameworks and their potential application to psychedelic therapies.

Czech Republic: With an emerging network of ketamine clinics and supportive regulatory environment, the Czech Republic is becoming an active player in novel mental health treatments. The country's engaged key opinion leaders and well-established psychedelic research communities create a favourable setting for advancing psychedelic medicine.

Scope Boundaries

This report focuses specifically on reimbursement pathways and access factors for psychedelic therapies in the selected countries. While insights may be applicable more broadly, healthcare system differences limit direct extrapolation to specific countries or other regions.

The analysis does not comprehensively review clinical efficacy, safety profiles, or legal status of these treatments.The report does also not attempt to review regulatory pathway-specific challenges and needs.



Introduction to **Psychedelics and Reimbursement**

2

2.1 Background on Psychedelic Therapies

2.1.1 Historical Use and Early Research

Psychedelic substances have been used for millennia in various indigenous cultures for religious, spiritual, and healing purposes. For instance, psilocybin-containing mushrooms have been integral to Mesoamerican rituals, while ayahuasca, a brew containing DMT and harmine, has been used in the Amazon basin for shamanic ceremonies. These practices recognised the profound psychological and spiritual effects of psychedelics long before they entered Western scientific awareness (Nichols, 2016; Garcia-Romeu et al., 2016).

In the mid-20th century, Western medicine began to explore the therapeutic potential of psychedelics. In 1938, Swiss chemist Albert Hofmann synthesised Lysergic Acid Diethylamide (LSD) at Sandoz Laboratories, and in 1943, he discovered its psychoactive properties (Hofmann, 1979). Throughout the 1950s and 1960s, psychiatrists and psychologists conducted extensive research and clinical practice using LSD, psilocybin, and other psychedelics for treating conditions such as alcoholism, anxiety, and depression. Notably, studies suggested that these substances could facilitate breakthroughs in psychotherapy by allowing patients to access repressed emotions and traumas. →

However, the increasing recreational use of psychedelics and their association with counterculture movements led to societal backlash. In 1971, the United Nations Convention on Psychotropic Substances classified many psychedelics as Schedule I substances, denoting a high potential for abuse and no accepted medical use (UN, 1971).

Multiple factors contributed to the halt in psychedelic research: the emergence of randomised controlled trials (RCTs) as the new gold standard, which posed methodological challenges for psychedelic studies; stricter pharmaceutical regulations following the Thalidomide disaster; and Sandoz's decision to stop producing LSD for research in 1965. Together, these developments made it exceedingly difficult to obtain approvals and funding for studies involving psychedelics (Hall, 2021). ■

2.1.2 Modern Resurgence

The early 21st century witnessed a renewed scientific interest in psychedelics, spurred by advancements in neuroscience and a growing recognition of the limitations of existing mental health treatments. Researchers began to revisit earlier studies and explore the mechanisms by which psychedelics could produce therapeutic effects.[5]

Key institutions like Johns Hopkins University in the U.S. and Imperial College London in the UK initiated rigorous clinical trials investigating the use of psychedelics for various mental health conditions. The 2006 study by Roland Griffiths and colleagues at Johns Hopkins was particularly significant as one of the first modern psychedelic studies at a major U.S. research institution. It not only demonstrated that psilocybin could safely induce mystical experiences with sustained personal and spiritual significance in healthy volunteers but also showed lasting positive changes in their psychological well-being, life satisfaction, and behaviour. This research helped establish the scientific credibility necessary for subsequent clinical studies in patient populations (Griffiths et al., 2016).

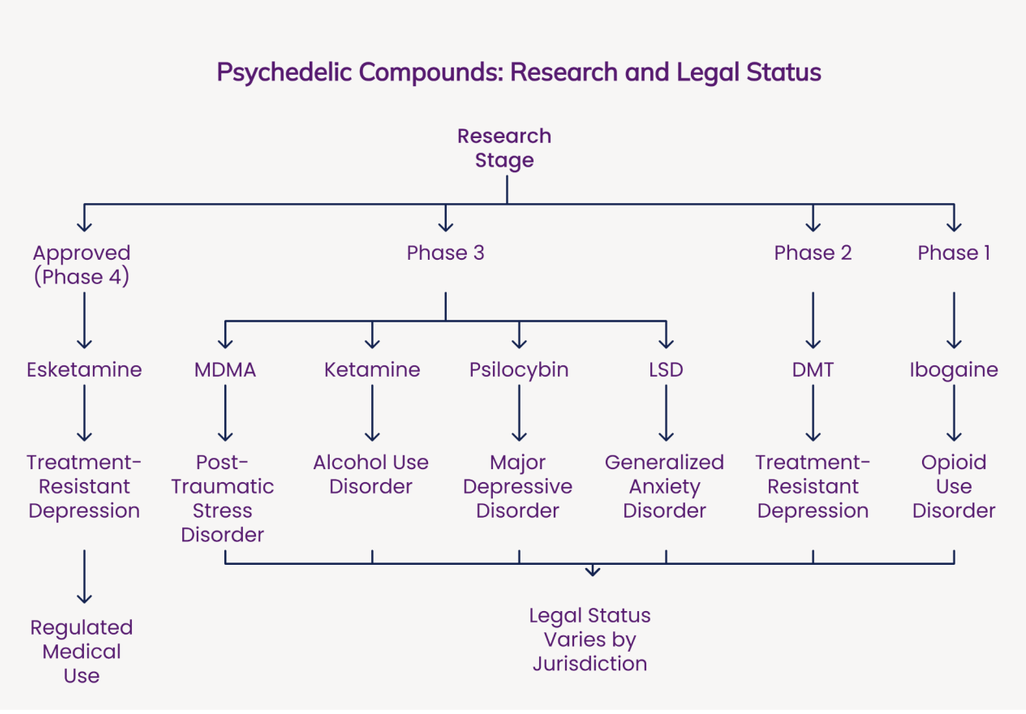
Regulatory bodies have started to acknowledge the potential of psychedelics as therapeutics. In 2017, the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy designation to MDMA therapy for post-traumatic stress disorder (PTSD), developed by the Multidisciplinary Association for Psychedelic Studies (MAPS) (FDA, 2017). This designation is intended to expedite the development and review of drugs that show substantial improvement over existing therapies.

Similarly, in 2018, the FDA granted Compass Pathways Breakthrough Therapy designation for its psilocybin therapy for treating treatment-resistant depression (TRD) (Compass Pathways, 2018). Subsequent Breakthrough Therapy designations have been awarded to Usona Institute for psilocybin therapy for major depressive disorder (MDD) (Usona Institute, 2019), Cybin for psilocybin analogue (CYB003) for MDD (Cybin, 2024), and Mind Medicine for its LSD-analogue (MM120) for generalized anxiety disorder (GAD) (MindMed, 2024a).

In 2022, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) awarded Compass Pathways an Innovation Passport under the Innovative Licensing and Access Pathway (ILAP), which is intended to facilitate greater engagement with authorities and potentially faster patient access to promising medicines (Compass Pathways, 2022). MAPS and Lykos Therapeutics (formerly MAPS PBC), the commercial arm of MAPS, also received the Innovation Passport from the MHRA for their MDMA therapy for PTSD (MAPS, 2022). More recently, the LSD programme for generalised anxiety disorder (GAD) from MindMed also received an Innovation Passport designation (MindMed, 2024b).

The EMA has also demonstrated a proactive approach to psychedelic medicines, organising a two-day workshop to discuss regulatory frameworks and clinical development (EMA, 2024). Through its PRIME (PRIority MEdicines) scheme, the EMA has signaled its openness to supporting the development of psychedelic medicines that address unmet medical needs. However, no psychedelic developers have yet applied for PRIME designation. ■

[5] The resurgence of psychedelic research actually began in the early 1990s when Rick Strassman conducted groundbreaking DMT studies at the University of New Mexico, marking the first FDA-approved psychedelic research in over two decades. However, widespread revival of the field didn't gain momentum until the early 2000s. ↗



2.1.3 Pharmacological Effects Combined with Psychotherapy

The therapeutic use of psychedelics often combines pharmacological intervention with psychotherapeutic support. However, perspectives on the necessity and optimal level of psychological support vary among stakeholders and may depend on the specific condition and patient population being treated. Many researchers and clinicians believe that psychedelics' ability to induce altered states of consciousness, when guided by trained clinicians, can lead to profound psychological insights and emotional healing. This synergistic effect is believed to enhance the therapeutic process beyond what might be achievable with medication or psychotherapy alone (Krediet et al., 2020).

For example, in MDMA therapy for PTSD, the drug's empathogenic effects can reduce fear and defensiveness, allowing patients to process traumatic memories more effectively during therapy sessions (Mitchell et al., 2021). Similarly, psilocybin therapy can facilitate a sense of interconnectedness and self-transcendence, which may help alleviate depressive symptoms (Davis et al., 2021).

While significant therapeutic benefits have been observed in clinical trials using supported models, ongoing research and debate continue regarding the optimal level of psychological support needed across different indications and treatment contexts. ■

2.1.4 Treatment Protocols

Psychedelic therapy protocols typically involve three key phases (Brennan & Belser, 2022):

1. **Preparation**: Before administering the psychedelic, patients participate in one or more preparatory sessions with trained healthcare providers. This phase aims to build trust, set intentions, and educate the patient about the upcoming experience. Preparation helps to minimise anxiety and establish a supportive therapeutic alliance. →

2. **Dosing Session (the "Trip"):** The patient receives the psychedelic substance in a controlled, safe environment under professional supervision. Sessions typically last anywhere from one to twelve hours, during which facilitators provide support but generally allow the patient's experience to unfold without direct intervention.[6] The setting is designed to be comfortable and calming, often with music and minimal distractions.

3. **Integration:** Following the dosing session, patients engage in integration sessions to process and make sense of their experiences. Mental health professionals help patients translate insights gained during the psychedelic experience into practical changes in thoughts, behaviours, and emotions. Integration is thought to be critical for achieving lasting therapeutic benefits.

2.1.5 Importance of Set and Setting

"Set and setting" are fundamental concepts in psychedelic therapy (Hartogsohn, 2017):

1. **Set (Mindset):** Refers to the individual's internal state, including their mood, expectations, and intentions. A positive mindset can enhance the therapeutic experience, while negative emotions or apprehensions may lead to challenging experiences.

2. **Setting (Environment):** Encompasses the physical and social surroundings during the psychedelic session. A safe, supportive, and controlled environment facilitates positive outcomes and minimises risks.

Healthcare practitioners play a crucial role in managing both set and setting, ensuring that patients are psychologically prepared and that the environment is conducive to healing.[7] ■

[6] Psychedelic trips can be very short, for instance a DMT or 5-MeO-DMT trip can last between 5 and 20 minutes. Typical trip durations for psilocybin last between 2 and 8 hours. Whilst trips with LSD and mescaline can last from 8 to 18 hours.

[7] In section 4.1.1 we examine the extent to which the therapist, or therapeutic alliance, is crucial to therapeutic outcomes and challenges associated with this aspect of psychedelic trials.

2.1.6 Rapid and Sustained Symptom Reduction

One of the most compelling aspects of psychedelic therapies is their potential for rapid symptom improvement after just one or a few treatment sessions, in contrast to conventional antidepressants, which typically require 4-6 weeks of daily administration to achieve therapeutic effects. While response rates vary among individuals, clinical trials have demonstrated that some patients may experience significant reductions in depression, anxiety, or PTSD symptoms within days of treatment, with effects lasting weeks, months, or even years (Bahji et al., 2023).

For instance, Compass Pathways' Phase IIb trial, with 233 patients with treatment-resistant depression (TRD), found that a single 25 mg dose of psilocybin, administered with psychological support, significantly reduced depressive symptoms within two days compared to lower doses (10 mg and 1 mg) in a subset of participants. Among those who responded to treatment, some patients' benefits persisted for up to 12 weeks (Goodwin et al., 2022). This rapid onset of action contrasts with traditional antidepressants, which often require continuous daily dosing and may take several weeks before patients experience meaningful improvement. ■

2.1.7 Emerging Evidence Across Mental Health Conditions

Psychedelic therapies have shown promise in treating conditions that are resistant to standard medical interventions, with an estimated 30-50% of patients not responding to traditional approaches (Howes et al., 2022; McIntyre et al., 2023). Patients who have not responded to established antidepressant pharmacotherapies or psychotherapy may benefit from the novel mechanisms of action offered by psychedelics.

In Lykos' Phase III trial for MDMA psychotherapy, 67% of participants with severe PTSD no longer met the diagnostic criteria for PTSD after three treatment sessions, compared to 32% in the placebo group (Mitchell et al., 2021). The second Phase III trial, →

which included patients with moderate PTSD, found that 71% of patients no longer met the PTSD diagnostic criteria (Mitchell et al., 2023). This is particularly significant given that participants had struggled with PTSD symptoms for an average of 16 years and had not found relief with existing therapies.

Beyond TRD and PTSD, clinical research is expanding rapidly across multiple conditions. Current trials are investigating psychedelic therapies for substance use disorders, including alcohol and tobacco dependence, and are showing promising early results. Studies are also exploring applications in anxiety related to terminal illness, eating disorders such as anorexia nervosa, and obsessive-compulsive disorder. This breadth of research indicates that psychedelic therapies represent not just isolated treatments but a broader therapeutic paradigm with potential applications across mental health conditions (Blossom, n.d.).[8]

Healthcare stakeholders must recognise that these developments represent a comprehensive wave of clinical innovation approaching health systems. These novel therapies share unique characteristics distinguishing them from conventional treatments, most notably in their requirement for supported psychoactive experiences. This core feature, combined with the integration of pharmacological intervention and psychotherapeutic support in controlled settings, sets them apart from traditional mental health treatments. This emerging therapeutic class will require adaptations in clinical practice and dedicated healthcare infrastructure for successful implementation..

This report addresses these critical challenges by examining existing healthcare frameworks, engaging key stakeholders, and developing actionable recommendations so these promising treatments reach those who most need them. Our analysis focuses on four key areas: addressing access barriers, supporting stakeholders across the healthcare ecosystem, mapping viable reimbursement pathways, and identifying implementation challenges that must be overcome to realise the full potential of psychedelic therapies. ■

[8] This report limits our scope to mental health treatments, but promising results have also been shown in fields ranging from ↗ pain (fibromyalgia, cluster headaches) to neurological disorders (traumatic brain injury, Alzheimer's) and creativity.

2.2 Current Reimbursement Landscape for Psychedelic Therapies in Europe

Getting new medical treatments to patients in the EU can be complicated, especially for innovative therapies like psychedelics. Following market authorisation by the EMA, each EU country independently assesses which treatments to offer and how to pay for them. The UK and Switzerland maintain separate marketing authorisation pathways. This section looks at how different European healthcare systems are handling psychedelic therapies, including who can access them and who pays for them.

At the moment, only a few psychedelic treatments are officially available in Europe. The only medication available for prescription is Spravato (esketamine) nasal spray for TRD, though access and funding vary by country. Ketamine therapy, available through off-label or compassionate use, is offered on a case-by-case basis or through private clinics. Other psychedelic therapies are not legally available outside of clinical trials.

2.2.1 Overview of European Healthcare Systems

European healthcare systems aim to provide universal health coverage but differ in how they organise and pay for healthcare. These differences affect how new treatments, including psychedelic therapies, become available to patients.

Healthcare Models

Most European countries use one of three main approaches to healthcare delivery. Public systems, like those in the UK, Denmark, and Sweden, rely primarily on public healthcare funded through taxes. The UK's National Health Service (NHS) is a prime example, providing free care at the point of need.

Insurance-based systems in Germany and the Netherlands use mandatory health insurance. In Germany, individuals are generally required to join a statutory health insurance fund up to a certain income threshold, above which individuals can opt for private health insurance. Costs are shared between employers and employees. In contrast, the Dutch system requires all residents to take out private health insurance with a government-regulated standard package, regardless of income, with costs shared between employers and employees.

Mixed systems operate in countries like France, Italy, and Spain. These systems combine public funding with private healthcare delivery. About half of the hospitals in these countries are private but receive public funding.

Decision Making

Countries also differ in how centralised their healthcare decisions are (Montagu, 2021). England and Wales, and the Netherlands have highly centralised systems, with national bodies making decisions about new treatments that apply across the country.

In contrast, countries like Spain and Italy give regions more power to make healthcare choices, including which treatments to fund. Germany represents a mixed approach. Statutory and private health insurances are generally required to cover treatments included in the national catalogue. Still, they can grant optional additional benefits and contract-based care models.

Timing for Access

The time it takes for patients to access new treatments varies widely across Europe (EFPIA, 2022; EFPIA, 2024a). Germany leads with the fastest access, with new treatments available on average 126 days after regulatory approval (products can access the German market immediately if the manufacturer is prepared). Denmark and Austria follow with averages of 149 and 283 days, respectively. Mid-range timelines are seen in countries like the Netherlands (371 days) and the Czech Republic (494 days). However, many countries take significantly longer—Bulgaria averages 723 days, Romania 778 days, and Poland 804 days. These differences mean that patients in some countries wait substantially longer for new →

treatments than others. Beyond the waiting time, however, the overall availability of treatments is also a critical issue— in certain countries, only a small proportion of EMA-approved treatments are accessible to patients. Therefore, both the time to access and the overall availability of treatments are crucial factors to consider.

Private Healthcare Options

While European countries have strong public healthcare systems, the role of private healthcare varies significantly across the region (Eurostat, 2024). Private insurance can provide extra coverage on top of public care or offer alternative services, with the balance varying significantly between countries. Private clinics often provide faster access to treatments not yet available through public systems, particularly for newer therapies.

However, this creates significant equity concerns, as demonstrated by the current ketamine clinic model, where treatments are primarily available through private clinics requiring substantial out-of-pocket payments. This approach risks excluding lower-income populations who often face higher rates of mental health challenges and substance use disorders, potentially deepening existing health inequities.

Impact on Psychedelic Therapies

The variety of healthcare systems across Europe creates several challenges for psychedelic therapies. These treatments combine drug treatment with a psychotherapeutic component, which many healthcare systems are not currently set up to evaluate and implement easily. Countries may take very different approaches to reimbursement (i.e., paying for) these combined treatments, leading to varied access across Europe.

While private clinics might offer these treatments before public systems do, relying primarily on private provision may create disparities in access, particularly affecting communities with higher rates of mental health challenges and substance use disorders. Ensuring equitable access through public healthcare systems represents a significant implementation challenge for these novel therapeutic approaches. ■

2.2.2 Status of Psychedelic Therapies Across Key Markets

Only two psychedelic treatments are currently available in European markets: esketamine, which has regulatory approval for TRD, and ketamine, which is available in select hospital settings and private clinics. However, regulatory approval does not guarantee payer acceptance, as demonstrated by the varied reimbursement status and accessibility of these treatments across healthcare systems. Here, we summarise the current status across four key markets.

Germany

In Germany, Spravato received a positive assessment from G-BA for treatment-resistant depression (TRD) in 2023—when used in conjunction with an SSRI or SNRI—acknowledging its considerable added benefit compared to existing treatments (G-BA, 2023). G-BA gave Spravato its second-highest possible clinical benefit rating (considerable benefit) for treating depression that has not responded to other treatments. Public insurance now covers Spravato treatment when delivered in specialised settings, though access remains limited by the availability of these facilities.

Beyond Spravato, off-label ketamine is used in a limited number of clinics, typically requiring private payment or case-by-case insurance approval. From a regulatory perspective, Germany's framework permits access to esketamine and ketamine therapies; however, practical implementation faces challenges, including limited specialised treatment facilities and relatively few physicians willing to prescribe these treatments. The country's research initiatives, including the completed EPIsoDE trial studying psilocybin for TRD and a planned Phase III study, may help pave the way for future treatments (NLM, 2021-2024).

Psychedelic Therapy Access in Europe

Country	Ketamine			Esketamine (Spravato)		
	Licensed?	**Reimbursement status**	**Level of patient access**	**Licensed?**	**Reimbursement status**	**Level of patient access**
Germany	No	No statutory health insurance (SHI) coverage; individual reimbursement applications via insurers	Very limited (individual hospitals)	Yes	Reimbursed; positive HTA outcome (GBA/IQWiG)	Limited, but expanding
United Kingdom	No	No national reimbursement status or routine funding via NHS	Very limited (private clinics, select NHS trusts)	Yes	Not recommended in England & Wales (NICE); recommended in Scotland (SMC)	Extremely limited in England & Wales; available through private clinics
Netherlands	No	Insurance coverage for clinical support costs	Limited, but expanding	Yes	Approved for coverage under basic health insurance (2021)	Very limited (few dozen patients yearly)
Czech Republic	No	Some insurance coverage with patient co-payment	Established clinical access since 2020	Yes	Exceptional reimbursement for TRD; standard reimbursement approved end of 2024	Limited, but expanding with major insurance coverage

Netherlands

The Netherlands provides greater access to psychedelic treatments than many other European countries. The healthcare system features comprehensive coverage for psychotherapeutic interventions and flexibility in provider arrangements and reimbursement structures. Several clinics currently offer ketamine therapy, and insurance covers up to 90% of the clinical support costs—specifically, the therapeutic sessions and professional expertise (Magnolia Therapy, n.d.).

While Spravato was approved for coverage under basic health insurance in September 2021, access remains severely limited (ZiN, 2020). Despite an estimated 1,500-2,000 patients with TRD being eligible annually, only a few dozen patients received treatment in 2022 (Depressie Vereniging, 2022).

Some hospital systems offer off-label use programs for ketamine treatment on a case-by-case basis. A consortium of researchers has initiated efforts to start a trial to evaluate ketamine's efficacy and safety for broader insurance coverage.

The country has also seen early adoption of psilocybin treatments in specific clinical settings, though these remain outside standard reimbursement pathways. While regulated medical centres focus on approved treatments, some practitioners offer psilocybin sessions in the unregulated market. The Netherlands' unique legal framework allows for the sale and use of psilocybin-containing truffles, which remain unregulated and widely available through smartshops.

In a significant development, the Dutch State Commission on MDMA recently recommended allowing MDMA therapy for PTSD treatment, advocating for a regulatory framework to enable medical use (Government of the Netherlands, 2024).

United Kingdom

In the UK, Spravato faced challenges gaining NHS coverage. NICE repeatedly declined to recommend it in England and Wales due to cost-effectiveness concerns (NICE, 2024a), but the Scottish Medicines Consortium (SMC) did recommend it for use in Scotland.

Access to ketamine treatment in the UK remains limited but is available through several specific routes. These include a small number of NHS clinics, Oxford Health NHS Foundation Trust's Interventional Psychiatry Service (offering both NHS-funded and self-pay options), and private clinics. Work to develop replicable care models continues, led by clinical advocates of ketamine therapy. A small TRD pilot using racemic ketamine is running in 2025 within the Central and North West London Foundation Trust, aiming to integrate with existing NHS depression care pathways (Oxford Health NHS Foundation Trust, 2024; Imperial College London, 2025). While private clinics offer both Spravato and ketamine treatments, high costs restrict accessibility.

The UK government has demonstrated increasing openness to psychedelic research through multiple funding channels. The Innovative Licensing and Access Pathway (ILAP) has granted designations to five psychedelic therapy developers (Small Pharma, 2021; Eleusis, 2022; Compass Pathways, 2022; MAPS, 2022; Mindmed, 2024b). Public funding supports numerous clinical trials, including two-thirds of Awakn's Phase III trial for alcohol use disorder (NICE, 2024b). Imperial College London's psilocybin studies have received support from the National Institute for Health Research (NIHR) and the Government's Office for Life Sciences for opioid addiction research, while their work on psilocybin for gambling disorders is backed by a UKRI Impact Acceleration Account grant (Imperial Biomedical Research Centre, 2024; Mundell, 2024).

Czech Republic

The Czech Republic has implemented ketamine therapy in clinical practice earlier than many other European countries, with a limited number of established clinics offering treatment. Building on its regulatory experience with ketamine and medical cannabis, the country provides a case study in integrating psychedelic therapies into healthcare. Some insurance coverage exists for ketamine treatments, though often requiring significant patient co-payment.

Since 2020, clinics have offered ketamine therapy to hundreds of patients (Šenk, 2023; Šenk, 2024). These treatments have expanded from TRD to now also covering eating disorders, PTSD, addictions, and anxiety disorders. The facilities are also participating in clinical trials of various psychedelic substances, including ketamine, 5-MeO-DMT, and upcoming studies with psilocybin.

A significant development is the establishment of insurance coverage agreements with major providers, including VZP, the country's largest insurer. Spravato (esketamine) is now listed among the reimbursed medicinal products by the State Institute for Drug Control (SÚKL, 2024), indicating its inclusion in public health insurance coverage. This advancement enhances patient access to esketamine therapy for TRD.

With a strong tradition of evidence-based policymaking in drug regulation, the Czech Republic may be emerging as a strategic country for psychedelic-assisted treatments. This evolving regulatory landscape extends beyond psychedelics to other previously unregulated psychomodulatory substances, such as kratom and THC, signalling a broader shift in policy and access.

Other European Markets

Looking at other European markets, Switzerland stands out for its well-established compassionate use framework, which has allowed limited access to MDMA, psilocybin and LSD therapies through specialised clinics from 1988-1993 and since 2014 (Liechti, 2019). Several psychiatrists have received special authorisations from the Federal Office of Public Health to provide these treatments.

In most other European countries, access to esketamine (Spravato) remains restricted primarily through hospital-based programs, with varying levels of public insurance or health system coverage. ■

2.2.3 Early Access and Alternative Pathways

While standard reimbursement pathways through national health systems are the assumed route to broader access, several alternative routes currently provide access to psychedelic therapies in Europe.[9] These pathways offer important insights into implementation challenges and opportunities while generating valuable real-world evidence.

Compassionate Use Programs

Several European countries operate compassionate use programs that can provide access to treatments before full regulatory approval. These programs typically focus on patients who have not responded to available therapies and have limited options. Next to Switzerland, clinicians in the Netherlands have a "gentlemen's agreement" with insurers to offer off-label ketamine treatments to patients who have exhausted other options.

Research-Based Access

Clinical trials and research programs currently serve as a key access route for psychedelic therapies. Beyond generating evidence for future approval and reimbursement, these programs help establish treatment protocols and train healthcare providers. Major academic centres and research hospitals across Europe are conducting trials with various psychedelic compounds, creating pockets of expertise that could support broader implementation.

Private Clinic Models

Private clinics have emerged as early adopters of psychedelic treatments, particularly for ketamine therapy. These clinics typically operate on a self-pay basis, though some have established relationships with private insurers or secured partial reimbursement for therapy components. While high costs limit access, these clinics provide valuable insights into practical implementation challenges and successful treatment delivery models.

Off-label and Pharmacy Preparation

Some countries allow physicians to prescribe approved medicines for off-label uses or have frameworks for pharmacy-prepared versions of ketamine. These pathways can provide flexible access options, though usually without insurance coverage. The Netherlands and Germany have established frameworks for the pharmacy preparation of ketamine. ■

[9] In Chapter 10 we discuss the full scope of access pathways.

3 Understanding the Drug Development to Reimbursement Pathway

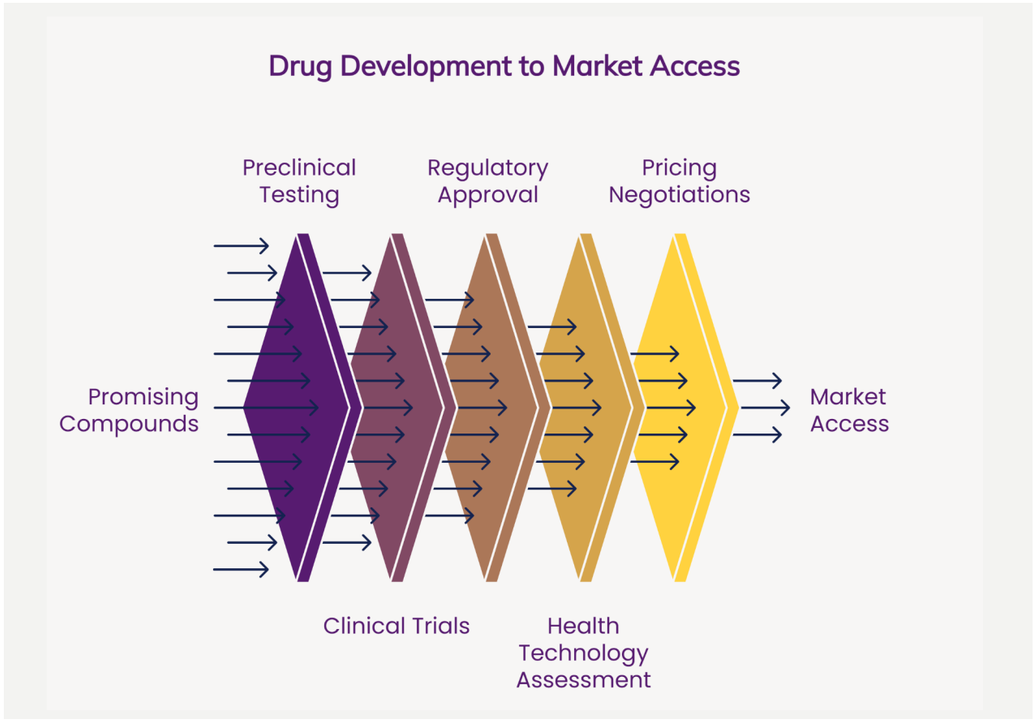
Bringing a new medicine to patients involves many steps, from drug creation to ensuring patient access. Each step presents unique challenges, from testing the drug to getting approval and making it affordable.

This chapter examines all the main steps: early testing, clinical trials, regulatory approval, and setting prices with health systems. We explain how these steps work together to provide safe and effective treatments for patients.

A critical part of this process is learning from each step to improve the others. For example, what we learn from health system reviews can help make better clinical trials. Similarly, choices made early in drug testing can affect how easily the treatment can be approved and paid for later.

Understanding these connections helps create a smoother path from developing a drug to helping patients.

This chapter also examines everyone involved—regulators, insurance companies, doctors, and patient groups. By understanding how these groups work together, we can better understand what it takes to bring new treatments like psychedelic therapies to patients who need them. ■



3.1 Drug Discovery and Preclinical Development

Creating new medicines starts with finding (drug discovery) and testing (preclinical development) potential drug compounds before clinical trials begin. This phase involves identifying and checking compounds that could become treatments. Scientists must find compounds that work and prove they are safe to test in humans.[10]

[10] For psychedelic therapies using well-known compounds like psilocybin, MDMA, or LSD, much of this early development work is already established through decades of research and human use. These compounds have known safety profiles and mechanisms of action, allowing developers to focus more on clinical development and therapy protocols. However, several companies are also working on novel psychedelic compounds or derivatives, aiming to maintain therapeutic benefits while potentially improving properties like duration of action or reducing unwanted effects. For these novel compounds, the full discovery and preclinical development process remains essential. This report primarily focuses on the development pathway for established psychedelic compounds, as these are currently closest to market approval.

Compound Identification

Scientists look for valuable compounds in several ways. They test extensive collections of chemicals, design compounds based on how diseases work, and study natural substances that might have medical benefits. They look for compounds that can affect specific parts of the body involved in diseases, checking how well they work and whether they have properties that make them good medicines.

After finding promising compounds, chemists work to improve them. They change the chemical structure to help the compounds work better and cause fewer side effects. They keep making improvements until they find the best possible version.

Preclinical Studies on Safety, Efficacy, Pharmacodynamics, and Pharmacokinetics

Scientists must prove that any new compound is safe before testing it on humans. They must collect specific information to demonstrate to regulators that starting human trials is reasonable.

Scientists test compounds in two main ways: in vitro (in lab dishes with cells or tissues) and in vivo (in living animals). Lab tests show how compounds affect cells and help predict possible problems. Animal studies show how compounds move through the body and what they do. These studies help determine proper doses and find any safety issues.

In vivo studies on animal models evaluate the compound's pharmacodynamics (PD) and pharmacokinetics (PK). Pharmacodynamic studies examine the compound's physiological effects and mechanism of action within a living organism. Pharmacokinetic studies assess how the compound is absorbed, distributed, metabolised, and excreted (ADME) over time. PD and PK studies help determine appropriate dosing regimens and identify potential safety concerns.

Toxicology studies help scientists determine whether new drugs are safe before testing them on humans. These studies look for harmful effects on different parts of the body. Scientists test the drug's effects in the short term and the long term. They check if the drug affects reproduction, damages DNA, or might cause cancer. They focus on how the drug affects critical bodily functions like the heart, breathing, and brain to catch dangerous side effects.

In Europe, preclinical studies must adhere to Good Laboratory Practice (GLP) standards and the European Medicines Agency (EMA) guidelines. The data generated form the basis of the Investigational Medicinal Product Dossier (IMPD), a critical Clinical Trial Application (CTA) component.

Impact of Regulatory Classifications on Preclinical Research

When developing new drugs, scientists must determine whether regulatory bodies classify them as controlled substances, which carry strict legal regulations. This classification is important because it affects the research's ability to proceed.

In Europe, different drugs have different levels of control. For example, Schedule I of the United Nations Convention on Psychotropic Substances considers ⤴ compounds listed under it to have a high potential for abuse with no recognised medical use (UN, 1971). Scientists need special permits to work with these drugs. They must keep them in secure places and keep detailed records of how they use them. These rules can make research take longer and cost more money. It can also be more challenging to work with scientists in other countries because different countries have different rules.

Considerations for Compounds with Existing Preclinical Data Versus New Entities

Scientists need different approaches when studying existing drugs versus completely new ones (called new chemical entities or NCEs). Here's what they consider:

The process can be faster for existing drugs that have already been tested and used. Scientists can try to find new uses for these drugs, which is called drug repurposing. Repurposing is helpful because researchers already know a lot about how safe the drug is and how it moves through the body.

A good example is ketamine. It was first developed and approved as an anaesthetic in 1970, but scientists later discovered its potential in treating depression. This repurposing led to the development of esketamine (Spravato) for treatment-resistant depression (TRD). When developing esketamine, researchers could build upon decades of safety and pharmacological data from ketamine's use in anaesthesia, though they still needed to prove its safety and efficacy specifically for depression treatment.

However, for NCEs (completely new drugs), scientists must conduct all possible tests from scratch. They must thoroughly check whether the drug is safe, how it works, and how the body handles it. This process takes more time and money because everything is new and needs complete testing. ■

3.1.1 Considerations for Psychedelics

Psychedelic compounds offer significant promise but also add layers of complexity in early development. For well-studied substances like psilocybin, MDMA, and LSD, existing preclinical data can reduce the duplication of efforts. However, regulators still require updated safety assessments when developers introduce new formulations, dosing regimens, or delivery methods.

In addition to standard in vitro and in vivo studies, evaluating the neurobiological and behavioural effects of these compounds is essential. Researchers must pay special attention to psychedelics' potential for misuse and adverse impacts on brain function.

Due to strict regulatory controls (often because these compounds are classified as Schedule I substances), developers must secure specialised licenses, maintain secure storage, and follow varying national and EU guidelines. Collaborative efforts with specialised research centres and adherence to Good Laboratory Practice (GLP) standards can help streamline this process.

3.2 Clinical Trial Phases

Following the successful completion of preclinical development, where researchers test potential new drugs in laboratories and on animals, the next crucial step evaluates these drugs in humans through clinical trials. Developers need these trials to obtain approval from regulatory authorities and secure reimbursement from healthcare systems, demonstrating that the treatment is safe and effective for patients. Researchers conduct clinical trials in four phases, each designed to answer specific questions about the new drug.

In 2024, the European Union launched a comprehensive "one-stop shop" initiative to support biotechnology companies throughout their development journey (European Commission, 2025). This initiative streamlines the process of bringing new therapies to market by providing centralised access to regulatory guidance, research infrastructure, and business development resources. For clinical trials specifically, it established a unified process for submitting, validating, and approving clinical trial applications across EU Member States while maintaining consistent standards and procedures.

Phase I: Safety and Dosage

Phase I trials are the first testing stage in human subjects and primarily focus on safety. In this phase, a small group of healthy volunteers—usually between 20 and 100 individuals—is given the drug. The main goals are:

- **Assessing Safety:** To determine if the drug is safe for human use and to identify any side effects.
- **Determining Dosage**: To find the optimal dose that provides the desired effect with minimal adverse reactions.
- **Understanding Drug Behaviour**: To study how the body processes the drug, including how it absorbs, distributes, metabolises, and excretes it (known as pharmacokinetics).

Researchers closely monitor participants to observe any adverse effects. They collect data on how the drug behaves in the human body, which helps plan the dosing for the subsequent phases.

Phase II: Efficacy and Side Effects

Phase II trials aim to evaluate the drug's efficacy in people with the condition it is meant to treat while continuing to assess its safety. This phase typically involves 100 to 300 patients. The main objectives are:

- **Evaluating Efficacy:** To see if the drug has a beneficial effect on the disease or condition.
- **Further Assessing Safety:** To monitor for side effects and determine how they relate to the dose.
- **Refining Dosage and Administration:** Adjust dosing schedules and methods based on patient responses.

Researchers gather data on the drug's efficacy and continue monitoring safety, which helps optimise the treatment protocol for Phase III trials.

Early collaboration with health technology assessment (HTA) bodies or payer advisory groups during the early clinical trial phases (usually at Phase II) can help developers anticipate reimbursement challenges, such as identifying the most appropriate patient population, relevant and recognised study endpoints and comparator therapies, which will help demonstrate the clinical and economic value required to support future reimbursement decisions.

Phase III: Confirmatory Trials

Phase III trials are conducted on a larger scale, involving several hundred to low thousands of patients across multiple locations. The primary goals are:

- **Confirming Efficacy:** To provide strong evidence that the drug is efficacious for its intended use.
- **Collecting Comprehensive Safety Data:** To identify less common side effects and gather more information on the drug's safety profile.
- **Comparing with Standard Treatments:** Sometimes included as a key objective where conditions have established standards of care.

Phase III trials are randomised and controlled studies designed to meet regulatory requirements for marketing approval in target regions, such as the Food and Drug Administration (FDA) in the United States or the EMA in Europe. Trial design, endpoints, and data collection are carefully planned in consultation with regulatory authorities to ensure the studies provide the evidence needed for drug approval and registration.

Designing Phase III trials also requires considering real-world applicability, patient quality of life, and impacting healthcare resource utilisation. Collaborating with payer representatives before finalising study protocols helps align trial objectives and outcomes, strengthening the therapy's value proposition during future pricing and reimbursement negotiations.

Phase IV: Post-Marketing Surveillance

After a drug has been approved and is available on the market, Phase IV trials continue to monitor its performance in the general population. The main objectives are:

- **Monitoring Long-Term Safety:** To detect rare or long-term side effects that may not have been apparent in earlier trials.
- **Evaluating Long-Term Effectiveness:** To assess how well the drug works over an extended period in real-world conditions.
- **Studying Diverse Populations:** To understand how the drug affects different groups of people, such as older adults, children, or those with other health conditions.

Data from Phase IV studies can lead to improvements in how the drug is used or provide information for additional warnings and precautions. Additionally, these studies are crucial in supporting label expansion initiatives to broaden the drug's approved indications, strengthening payor negotiations through real-world evidence of clinical and economic value, validating treatment protocols in specific patient subgroups, and informing healthcare system decision-making regarding optimal therapeutic positioning and resource allocation. ■

3.2.1 Considerations for Psychedelics

Clinical testing for psychedelic therapies demands tailored protocols at every phase. In Phase I trials, extra safeguards are implemented to monitor physical and psychological responses. Enhanced observation protocols and carefully controlled clinical environments help manage the acute, often intense, effects.

Phase II trials introduce further complexity. The treatment setting—including providing psychological support—can significantly influence patient outcomes. Therefore, structured therapeutic environments are critical to ensuring robust safety and efficacy data.

Phase III trials face the inherent challenge of functional unblinding. The unmistakable subjective effects of psychedelics make it difficult to maintain true double-blind conditions. Alternative designs, such as using active placebos, may mitigate this issue but require careful interpretation of results.

Phase IV studies remain indispensable. They capture long-term safety and real-world effectiveness, which are particularly important for therapies that may offer rapid and sustained benefits from limited dosing.

3.3 Regulatory Approval

Once a new therapy has completed the clinical trial phases, it must obtain regulatory approval before being marketed and made available to patients. The EMA oversees this process in the EU, while the FDA plays a similar role in the United States. The Medicines and Healthcare products Regulatory Agency (MHRA) serves as the independent regulator in the UK. Most often, global drug developers target FDA approval first, driven primarily by the size and value of the U.S. pharmaceutical market. The U.S. market is the largest by value, making it a strategic priority for most companies.

Following FDA approval, developers typically prepare a dossier for submission to the EMA and MHRA. The requirements between these regulatory agencies can differ, and additional confirmatory studies may be necessary to meet their specific standards. In the UK, the MHRA operates an International Recognition Procedure (IRP), whereby eligible drugs with approvals in countries including the U.S., Canada, Switzerland and EU can request an expedited review by the MHRA. Importantly, the EMA maintains its own rigorous evaluation process and doesn't automatically accept FDA approvals. While the EMA does not specify a required percentage of European trial sites, they do require that clinical trials included in marketing authorisation applications comply with EU standards, including Good Clinical Practice (GCP) and ethical principles, regardless of where researchers conduct the trials. The EMA evaluates whether the submitted data is sufficiently relevant to European populations and healthcare contexts. Similarly, the MHRA often requires evidence of safety and efficacy in UK populations.

Manufacturers can pursue several regulatory pathways within the EU to obtain marketing authorisation. The Centralised Procedure, coordinated by the EMA, results in a single marketing authorisation valid throughout all EU Member States and is mandatory for certain products, including most novel therapeutics and those for specific conditions. Alternatively, the Decentralised Procedure allows applications in multiple EU countries simultaneously when no prior authorisation exists, while the Mutual Recognition Procedure (MRP) enables a marketing authorisation granted by one EU member state to be recognised by other Member States. Finally, National Procedures permit companies to seek authorisation in a single EU country, though this approach is less common for innovative therapies.

Submission to Regulatory Authorities

The journey towards regulatory approval includes preparing and submitting a comprehensive dossier to the relevant regulatory authorities. In the United States, this involves compiling a New Drug Application (NDA) for the FDA, while in the EU, it requires a Marketing Authorisation Application (MAA) for the EMA.

These dossiers must include detailed information from all stages of drug development, encompassing preclinical data, clinical trial results, and quality control measures. The goal is to demonstrate that the drug is safe and effective, has a positive and acceptable benefit-risk profile, and is manufactured to high-quality standards.

Beyond the centralised EMA pathway, companies can pursue country-specific regulatory strategies within the EU. One approach is to initially seek approval in a single EU member state through its national regulatory authority and then expand to other countries through the MRP.

This strategy might be particularly relevant for psychedelic therapies, where regulatory and cultural attitudes vary significantly across Member States. For instance, a company might first pursue approval in countries with more progressive policies towards psychedelics, such as the Netherlands, and then leverage this approval to expand into selected other EU Member States based on their policy environment and market access conditions.

Regulatory Requirements

Regulatory authorities require robust evidence to ensure that any new therapy meets stringent safety, efficacy, and quality standards. This evidence includes comprehensive clinical trial data showing the drug effectively treats the intended condition without unacceptable risks. Additionally, manufacturers must provide detailed information about the drug's manufacturing process to ensure consistency and purity.

For drugs classified as controlled substances, such as many psychedelics, there are additional layers of regulation. Companies must address specific requirements related to the handling, storing, and distribution of these substances to prevent misuse and ensure safety. These requirements vary by jurisdiction and require separate review and sign-off in each country where the drug will be developed or marketed.

Regulatory Pathways for New Therapies

Various regulatory pathways are available for new therapies, each designed to expedite the approval process under certain conditions. The standard approval pathway involves thoroughly reviewing all submitted data, typically taking the EMA up to 210 days to decide. This timeline does not include the necessary pauses (known as clock stops) needed for the company to answer questions and provide additional information.

However, accelerated pathways are available for therapies that offer significant benefits over existing treatments or address unmet medical needs. These include the EMA's Accelerated Assessment, which reduces the review time to 150 days, and the EMA's Conditional Marketing Authorisation, which allows for earlier approval based on less complete data, provided the company commits to further studies after approval. The EMA's PRIME (Priority Medicines) scheme is another potential option, offering enhanced support for developing medicines targeting unmet medical needs and potentially speeding up the evaluation process. ■

Timelines and Expectations for Regulatory Submissions

Understanding the timelines and expectations associated with regulatory submissions is vital for planning and strategising the approval process. While the FDA and EMA share many similarities in their requirements, there are notable differences that companies must account for. For example, the EMA may request additional studies not required by the FDA, such as trials in specific populations or longer-term safety data. This means that even after obtaining FDA approval, companies may need to conduct further research to meet the EMA's standards.

When a country or regional regulatory approval is obtained, it may allow some drugs to be accessed in countries outside its jurisdiction, depending on the country's specific rules and regulations and the level of perceived unmet clinical need. A regulatory approval may also be used as a reference filing to request accelerated reviews or mutual recognition approvals in other countries. ■

3.3.1 Considerations for Psychedelics

The pathway to regulatory approval for psychedelic therapies is inherently complex. Due to their potent effects on the central nervous system, these compounds require a more rigorous risk management approach. Developers must obtain specialised licenses and submit comprehensive safety and efficacy data that address both conventional endpoints and the unique challenges posed by these agents.

Detailed documentation on pharmacodynamics and pharmacokinetics is critical. This data must show that the therapy effectively treats the condition and that robust control measures adequately manage its potential for misuse.

Early and frequent engagement with regulatory bodies can clarify expectations. Scientific advice meetings help ensure that companies fully leverage accelerated or conditional approval pathways when addressing the unmet needs in mental health and other areas.

3.4 Health Technology Assessment

Following regulatory approval, a new therapy commonly undergoes an HTA and/or payer review process before it can be widely adopted and reimbursed within healthcare systems. HTA bodies systematically evaluate a health technology's value depending on the criteria adopted by the reviewing body. These criteria may include clinical effectiveness, relative clinical effectiveness versus standard of care, budget impact, cost-effectiveness, and broader impacts on the health system and society. The primary goal is to inform policy and decision-making to ensure healthcare systems use resources efficiently and effectively.

In many European countries, HTA has become so deeply integrated into pharmaceutical market access that a poor HTA outcome can lead to no reimbursement for the medicine or potentially reimbursement but at a relatively low price. This integration makes the HTA process a critical step in determining the clinical adoption of a new therapy and its commercial viability in these markets.

Evaluation by HTA Bodies

HTA bodies may assess both the clinical and economic value of new therapies. This assessment is crucial across Europe for determining whether public health systems should fund a treatment. Such an evaluation may include:

- **Clinical Importance of Therapy:** Determining the clinical relevance of the new therapy through a review of the indicated patient population, the severity of the condition and perceived unmet clinical need in the local population.
- **Clinical Effectiveness:** Examining the therapy's clinical and patient-relevant benefits, including comparison to existing treatments and standard of care, based on data from clinical trials and other available literature.
- **Cost-Effectiveness:** Analysing the overall costs and cost-savings associated with the therapy relative to the health benefits it provides, often using metrics like the cost per quality-adjusted life year (QALY) gained.
- **Budget Impact:** Assessing the financial implications of adopting the therapy on the pharmaceutical medicines budget or the broader healthcare system's budget.
- **Health System Impact:** Identifying if the therapy can be integrated into existing care pathways or if new care pathways, new infrastructure, or companion services will be required to enable the use of the therapy or technology.

Common European Pathway

The European Union has established a collaborative network with a goal of streamlining some HTA processes across Europe (Joint Clinical Assessments, JCAs). Under the new EU Regulation on HTA, which began implementation in January 2025, there is a move towards JCAs at the EU level. The EU will gradually phase in this regulation until 2030, when the system will evaluate all new medicines approved by the EMA.

This regulation means that for certain health technologies, including new medicinal products, the EU will conduct a single clinical assessment that all EU Member States can use. This joint assessment will focus on the clinical aspects, while individual countries will retain responsibility for economic evaluations and reimbursement decisions.

Differences in HTA Processes Between Countries

Significant differences in the approach to HTA exist in different countries and even across regions within a country. Consequently, it is common for the same drug therapy to receive very different HTA outcomes regarding pricing and reimbursement across Europe.

Clinical value recognition varies significantly. All HTA processes include an element of defining clinical value, and some country processes, such as Germany and France, include formal criteria for publicly ranking clinical value and/or additional clinical value compared to the standard of care.

Definitions of what constitutes clinical value may differ. HTA bodies typically recognise objective clinical outcomes from clinical studies; however, →

Specificities exist in each process. For example, Germany's HTA process recognises only patient-relevant outcomes to inform the clinical benefit rating. One country's HTA may accept an indirect comparison of the therapy in question to the standard of care in that country. Still, other countries' HTAs may recognise comparative clinical value only where researchers have completed a head-to-head randomised controlled trial (RCT).

Cost-effectiveness thresholds are another significant source of variation between countries. Differences in these thresholds mean that a therapy deemed cost-effective in one nation might fail to meet the threshold in another, leading to disparate access to treatments across borders. The underlying methodology, differences in treatment pathways between countries, or differences in the overall willingness-to-pay threshold may drive this.

The variation also extends to evidence requirements, with some countries demanding additional real-world evidence or long-term data beyond what companies submitted for regulatory approval. Furthermore, countries often differ in their preferred economic models and methodological approaches to evaluations, which can substantially affect how they assess outcomes.

The handling of productivity effects represents one central area of divergence among countries. Some nations, like the Netherlands, allow for the inclusion of productivity gains or losses in their economic evaluations, considering how a therapy might affect a patient's ability to work and contribute economically.

In contrast, the UK typically excludes these effects from the National Institute for Health and Care Excellence (NICE) cost-effectiveness assessments. This fundamental difference in approach can lead to varying assessments of the same therapy across different jurisdictions.

Preparing for HTA Evaluations

Developers must take several key steps throughout development to maximise their chances of successful HTA outcomes. They should understand evidence requirements early, including preferred endpoints, comparators, and relevant patient sub-populations that different HTA bodies will evaluate.

Engagement with HTA bodies is essential, as many countries offer scientific advice or early dialogue opportunities. These interactions help clarify expectations and allow developers to adapt their evidence generation. Developers can optimise their resources by designing clinical trials that meet regulatory and HTA requirements. This might include selecting appropriate comparators, gathering health-related quality-of-life data, and choosing study populations that reflect likely treatment recipients.

Developers should begin HTA analysis during Phase III trials and can finalise an HTA dossier within six months of trial completion. However, work on comparing outcomes against current treatments can start earlier, before Phase III data is available. This preparation is crucial, as showing medical benefit or outcome superiority alone will not suffice for HTA approval.

Given significant country differences, developers must prepare country-specific submissions matching national requirements. This tailored approach, while demanding, helps navigate varying HTA body requirements and achieve better market access outcomes. ■

3.4.1 Considerations for Psychedelics

HTA evaluations for psychedelic therapies must reflect their integrated nature, which combines drug administration with psychological support. Standard HTA models, typically designed for conventional pharmaceuticals, may struggle to evaluate therapy with both drug and non-drug components of care. Current HTA methodologies may also not acknowledge indirect and societal benefits where these are present.

Assessment frameworks should consider long-term remission rates and improvements in quality of life that may arise from a single or a few dosing sessions. These benefits differ markedly from the outcomes of daily medications and require bespoke cost-effectiveness models.

Proactive engagement with HTA bodies is essential. By adapting trial designs to include endpoints that mirror real-world outcomes, developers can better demonstrate the holistic value of psychedelic therapies. Addressing methodological challenges, such as functional unblinding, early on is also critical.

3.5 Pricing and Reimbursement Negotiations

After HTA bodies have assessed a new therapy, and assuming they have determined some degree of therapeutic value, manufacturers must next negotiate its price and reimbursement terms with payers. A group with overarching authority may manage the whole HTA, pricing and reimbursement process within a single process, or different groups containing different stakeholders may manage entirely separate processes.

Payers, including national health services, insurance companies, and other funding bodies, are pivotal in determining whether patients can access the therapy and under what conditions. Effective engagement with payers is essential to ensure that the treatment is accessible to patients and financially viable for the manufacturer.

Engaging with Payers

Engaging with payers may involve presenting a compelling and succinct value proposition for the new therapy. Creating a compelling value proposition means demonstrating how the therapy benefits patients and the healthcare system compared to existing treatments. The value proposition should encompass clinical effectiveness, safety, and additional benefits, such as improved quality of life or reduced need for other healthcare services.

Negotiating Pricing Based on Value

Manufacturers centre pricing negotiations around the therapy's perceived value, which HTA bodies may have already formally evaluated and summarised in an HTA report. Manufacturers must justify the proposed price by aligning it with the therapy's benefits. To achieve favourable pricing relative to existing standards of care, manufacturers may focus on:

- **Clinical Benefits:** Highlighting significant improvements in health outcomes, such as increased survival rates, faster recovery times, or better symptom management.
- **Economic Benefits:** Demonstrating cost savings for the healthcare system, such as reduced hospitalisations, fewer doctor visits, or decreased need for supportive care.
- **Societal Benefits:** Considering broader impacts like improved productivity, where patients can return to work sooner or require less caregiving support.

Factors Influencing Pricing Decisions

Several factors influence the outcome of pricing and reimbursement negotiations:

- **Budget Impact:** Payers assess the financial implications of adopting the new therapy on their budgets. High-cost therapies may face challenges if they significantly increase expenditure, even if they show clear therapeutic benefits.
- **Therapeutic Need:** Therapies that address unmet medical needs may be viewed more favourably. This can justify higher prices due to the added value they bring.
- **Additional Clinical Benefit:** Where products have been formally determined to show additional clinical benefit over the standard of care, many payer pricing methodologies recognise and reward this with premium pricing.
- **Policy Considerations:** Government policies and healthcare priorities can affect negotiations. For example, initiatives to promote access to innovative treatments or to manage costs within certain therapeutic areas may influence decisions.
- **Comparator Prices:** The cost of existing treatments is considered when evaluating the price of a new therapy. If the new therapy only offers benefits similar to existing therapies, payers may fix the price at the same level or request a slightly discounted price.
- **Clinical Advocacy: T**he presence of clinicians, clinical groups or patient groups advocating for product reimbursement may positively affect reimbursement and pricing decisions. Not all payer decision-making includes reviewing advocacy considerations, but in most decision-making, there is at least an indirect influence from these groups.

Impact of Innovative Therapies on Pricing Models

Psychedelic therapies present unique challenges that do not easily fit into traditional pricing and reimbursement frameworks. The potential for drug and psychotherapeutic support combination, higher upfront costs compared to standard treatments, and potentially large patient populations, require considering alternative pricing approaches.

Innovative therapies, such as personalised medicines, gene therapies, or treatments requiring specialised administration, challenge traditional pricing models. These therapies often come with high development costs and offer significant benefits, but their high up-front prices can strain healthcare budgets. Like psychedelics, they face similar challenges: the drug cost represents only part of the overall therapeutic approach, implementation requires specialised infrastructure and delivery, and there are often data gaps regarding medium to long-term benefits.

Additionally, in many indications being studied for psychedelics, particularly in mental health, the existing standard-of-care drugs are generic and priced too low to serve as meaningful pricing benchmarks for new therapies, despite the potential for significant therapeutic advances.

Adaptive Pricing Models

To accommodate innovative therapies, different pricing models can be explored, such as:

- **Value-Based Pricing / Performance-Based Pricing / Risk-Sharing Agreement:** Prices are linked to the real-world outcomes achieved by the therapy. The manufacturer receives the agreed-upon price if the therapy delivers the expected benefits. If not, rebates or price adjustments may apply.
- **Managed Entry Agreements:** These are arrangements where access to the therapy is provided under specific conditions, such as collecting additional data on effectiveness or initially restricting use to certain patient groups.
- **Annuity Payments:** For very high-cost therapies with long-term patient impacts, payments can be spread over several years rather than paid upfront, easing the immediate financial burden on payers.

- **Indication-Based Pricing / Tiered Reimbursement:** Different prices may be set for the therapy based on the different conditions or patient groups being treated, reflecting variations in effectiveness and perceived value across indications. In practice, a single 'blended' price is often calculated and used for all purchasing.
- **Budget Caps:** Agreements may include limits on the total expenditure for the therapy within a certain period. Once the cap is reached, additional treatments may be provided but are often provided free of charge by the manufacturer.
- **Population Restriction Strategies:** The reimbursed population may be narrower than the approved indication, focusing on specific patient subgroups where the therapy demonstrates the highest value.
- **Volume-linked Pricing:** The price per unit of medicine decreases once certain thresholds are passed, most often calculated over a 3-month or 12-month period.

It is important to note that population restrictions in reimbursement can emerge through two pathways: payer-driven, where healthcare systems identify and limit coverage to the highest-value patient segments, or manufacturer-driven, where companies proactively request reimbursement for a narrower patient population in anticipation of pricing pressures. This strategic approach helps optimise the therapy's value proposition and pricing while managing budget impact concerns.

Preparing for Pricing and Reimbursement Negotiations

Manufacturers can significantly enhance their negotiation position through key strategies focusing on engagement, evidence, and flexibility. Early engagement with payers is crucial, and manufacturers should initiate discussions during the development process to understand payer expectations and concerns clearly. Seeking expert advice on the methodologies payers use for the pricing and reimbursement process is also crucial to identify negotiation approaches and pricing and reimbursement requests that payers can accept. This proactive approach allows companies to address potential issues before the pricing and reimbursement process is initiated, where they become barriers to access and result in limited or no reimbursement outcomes.

Demonstrating real-world value forms another essential component of a strong negotiation strategy. Manufacturers can strengthen their position by providing compelling evidence from real-world studies or early access programs demonstrating the therapy's effectiveness and impact on patient quality of life. This real-world data often carries significant weight in negotiations, as it helps payers understand how the treatment performs in actual clinical practice rather than just in controlled trial conditions.

Flexibility in pricing strategies is equally essential for successful negotiations. Manufacturers should remain open to alternative pricing models that align with payer needs and policy frameworks. This might include innovative approaches such as outcomes-based agreements, risk-sharing arrangements, or other novel pricing structures that can help bridge gaps between manufacturer and payer perspectives.

A collaborative approach with both payers and the broader healthcare system rounds out an effective engagement and negotiation strategy. By working with payers from an early stage to find mutually beneficial solutions, manufacturers can help ensure patient access and system sustainability. This partnership-oriented approach often leads to more productive discussions and better outcomes than adversarial negotiating stances. For example, partnering with health system stakeholders to define what a service specification for a new therapy should be, will help the system prepare early while also reducing uncertainty for payers. The focus should remain on finding common ground that serves the healthcare system's sustainability needs and the shared goal of providing patients with access to innovative therapies. ■

3.5.1 Considerations for Psychedelics

Psychedelic therapies differ substantially from more conventional, compound-based chronic medications. They typically involve a limited number of drug administrations alongside psychological support, leading to a hybrid cost structure.

Manufacturers must clearly articulate a value proposition that justifies the higher upfront costs. This involves demonstrating long-term benefits such as sustained symptom relief and reduced reliance on ongoing medications. Value-based or performance-based pricing models can help align initial expenses with downstream savings.

Negotiations should also account for market-specific challenges. In mental health, where existing treatments may be generic and very low-cost, targeting reimbursement for treatment-resistant subgroups might be necessary. Early engagement with payers to address potential stigma and regulatory concerns is critical for smoothing the negotiation process.

3.6 Local Market Access and Uptake

After regulatory authorities have approved a new therapy and stakeholders have determined pricing and reimbursement terms, manufacturers must ensure that the treatment reaches patients effectively. Local market access and uptake involve a series of activities aimed at integrating the new therapy into healthcare systems, making it available to prescribers and patients, and ensuring that patients realise its benefits in real-world settings.

Inclusion in Formularies

One hurdle in market access is getting the new therapy included in a timely manner in national or insurer formularies and healthcare provider formularies, such as a hospital or hospital network. Formularies are official lists of medicines approved for prescription within a particular healthcare system or insurance plan. Inclusion in these lists is essential for the therapy to be prescribed and reimbursed.

To achieve formulary inclusion, manufacturers often need to:

- **Provide Comprehensive Evidence:** Supply all necessary clinical and economic data that demonstrate the therapy's value compared to existing alternatives.
- **Meet Specific Criteria:** Comply with any additional requirements set by formulary committees, which may include demonstrating cost-effectiveness within the context of the specific healthcare setting (at the national or regional level).
- **Localisation of Data:** Provision of an estimate of the patient population served by the formulary, likely dosing patterns and cost estimates.
- **Engage with Stakeholders:** Work closely with healthcare authorities, insurance companies, and other stakeholders to address concerns and facilitate acceptance.

Successful inclusion in formularies ensures that the healthcare system recognises the therapy and prescribers can access it for their patients.

Implementation in Clinical Practice

Once included in formularies, the next challenge is implementing the therapy in clinical practice. This involves several key aspects:

- **Training Providers:** Healthcare professionals must be educated about the new therapy, including its indications, administration procedures, potential side effects, and monitoring requirements. Training may involve workshops, seminars, online courses, and informational materials.
- **Establishing Infrastructure:** Some therapies require specific equipment, facilities, or support services. Ensuring that healthcare settings have the necessary infrastructure is crucial. This might include setting up dedicated treatment rooms, acquiring specialised equipment, or establishing protocols for handling and administering the therapy.
- **Integrating into Clinical Pathways:** The new therapy should be incorporated into clinical guidelines and treatment pathways to promote its appropriate use. Collaboration with professional societies and guideline committees can facilitate this integration.
- **Supporting Adherence:** Providing resources to help patients adhere to their treatment regimens, such as patient education materials, support programs, or mobile applications, can enhance the therapy's effectiveness.

Effective implementation ensures that healthcare professionals are confident in prescribing the therapy and that patients receive it safely and effectively.

Data collected from initial market access efforts, such as patient uptake rates and healthcare provider feedback, can inform iterative improvements in training programs, infrastructure investments, and treatment protocols.

Patient Access

Ensuring equitable patient access is a fundamental goal of European health systems. Various barriers, including geographical disparities, socioeconomic factors, and awareness levels, can hinder patients from receiving new therapies.[11] Healthcare providers and manufacturers must work within national frameworks and regulations that govern how treatments reach patients.

Getting treatments to patients across different geographies is challenging, especially for therapies that need special facilities or trained staff. This is usually solved in Europe by setting up a network of approved treatment centres and working with existing specialist hospitals. Some countries choose specific hospitals to become expert centres for certain treatments, which helps gather skilled staff and equipment in one place.

Healthcare staff need proper training approved by official medical bodies. Drug companies help with this by funding training programs or running educational courses. This training teaches healthcare workers how to choose the right patients, give treatments correctly, and monitor for safety issues.

Patient groups participate in HTA processes to review new treatments and determine what might stop patients from getting them. These groups also help create support programs for patients, working within European rules about what help can be offered.[12]

Challenges in Implementing New Therapies

Implementing new therapies in real-world settings presents several challenges. Healthcare facilities often face resource constraints and may lack the funding, staff, or equipment needed to adopt new therapies. There can also be resistance to change, as healthcare professionals may hesitate to alter established practices, especially if the new treatment requires significant workflow adjustments or additional training.

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[*] For a deeper dive into equitable patient access, see Chapter 9.

[11] Notable differences exist between European and U.S. patient access systems. The U.S. permits manufacturers to offer direct financial assistance and rebate programmes to patients, practices that are not legally permitted in European healthcare systems, where such mechanisms remain under strict regulatory control.

Adopting new therapies can be complicated and time-consuming due to regulatory and administrative hurdles. Additionally, ongoing monitoring of the therapy's effectiveness and safety in real-world use is essential but can be challenging to implement.

Facilitating Uptake Among Healthcare Professionals

Several supportive activities aid appropriate adoption and uptake among healthcare professionals. Manufacturers—or third-party organisations—must provide education and training by offering accessible and practical training opportunities to familiarise professionals with the new therapy. They must ⤴ demonstrate value by sharing evidence of the therapy's benefits through clinical studies, real-world data, and case studies.

Manufacturers should simplify the implementation process by developing tools and resources that make it easier to incorporate the therapy into existing practices, such as treatment algorithms or electronic health record templates. Finally, they should engage key opinion leaders through collaboration with respected professionals who can advocate for the therapy and share their experiences to ensure successful implementation. ■

3.6.1 Considerations for Psychedelics

Introducing psychedelic therapies into clinical practice involves overcoming both practical and perceptual challenges. These treatments require dedicated treatment rooms equipped to provide safe, controlled environments.

Healthcare professionals must undergo comprehensive training that covers both the pharmacological and psychological aspects of psychedelic therapy. This training ensures clinicians can guide patients through the experience and manage any acute or long-term effects.

Overcoming historical stigma is another key hurdle. Manufacturers and clinical providers need to collaborate together to educate stakeholders—from prescribers to patient advocacy groups—about the robust evidence base and established safety protocols.

Local market access strategies should focus on piloting expert centres and gathering real-world data. This evidence will be crucial in refining training programmes, optimising treatment protocols, and demonstrating the therapy's value to broader healthcare systems.

3.7 Key Stakeholders in European Psychedelic Medicine

The development and implementation of psychedelic therapies in Europe involves multiple stakeholder groups, each playing distinct roles in bringing these treatments to patients. These include drug developers, regulatory authorities, HTA bodies, insurance and reimbursement organisations, healthcare professionals, mental health facilities, medical societies, patient advocacy groups, and patients.

Drug developers lead the advancement of psychedelic therapies through clinical trials and regulatory processes. However, many major players currently focus on the U.S. market, with limited direct engagement in European regulatory and reimbursement pathways.

Key players include Compass Pathways, developing psilocybin treatment for TRD, Lykos Therapeutics (formerly MAPS PBC), advancing MDMA therapy for PTSD, Cybin, working on novel psychedelic compounds, Usona Institute, developing psilocybin therapy for major depressive disorder through a non-profit approach, and MindMed, researching various compounds including LSD and novel psychedelics for mental health conditions.

These companies collaborate with contract research organisations (CROs) and contract manufacturing organisations (CMOs) to conduct trials and produce therapies under strict quality controls.

Regulatory authorities oversee the approval and safety monitoring of psychedelic therapies. The EMA leads centralised marketing authorisation across the EU, while national agencies like Germany's BfArM, the UK's MHRA, and the Netherlands' CBG-MEB maintain oversight within their jurisdictions. These bodies evaluate safety, efficacy, and quality data while ensuring compliance with controlled substance regulations.

HTA bodies evaluate new therapies' clinical and economic value after regulatory approval. Organisations like Germany's IQWiG, England and ⤴ Wales' NICE, and the Netherlands' ZiN assess evidence to inform pricing and reimbursement decisions. HTA evaluationrs may consider not only clinical effectiveness but also cost-effectiveness and broader societal impact. HTA may be particularly challenging for psychedelic therapies given their unique delivery model combining drug administration with psychotherapy.

Insurance and reimbursement stakeholders determine patient access through coverage decisions. In Europe, this primarily involves public health insurance systems and national health services, though private insurers play varying roles across countries. These organisations face the challenge of evaluating the complex cost structure of psychedelic therapies, which includes both medication and intensive therapeutic support.

Healthcare professionals represent a crucial link in delivering psychedelic therapies safely and effectively. This group includes psychiatrists, psychologists, specialised therapists, nurses, and pharmacists. Their expertise and willingness to adopt these novel treatments will significantly influence implementation success.

Mental health facilities and treatment centres provide the physical infrastructure and operational framework for delivering psychedelic therapies. These include hospitals, specialised clinics, and community mental health centres. They must adapt their facilities to accommodate the unique requirements of psychedelic sessions, including dedicated therapy rooms and extended monitoring capabilities. Private clinics like Clerkenwell Health in the UK are pioneering the integration of these treatments, while established healthcare institutions are beginning to develop protocols for future implementation.

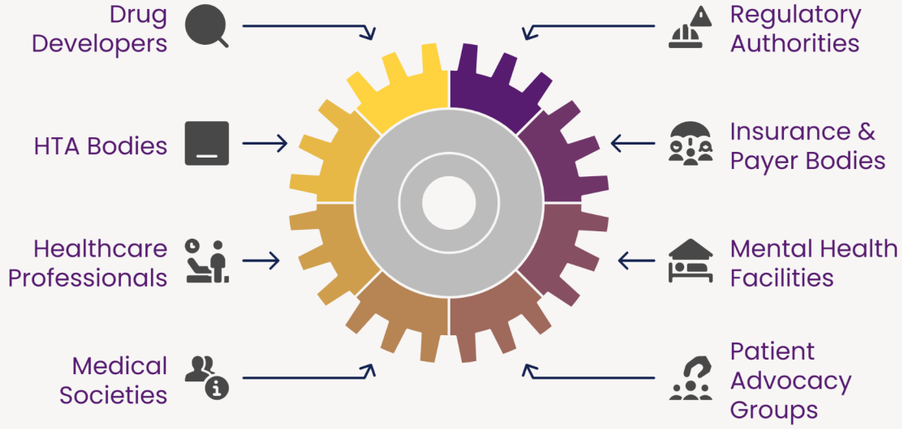
Medical societies and professional associations shape standards and guidelines for clinical practice. Organisations like the Royal College of Psychiatrists in the UK and the Dutch Psychiatric Association (NVvP) influence how their members approach new therapies. These bodies play crucial roles in developing training requirements, ethical guidelines, and best practices for implementing psychedelic →

therapy. Their endorsement and guidance significantly impact the acceptance of these treatments within the medical community.

Patient advocacy groups and other multistakeholder alliances represent the interests of those who might benefit from psychedelic therapies. Organisations like the Psychedelic Access and Research European Alliance (PAREA) and Psychedelic Participant Advocacy Network (PsyPAN) advocate for patient access and safety. Mental health advocacy groups representing patients in health systems currently have limited engagement with psychedelic therapies but might become important allies when implemented.

Patients themselves, particularly those with treatment-resistant conditions, form the final and arguably the most important stakeholder group. They include individuals with depression, PTSD, addiction, and other mental health conditions who have not found adequate relief through conventional treatments. Their experiences, needs, and concerns directly influence the development and implementation of psychedelic therapies. Many patients actively seek information about these treatments, some participate in clinical trials, while others express concerns about safety, accessibility, and affordability.

Please refer to Appendix 14.3 for a detailed analysis of the stakeholder landscape. This appendix includes comprehensive profiles of key organisations within each stakeholder group and their specific concerns regarding the implementation of psychedelic therapies in European healthcare systems. It explores each stakeholder group's roles, interactions, and individual stakeholders, providing deeper insight into the ecosystem supporting the development and delivery of psychedelic therapies. ■



National HTAs

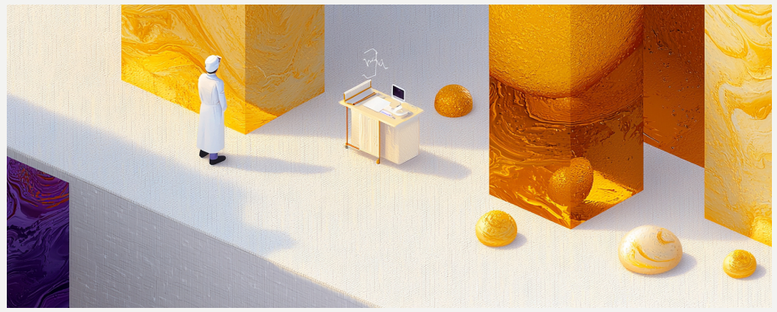
The **Healthcare Institute of the Netherlands** (Zorginstituut Nederland; ZiN) is the Dutch HTA body that evaluates new therapies' cost-effectiveness and societal impact. It determines whether treatments, including psychedelic therapies, are eligible for reimbursement under the Dutch universal healthcare system. ZiN evaluates drugs based on their clinical outcomes and broader healthcare implications, such as implementation challenges and the burden on healthcare providers. ZiN operates as an independent body under the Ministry of Health, Welfare, and Sport (Ministerie van Volksgezondheid, Welzijn en Sport; VWS).

The **Institute for Quality and Efficiency in Healthcare** (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; IQWiG) is Germany's primary HTA body. IQWiG assesses the clinical benefit of medicines, medical devices, and procedures, producing recommendations for the **Federal Joint Committee** (Gemeinsamer Bundesausschuss; G-BA), which makes final decisions on pricing and reimbursement. While IQWiG operates independently, its evaluations form the foundation for G-BA's policy decisions.

The **State Institute for Drug Control** (Státní ústav pro kontrolu léčiv; SÚKL) performs HTA to evaluate pharmaceuticals for pricing and reimbursement decisions. Considering cost-effectiveness and budget impact, SÚKL's process ensures transparency in introducing new medicinal products into clinical practice. As a smaller market, the Czech Republic often references HTA evaluations from larger EU Member States while adapting them to local healthcare needs and involving local stakeholders such as healthcare funds and clinical expert groups.

The **National Institute for Health and Care Excellenc**e (NICE) in England and Wales is the HTA body responsible for assessing new treatments' clinical and economic value for the National Health Service (NHS). NICE conducts its evaluations independently of MHRA, which approves medicines for marketing. NICE's assessments are highly detailed, often considering long-term cost-effectiveness and real-world implementation challenges, making its recommendations critical for the adoption of psychedelic therapies. NICE operates under the Department of Health and Social Care (DHSC) and collaborates with NHS bodies to integrate approved treatments into healthcare delivery. In Scotland, the **Scottish Medicines Consortium** (SMC) performs a similar role in assessing and providing advice about newly licensed medicines to NHS Scotland. In Northern Ireland, the Department of Health considers both NICE and SMC guidance when making local decisions about medicine availability.

Clinical Development of Psychedelic Therapies 4



The development of psychedelic therapies is rapidly advancing, with several promising compounds progressing through Phase II and Phase III clinical trials, particularly in the United States. However, within Europe, the regulatory and clinical landscapes remain relatively uncharted. This chapter explores key considerations developers must address to successfully navigate this landscape.

From ensuring safety and tolerability to engaging with regulators and other key stakeholders, this chapter emphasises the critical areas that will shape the future of psychedelic therapies in Europe. While the potential therapeutic promise of these compounds is clear, their unique characteristics—such as the intertwining of drug effects with psychotherapeutic support—pose novel challenges for trial design, patient selection, and endpoint measurement. Issues like the choice of appropriate therapeutic effects, and the integration of patient-reported outcomes require thoughtful planning to align with the expectations of European regulatory frameworks.

Stakeholder collaboration is another central theme. Developers must proactively engage with regulators, health technology assessment (HTA) bodies, payers, and patient advocacy groups to ensure their therapies are both approvable and accessible. The chapter outlines practical strategies for addressing these challenges, from leveraging good manufacturing and distribution practices to scaling production and engaging with diverse stakeholder groups. As the field continues to evolve, these considerations will be crucial in unlocking the potential of psychedelics to transform mental healthcare across Europe and beyond. ■

4.1 Designing Clinical Trials for Psychedelic Therapies

4.1.1 Unique Challenges in Trial Design

Blinding and Placebo Control

Blinding, also called masking, is a critical component of randomised controlled trials (RCTs). It safeguards that neither participants nor investigators know which treatment group a participant belongs to. This approach minimises bias and allows researchers to attribute outcomes solely to the treatment. However, psychedelic therapies present unique challenges due to their noticeable psychoactive effects, which often lead to functional unblinding. In this situation, participants or investigators (clinicians, raters, and other study staff) infer treatment assignment based on observable effects.

For instance, in a Phase III trial of MDMA therapy for PTSD, 79% of participants in the MDMA group correctly guessed they had received the active drug. In comparison, only 16% of placebo participants believed they had received MDMA (Mitchell et al., 2021). Similarly, in a single-blind study (only participants were blinded) of psilocybin for depression, 80% of participants accurately identified whether they had received psilocybin or placebo, further highlighting this challenge (Sloshower et al., 2024).

Unblinding is not unique to psychedelics; it is a broader challenge in psychotropic drug trials. A systematic review found that masking efficacy is often unreported or poorly tested in psychotherapy and pharmacology trials, with unblinding detected in a majority of cases when assessed (Boutron et al., 2006). For example, only 59% of psychiatric trials published in top journals in 2017 and 2018 adequately reported masking outcomes (Juul et al., 2021).

Expectancy effects compound the challenge of unblinding, as participants' expectations about receiving an active treatment influence their outcomes. This effect is not unique to psychedelics; studies of psychotropic drugs often report significant and positive placebo responses (Khan et al., 2005). ⤴

Within psychedelics, a meta-analysis of depression trials involving ketamine or esketamine revealed that the placebo effect might account for up to 72% of the overall treatment response (Matsingos et al., 2024).

The placebo effect, influenced by expectation, social interaction, and cultural factors, further complicates the interpretation of psychedelic trials. For instance, greater interaction with care providers can improve placebo response rates from 44% to 62%, highlighting the role of non-pharmacological factors (Hartogson, 2016). In psychedelic trials, participants who correctly identify their treatment group may experience amplified therapeutic effects, while those in the placebo group may feel disappointment, potentially diminishing their response. This expectancy-driven bias underscores how perceived treatment allocation can amplify outcomes in active groups and attenuate responses in placebo groups, complicating the interpretation of trial results.

Researchers have developed several strategies to mitigate functional unblinding. One approach involves using active placebos, such as low doses of the investigational psychedelic or other psychoactive substances, to mimic some effects of the active drug. For example, studies involving MDMA therapy have explored using low doses of MDMA or alternative psychoactive substances like d-amphetamine as active placebos (NLM, 2023-2026). However, such designs introduce their own challenges, including potential safety concerns with low-dose psychedelics and the possibility that active placebos may exert therapeutic effects (Psychedelic Alpha, 2024b).

Another approach involves 'firewalled' reporting systems, as seen in Cybin's Phase III study of CYB003. In this design, only dosing monitors collect data on participants' experiences during sessions, and these data are inaccessible to raters who assess outcomes and site staff. This separation hopes to minimise the potential for expectancy bias to influence assessments (Cybin, 2024). Additionally, studies often use blinded central raters to evaluate primary endpoints, such as depression scores, further reducing bias from unblinding among site staff.

Despite these mitigation efforts, functional unblinding remains a persistent concern, with regulators increasingly scrutinising its impact on trial outcomes. The FDA's rejection of Lykos Therapeutics' MDMA therapy for PTSD highlighted the role of unblinding and expectation bias in undermining efficacy data (Psychedelic Alpha, 2024a). To address these concerns, future trials may need to incorporate comprehensive unblinding surveys and subgroup analyses to assess the extent and impact of functional unblinding. While these strategies add complexity, they are crucial for ensuring the reliability and validity of psychedelic clinical trial data.

Comparator Selection

In evaluating psychedelic therapies, selecting appropriate comparators is critical to generating robust clinical evidence. Comparator selection falls under the broader framework of relative effectiveness assessment (REA). REA involves comparing the investigational therapy against current standard treatments, placebo, or alternative interventions to establish its added therapeutic value in real-world clinical practice. The choice of comparator is pivotal not only for regulatory approval but also for HTA and reimbursement decisions, as payers prioritise evidence of superiority or at least equivalence to existing therapies.

Current Comparator Strategies in Psychedelic Trials

In psychedelic trials with multiple study arms, researchers have typically compared the investigational therapy to placebo or, more recently, to lower doses of the same psychedelic. This design aims to allow researchers to characterise the effects of the active drug while managing functional unblinding caused by the noticeable psychoactive effects.

Although researchers have conducted limited head-to-head comparisons with standard treatments in the psychedelic space, esketamine (Spravato) provides a notable exception. A recent Phase IIIb trial compared esketamine nasal spray to extended-release quetiapine in treatment-resistant depression (TRD), both combined with standard antidepressants (Reif et al., 2023).

For emerging psychedelics, trials have taken varied approaches. Usona's Phase III psilocybin trial incorporates three groups: inactive placebo, 5 mg psilocybin, and 25 mg psilocybin (NLM, 2024-2026). MDMA therapy trials have used specialised therapy protocols tailored to psychedelics but have shied away from using low-dose comparators (Mitchell et al., 2021; FDA, 2024).

Other trials aim to minimise the therapeutic component to present psychedelics as drug-based interventions, simplifying regulatory and payer assessments (NLM, 2023-2025). However, this approach might diminish the unique therapeutic framework in which psychedelics operate, potentially causing researchers to underestimate their full impact.

A notable limitation across these studies is the absence of head-to-head comparisons with the standard of care, such as selective serotonin reuptake inhibitors (SSRIs) for depression or cognitive-behavioural therapy (CBT) for anxiety disorders. Without these comparisons, it becomes challenging for payers and HTA bodies to evaluate the relative benefits of psychedelics in routine clinical practice.

Regulatory and HTA Requirements for Comparators

Regulatory agencies like the FDA and EMA do not explicitly require head-to-head comparisons with the standard of care for drug approval. Instead, they focus on demonstrating safety and efficacy relative to a placebo or an alternative control. For example, the FDA has approved therapies based solely on placebo-controlled studies, provided the evidence meets rigorous standards of statistical and clinical significance (FDA, 2001). Similarly, the EMA evaluates efficacy, safety, and quality without mandating direct comparisons to existing treatments, though it does emphasise the importance of demonstrating added therapeutic value (EP, 2021).

Examples of Head-to-Head Comparisons and Challenges

One of the few head-to-head studies on psychedelics compared psilocybin to the SSRI escitalopram in patients with moderate-to-severe depression (Carhart-Harris et al., 2021). Although the psilocybin group showed significantly greater improvements than the escitalopram group on several secondary outcomes—including HAM-D-17, MADRS, higher remission rates, and improved quality of life—the primary outcome measure (QIDS-SR-16) did not show a statistically significant difference between groups. A six-month follow-up study indicated sustained benefits for both treatments but noted limitations such as low statistical power and reliance on self-reported outcomes (Erritzoe et al., 2024).

Despite their importance, head-to-head studies are resource-intensive, particularly for psychedelics. These therapies already involve substantial costs due to the controlled nature of the drugs, therapist hours, and specialised infrastructure. Combined with the uncertainty surrounding commercialisation and reimbursement, sponsors often operate on limited budgets, making such trials financially daunting. Additionally, introducing head-to-head comparators based on the existing standard of care may increase functional unblinding and the potential for bias, as described above.

Regional Variations in Comparator Expectations

The necessity for head-to-head studies also varies by country. In the Netherlands, HTA bodies like the National Healthcare Institute (ZiN) emphasise the inclusion of productivity effects and comparative effectiveness data in their evaluations. Germany's Institute for Quality and Efficiency in Healthcare (IQWiG) predominantly accepts direct study comparisons with standard treatments to assess the clinical benefit; indirect comparisons are often not considered, mostly due to a lack of comparability. In the Czech Republic, HTA processes are less formalised but increasingly align with EU-wide standards, including the expectation of comparative data. The UK's National Institute for Health and Care Excellence (NICE) evaluates new therapies against the current standard of care but may accept indirect comparisons in some instances.

Moving Forward: Comparator Strategies for Psychedelics

While head-to-head studies are highly valuable for HTA and reimbursement, there may be alternatives in specific scenarios. For example, network meta-analyses (NMAs) can compare multiple interventions indirectly using existing data, potentially reducing the need for direct comparisons. Early engagement with HTA bodies can clarify expectations and guide evidence-generation strategies. Developers must balance the scientific rigour that regulators require with the comparative data necessary for market access, optimising trial designs to balance the demands of all stakeholders.

As psychedelic trials advance, the inclusion of comparators reflecting real-world clinical practice will be critical for demonstrating their value.[13] Future research should prioritise cost-effective study designs that address these gaps while maintaining the therapeutic integrity of psychedelic treatments.

Integration of Psychotherapy

Psychedelic clinical trials face a significant challenge in balancing the roles of pharmacological intervention and psychotherapy. Drug developers often aim to standardise or minimise the psychotherapeutic component for several reasons: to manage operational complexity and costs, and, crucially, to align with traditional regulatory frameworks that evaluate drugs primarily based on their pharmacological effects. While this approach may facilitate regulatory approval pathways, it creates tension with many clinicians who emphasise the therapeutic relationship and psychological support as important elements of treatment. These competing perspectives influence trial design, outcomes, and the broader acceptance of psychedelic therapies.

[13] Common comparators for TRD, PTSD, and other conditions—such as SSRIs, quetiapine extended-release (for TRD), and CBT—are detailed in Appendix 14.4.1.

Psychotherapy as a Core Component or Supportive Measure?

The relationship between psychotherapy and psychedelics in clinical applications remains a subject of ongoing discussion. Traditional approaches have emphasised intensive therapeutic support, with protocols including preparation, dosing, and integration sessions. For instance, in MDMA therapy trials, researchers have argued that establishing a strong, empathic, and collaborative therapeutic alliance is critical; this trusted relationship not only supports the participant during the altered state but also facilitates deeper emotional breakthroughs and effective integration of the experience (O'Donnell et al., 2024). Similarly, psilocybin trials have historically emphasised the need for structured preparation, dosing, and integration sessions where therapists actively create a safe environment to help patients navigate challenging material and reframe their experiences (Phelps, 2017).

However, drug developers are increasingly pursuing models that position psychological support as a supportive rather than a central component. Companies like Compass Pathways and MindMed have demonstrated meaningful clinical responses with minimal therapeutic intervention, with data suggesting that treatment effects in responders emerge rapidly after dosing, independent of integration sessions (Goodwin et al., 2023; Goodwin et al., 2024; Holze et al., 2023). While this streamlined approach could significantly improve treatment accessibility by reducing implementation barriers and aligning better with existing regulatory frameworks and healthcare systems, further investigation is needed to fully understand the relationship between pharmacological effects and different levels of therapeutic support (Goodwin et al., 2023; Gründer et al., 2024).

The field now faces important questions about optimising the balance between therapeutic support and practical implementation. While more intensive therapeutic approaches might benefit some patients, they could limit broader access due to regulatory, reimbursement, and infrastructure challenges. Understanding how different psychological support levels affect outcomes, cost-effectiveness, and real-world implementation will be crucial for developing sustainable treatment models.

Standardisation and Variability Across Sites

A key challenge in trial design is ensuring consistency of psychotherapy protocols across study sites. Intensive therapy models, such as the one developed by Lykos for MDMA therapy, emphasise a variety of psychotherapeutic methods that could be employed. Independent monitors verify that raters report strong adherence to the protocol, including elements like trauma-focused care and relational skilfulness. Although these components may introduce some variability—particularly in international trials where cultural and regulatory differences exist—the robust adherence observed suggests that the approach maintains a reliable framework for clinical delivery (O'Donnell et al., 2024).

Companies like Compass Pathways and MindMed have developed protocols with reduced psychotherapeutic components, which may facilitate broader site participation and implementation. This development raises important questions about how different levels of therapeutic support might influence treatment outcomes across diverse clinical settings. Future research may help clarify the relationship between protocol intensity, site variability, and treatment effectiveness, particularly as these therapies move toward real-world implementation (Cavarra et al., 2022).

Therapy or Attention?

Meta-analyses have indicated that psilocybin therapy offers significant benefits over placebo in reducing depression symptoms (Metaxa & Clarke, 2024). However, the observed improvements in placebo groups receiving psychotherapeutic support highlight the substantial impact of the therapeutic environment itself. This raises questions about the extent to which patient outcomes are influenced by the specific pharmacological action of psilocybin versus the supportive context provided during treatment.

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Patient input also underscores the value of long-term support. Anecdotal evidence suggests that peer support networks emerge informally during and after trials, supplementing the formal therapeutic process. These networks may sustain long-term benefits, but they are rarely captured in trial designs or outcome reporting, leaving a gap in understanding the full impact of the therapeutic ecosystem.

The Path Forward: Evolving Perspectives

The necessity and sufficiency of psychotherapy in psychedelic treatments remain open empirical questions. While researchers widely incorporate psychotherapeutic support into clinical trials, limited systematic evidence delineates which therapeutic elements ensure safety and efficacy or whether psychotherapy is necessary at all (Aday et al., 2024). This uncertainty has practical implications for trial design and implementation, with regulatory approval pathways and healthcare system capabilities significantly influencing developers' approaches. Some protocols emphasise in-depth therapeutic frameworks, whereas others adopt more streamlined, predominantly pharmacological approaches.

The industry's framing of psychedelics as "psychoplastogens," as seen in the EFPIA 2024 Pipeline Review, reflects an evolving scientific understanding of these compounds (EFPIA, 2024b). While neurobiological endpoints provide valuable mechanistic insights, balancing these measures and patient-reported outcomes in mental health conditions will likely become an increasingly important consideration in trial design and regulatory discussions.

Moving forward, the field must address several key questions about optimal treatment delivery. Understanding which elements of psychotherapy—specific techniques, relational factors, or general support—most significantly contribute to outcomes remains crucial. However, clinical and academic investigators might pursue this research better than drug developers, particularly after initial regulatory approvals. This approach would allow developers to focus on establishing basic safety and efficacy, while the broader medical community can subsequently optimise treatment protocols through real-world implementation studies. Clinical guidelines, rather than regulatory requirements, may ultimately be the more appropriate mechanism for defining best practices in psychedelic therapy delivery. ■

Key Challenges in Psychedelic Trial Design

Blinding and Placebo Control
Functional unblinding is prevalent in psychedelic trials due to noticeable psychoactive effects. In MDMA trials, up to 79% of participants correctly guessed their treatment group, complicating data interpretation and introducing expectancy bias.

Comparator Selection
Most psychedelic trials use placebo or lower doses as comparators rather than standard treatments. This limits evidence for relative effectiveness assessment (REA), creating challenges for reimbursement decisions in particular.

Integration of Psychotherapy
Tension exists between standardising/minimising psychotherapy (which aligns better with regulatory frameworks) and preserving the therapeutic relationship that many clinicians consider essential. This balance affects trial design, outcomes, and broader clinical acceptance.

4.1.2 Regulatory Considerations

International drug control treaties, particularly the 1971 UN Convention on Psychotropic Substances, primarily shape the regulatory framework for psychedelic research. Under this convention, most psychedelics fall into Schedule I substances, which the convention deems to have high abuse potential and no recognised medical use (UN, 1971). This classification creates unique challenges for clinical research and future commercialisation (Demireva & Brun, 2023).

While the EU Clinical Trials Regulation has harmonised many aspects of drug development across Europe, additional requirements apply to controlled substances (EU, 2014). Sponsors must navigate country-specific regulations and bureaucracies, which can vary significantly.

There are signs of regulatory evolution. Australia's recent down-scheduling of psilocybin and MDMA for specific psychiatric indications suggests a growing acceptance of psychedelics' medical potential (TGA, 2023). Similar discussions are emerging in Europe, where successful market authorisation will necessitate rescheduling—of the drug product—potentially simplifying future research and treatment access (Haberkamp, 2024).

4.1.3 Patient Selection and Inclusion Criteria

Defining Target Populations

Psychedelic clinical trials target specific patient populations based on multiple factors, including expected treatment response, market size, ethical considerations, and regulatory and HTA requirements. These population choices influence trial outcomes, drug approval pathways, and eventual access to treatment.

Identifying Beneficiaries: Balancing Precision and Generalizability

Clinical trials for psychedelic therapies often focus on treatment-resistant populations, such as individuals with TRD or chronic post-traumatic stress disorder (PTSD). Developers choose these populations because they present an unmet medical need, which can expedite regulatory approval and lead to preferential reimbursement and pricing considerations (Sabé et al., 2024).

While broader inclusion criteria, such as enrolling MDD patients rather than those with TRD, might lead to higher response rates, the overall magnitude of improvement may be less pronounced. Patients with milder forms of depression typically have less room for symptom improvement compared to those with severe or treatment-resistant depression, potentially resulting in smaller effect sizes. Moreover, achieving access and having clinicians choose psychedelics as a treatment option before established medicines is unlikely in real-world practice. European regulators, payers, and clinicians will likely favour a more restricted patient population with limited treatment options.

Conversely, excessively narrow criteria may limit the trial's applicability to real-world practice and commercial viability. Developers must carefully navigate this balance, as seen in the selective inclusion criteria used in trials like EPIsoDE, which excluded patients with comorbid conditions or recent psychedelic use to maintain experimental rigour (Mertens et al., 2022).

Comorbidities and Real-World Complexity

Psychedelic clinical trials often exclude participants with comorbid conditions, such as co-occurring depression, addiction, or anxiety disorders. This practice, aimed at reducing variability and confounding factors, contrasts starkly with real-world clinical settings, where overlapping conditions are the norm (van Elk & Fried, 2023). Studies have shown that applying exclusion criteria from clinical trials to real-world populations could disqualify up to 99% of patients with depression, raising significant concerns about the generalizability of trial findings (Zimmerman et al., 2005).

For psychedelic trials, this discrepancy underscores the importance of designing studies that better reflect the complexity of real-world patient populations. Allowing for limited comorbidities, for example, could improve the external validity of trial results while still maintaining methodological rigour (Johnson et al., 2008).

This tension is exemplified in the stringent exclusion criteria of the Lykos Phase III trial of MDMA for PTSD, which aimed to mitigate risks and maintain trial integrity (NLM, 2018–2020). Investigators excluded participants if they had uncontrolled hypertension, significant medical disorders (e.g., myocardial infarction or cerebrovascular accident), or conditions like prolonged QT intervals that increase susceptibility to cardiac events. Additional exclusions included a history of hyponatremia, hyperthermia, or substance use disorders, as well as participants who had used MDMA excessively or recently. While these criteria are crucial for ensuring participant safety, they limit the applicability of trial findings to broader, more diverse patient populations.

To bridge this gap, future trial designs must balance the need for rigorous safety protocols with inclusivity that mirrors real-world complexity. These designs could include relaxing restrictions on mild or stable comorbidities or designing adaptive trial protocols to assess outcomes in broader, heterogeneous populations. Such approaches could ensure that findings are more representative of the patients who will ultimately receive these therapies in clinical practice.

Participant Motivation and Psychedelic Hype

Media coverage and societal enthusiasm for psychedelics influence participant recruitment in complex ways. While some individuals approach trials with optimistic expectations that may enhance engagement and placebo responses, others view psychedelic therapy as a last resort after exhausting conventional treatments. These contrasting motivations present distinct challenges: highly motivated participants might skew efficacy data positively, whilst treatment-resistant individuals who do not respond could face heightened risks of suicidality or self-harm behaviours. Additionally, participants with prior psychedelic experience may respond differently than those who are naïve to the substances, further complicating data interpretation and raising questions about replicability in real-world populations (Aday et al., 2022; Noorani & Mathukumaraswamy, 2023).

Feed-Forward Effects on Regulators and Payers

The choice of target population also has downstream effects on regulators and payers. Smaller, well-defined populations—such as those with treatment-resistant conditions—can lower budget impact estimates, increasing the likelihood of reimbursement approval. However, this narrow focus may necessitate additional studies to demonstrate effectiveness in broader populations, particularly for HTA evaluations that emphasise generalisability and long-term outcomes.

Inclusion of Diverse Populations

Psychedelic clinical trials face significant challenges in achieving demographic representativeness, often overrecruiting individuals with higher socioeconomic status and fewer time constraints. A recent review indicates that approximately 85% of participants identified as non-Hispanic White, while Black, Hispanic/Latino, and Asian individuals comprised only 2.9%, 5.9%, and 3.2% of participants, respectively (Hughes & Garcia-Romeu, 2024). Though some progress has been made, such as in MDMA trials, where Mitchell et al. (2023) achieved 33.7% non-White participation, significant disparities persist.

Addressing these disparities requires targeted strategies to overcome structural and practical barriers, particularly in Europe, where challenges focus on representing immigrant populations and ethnic minorities. Financial constraints, institutional mistrust, and cultural barriers often deter marginalised populations from participating (Noorani & Mathukumaraswamy, 2023). Solutions may include providing stipends, engaging community leaders, and offering multilingual materials to ensure broader accessibility (Haft et al., 2024). ■

4.2 Clinical Evidence Generation

4.2.1 Efficacy Outcomes

Primary and Secondary Endpoints

Psychedelic clinical trials measure success through specific outcomes called endpoints. The main (primary) endpoints typically look at how well symptoms improve or resolve, for example, tracking depression scores in TRD or anxiety levels in generalised anxiety disorder (GAD). Researchers measure these improvements using standard rating scales like the Montgomery–Åsberg Depression Rating Scale (MADRS) for depression or the Clinician-Administered PTSD Scale (CAPS) for PTSD. [14]

For example, in a Phase II trial of psilocybin for TRD, researchers measured changes in MADRS scores over three weeks as the primary endpoint. Secondary endpoints tracked the number of patients who showed significant improvement or reached remission (Goodwin et al., 2022).

While symptom reduction remains the primary focus, psychedelic trials may be suitable candidates for measuring secondary outcomes like quality of life (QoL) and functional improvements using tools such as the World Health Organization Quality of Life questionnaire. However, in most cases, regulators and payers prefer clear, symptom-based outcome measures (EMA, 2006).

The Disconnect Between Endpoints and Psychedelic Effects

Research shows that psychedelics produce multi-dimensional benefits that defy traditional endpoint structures. For instance, while symptom remission (e.g., achieving a MADRS score ≤10) is clinically meaningful, it may not capture the qualitative improvements patients report, such as a renewed sense of purpose or increased emotional clarity. Critics argue that focusing solely on reductionist measures, like symptom scores, underestimates the transformative effects of psychedelic therapy (Gründer et al., 2024).

To address this, researchers must integrate endpoints measuring quality of life and functional outcomes alongside symptom scales. This dual approach would align trial endpoints more closely with patient experiences and the broad therapeutic potential of psychedelics.

Regulatory and Payer Perspectives on Endpoint Selection

Endpoint selection is a product of negotiation between developers, regulators, and, increasingly, payers. Regulators like the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) prioritise clinically meaningful efficacy endpoints, often based on well-established scales. EMA guidelines, supported by ICH E9 and E10 principles, emphasise the need for validated endpoints that measure primary disease symptoms (e.g., CAPS for PTSD), ensuring robust evidence for approval. Secondary endpoints, including QoL measures, are considered supplementary and typically support broader claims beyond the core indication (EMA, 1998).

In contrast, HTA bodies focus on endpoints that reflect real-world benefits, such as functional recovery and productivity improvements. For example, achieving sustained remission and demonstrating long-term cost offsets would be highly influential factors supporting reimbursement. This dynamic creates tension in endpoint selection: developers must balance the need to satisfy regulatory requirements for efficacy with the evidence payers require to demonstrate economic and societal value.

Future Directions for Endpoints in Psychedelic Trials

As psychedelic clinical trials evolve, there is growing recognition that traditional endpoints may only partially capture the holistic effects of these therapies. Trial designs may need to include patient-reported outcomes that assess well-being, life satisfaction, and connectedness as core measures alongside symptom reduction.

[14] A table outlining endpoints used in recent psychedelic trials for TRD, PTSD, and anxiety disorders can be found in Appendix 14.4.2.

Duration of Effect

The duration of therapeutic effects following psychedelic therapy varies across studies and patient populations, shaping discussions among developers, regulators, and payers about cost-effectiveness. While proponents highlight the potential for long-lasting benefits from a single treatment course, closer examination of long-term follow-up data suggests a more nuanced reality. Studies often report sustained efficacy, but many patients engage in additional interventions, such as peer support, therapy, or conventional treatments, raising questions about the standalone impact of psychedelics over time.

Evidence for Long-Term Efficacy

Several clinical trials and follow-up studies have demonstrated sustained symptom reductions across conditions like depression, PTSD, anxiety, and addiction. Long-term follow-up data for psilocybin therapy in TRD have shown durable antidepressant effects, with treatment response and remission rates of 75% and 58%, respectively, at 12 months (Gukasyan et al., 2022). A 6-month follow-up study comparing psilocybin to escitalopram found sustained improvements in depressive symptoms, with psilocybin showing greater psychosocial gains, such as improved connectedness and meaning in life (Erritzoe et al., 2024).

Early studies also highlight the enduring psychological significance of a single psychedelic experience. All psilocybin participants in the Good Friday Experiment still attributed lasting spiritual and personal significance to their experience 27 years after the intervention (Doblin, 1991). For PTSD, MDMA therapy data reveal therapeutic gains persisting for up to 74 months, with significant reductions in CAPS scores, though 26% of participants sought additional therapy and 10% reported self-administering MDMA post-trial (Mithoefer et al., 2013; Jerome et al., 2020).

In anxiety-related conditions, LSD therapy has shown reductions in both anxiety and comorbid depression lasting up to 94 weeks (Holze et al., 2024). For cancer patients with existential distress, 60-80% experienced symptom relief even 3.8 years after psilocybin therapy (Agin-Liebes et al., 2020). In addiction treatment, 67% of participants in a smoking cessation trial remained abstinent at 12 months, and 60% at a mean of 30 months post-treatment, with participants rating their psilocybin experiences as among their most meaningful life events (Johnson, Garcia-Romeu & Griffiths, 2017).

Role of Additional Interventions

Long-term follow-up data consistently reveals that patients often rely on additional therapies or interventions to maintain benefits after psychedelic treatments. According to Jerome et al. (2020), a significant proportion of PTSD patients sought further treatment. Likewise, patients from a psilocybin TRD trial described seeking peer support, additional therapy, or microdosing to sustain initial gains (Breeksema et al., 2024).

These findings suggest that while psychedelic interventions may catalyse change, additional resources frequently support long-term efficacy. Trial outcomes or economic evaluations typically do not reflect such factors. For payers, this potential reliance on adjunctive care complicates arguments for long-term cost-effectiveness, particularly given the potentially high upfront costs.

Differences Between Trials and Real-World Implementation

Clinical trials often involve intensive psychotherapeutic support, which may amplify and prolong therapeutic outcomes compared to real-world settings. For instance, both psilocybin and escitalopram groups benefited from psychological support during a clinical trial (Erritzoe et al., 2024). This trial may not mirror clinical practice, where doctors generally prescribe SSRIs without therapy. Patient motivation, trial-specific attention, and controlled environments also contribute to more favourable outcomes, raising concerns about external validity.

In real-world implementation, repeated treatments may be necessary to sustain the effects. Evidence from ketamine trials—such as the SUSTAIN-3 study—indicates that patients who relapse after initial →

gains may require—and benefit from—re-induction protocols (Castro et al., 2024). Similarly, patients from psilocybin trials expressed a desire for additional sessions to reinforce therapeutic effects, arguing that a single session was insufficient for lasting change (Breeksema et al., 2024).

Repeated Treatments and Cost-Effectiveness

The absence of robust data on redosing protocols complicates cost-effectiveness analyses. While researchers have modelled MDMA therapy for PTSD as a one-time intervention with long-term savings, patient perspectives and trial follow-ups suggest that periodic treatments, peer support, or adjunctive therapies are common (Marseille et al., 2022). For classical psychedelics, researchers have observed long-term effects, but evidence remains limited to small—often open-label—studies. In contrast, ketamine's short-lived effects underscore the need for maintenance protocols (Price et al., 2023).

Regulatory Considerations

Regulatory frameworks, such as the EMA Clinical Efficacy and Safety Guidelines, prioritise sustained efficacy when evaluating new therapies (EMA, n.d.). However, the standard timeframes for assessing primary endpoints—typically 6 to 12 weeks—may not align with the prolonged effects of psychedelic therapies. The absence of long-term follow-up data in many trials further complicates regulatory assessments and raises questions about the durability of psychedelic treatments relative to established interventions.

4.2.2 Safety and Tolerability

Acute Adverse Events

Most adverse events (AEs) in psychedelic trials are transient and manageable, though systematic reporting remains inconsistent. A meta-analysis of 214 studies found serious adverse events occur in approximately 4% of participants with preexisting neuropsychiatric disorders, though only 23.5% of studies used systematic AE assessment methods (Hinkle et al., 2024). This meta-analysis highlights a crucial gap in safety data quality that may concern healthcare technology assessment bodies.

Unlike traditional antidepressants that require daily administration and chronic exposure to medication, psychedelic treatments typically involve one or several discrete dosing sessions. This fundamental difference in treatment approach has important implications for the overall safety profile and risk of cumulative adverse effects.

The requirement for specialised monitoring during administration represents a significant consideration for healthcare systems. Acute psychological reactions such as anxiety, dysphoria and paranoia necessitate trained personnel during dosing sessions. Additionally, compounds like MDMA can produce cardiovascular effects requiring medical oversight, whilst ibogaine presents more serious cardiac risks, demanding specialised monitoring protocols (Makunts et al., 2023; Ona et al., 2021).

Drug interactions remain an understudied area, particularly concerning common psychiatric medications. Whilst some combinations appear safe, others may alter therapeutic effects or safety profiles, necessitating careful management of pre-treatment medication discontinuation and potentially complicating real-world implementation (Becker et al., 2022; Halman et al., 2023). Real-world safety data from FAERS has revealed additional adverse events not captured in trials, including flashbacks and increased suicidal ideation, emphasising the importance of robust post-marketing surveillance (Jiang et al., 2023; Gastaldon et al., 2020).

Long-term safety considerations extend beyond immediate adverse events. Many patients require ongoing therapeutic support or return to conventional treatments post-intervention (Jerome et al., 2020; Gukasyan et al., 2022). While rare, researchers have documented phenomena like Hallucinogen-Persisting Perception Disorder (HPPD). HPPD can manifest as persistent visual disturbances and perceptual changes following psychedelic use. They are typically mild and non-distressing in controlled settings (Ford et al., 2022; Zhou et al., 2022).

These various safety considerations have important implications for treatment protocols, healthcare resource utilisation, and long-term monitoring requirements—factors that may significantly influence cost-effectiveness assessments and implementation planning. ■

4.2.3 Real-World Evidence (RWE)

Postmarketing Surveillance

Postmarketing surveillance (PMS) for psychedelic therapies will generate crucial data on their performance outside controlled clinical environments. These studies collect real-world evidence (RWE) from diverse healthcare settings and patient populations, offering insights that complement and extend beyond clinical trial findings. RWE becomes particularly relevant given the complex nature of psychedelic treatments, where factors like setting, therapist expertise, and patient characteristics may significantly influence outcomes.

The regulatory landscape increasingly recognises RWE's value. The EMA integrates it across product lifecycles through initiatives like the DARWIN EU network (EMA, n.d.). In the United Kingdom, NICE similarly emphasises real-world data to resolve uncertainties in clinical trial findings and inform decisions on patient access to innovative treatments.

How RWE Supports Efficacy and Safety Claims

RWE provides crucial insights into long-term efficacy and safety, especially in populations excluded from clinical trials due to comorbidities or demographic factors. Studies on ketamine's implementation have generated valuable RWE post-approval through observational studies and real-world registries, identifying specific usage patterns and refining safety monitoring protocols (e.g. Alnefeesi et al., 2022; Martinotti et al., 2022). Similarly, RWE can help validate findings for psychedelic therapies in more representative patient populations, ensuring their broader applicability.

Regulatory and Payer Perspectives

The EMA's DARWIN EU program and catalogues of real-world data sources enable structured and transparent RWE collection. This information helps regulators and payers evaluate the generalisability of clinical trial outcomes and ensure that evidence supports healthcare system needs. RWE is increasingly used in HTAs, providing data on cost-effectiveness and informing reimbursement decisions. ■

Key Challenges in Clinical Evidence Generation

Primary and Secondary Endpoints
Standard symptom reduction scales (MADRS, CAPS) serve as primary endpoints, but may not fully capture psychedelics' multidimensional benefits. Balancing regulatory requirements with measures that reflect patients' subjective transformative experiences remains challenging.

Duration of Effect
Psychedelics show promising long-term benefits across conditions, with studies reporting sustained effects 6-12+ months post-treatment. However, many patients seek additional interventions (therapy, peer support) to maintain benefits, raising questions about standalone efficacy and complicating cost-effectiveness calculations.

Safety and Tolerability
Most adverse events are transient and manageable, occurring during discrete dosing sessions rather than from chronic exposure. Specialised monitoring requirements, potential drug interactions, and rare long-term effects like HPPD must be considered in implementation planning and cost-effectiveness assessments.

Real-World Evidence
Postmarketing surveillance will be crucial for understanding psychedelics' performance outside controlled environments. Regulatory bodies and payer groups increasingly value RWE to validate clinical findings, assess generalisability, and inform reimbursement decisions.

4.3 Collaboration with Stakeholders During Development

Engaging Regulators

The EMA facilitates the regulatory process in the EU through Scientific Advice Meetings and early dialogue mechanisms. These platforms allow developers to seek guidance on clinical trial designs, dose-response studies, and regulatory expectations. Notably, while the EMA has recently acknowledged psychedelics in its draft depression treatment guidelines, there remains no specific regulatory guidance for psychedelic drug development in Europe (EMA, 2023b).

The April 2024 "Multi-stakeholder Workshop on Psychedelics – Towards an EU Regulatory Framework" highlighted the need for early regulatory engagement (EMA, 2024). Developers can present their plans and explore approaches through the Scientific Advice Procedure, with the EMA offering quality, clinical, and methodological feedback. Other valuable pathways include early involvement in the Innovation Task Force, which provides informal guidance on emerging therapies, and engagement with the Scientific Advice Working Party for specialised scientific input. However, no psychedelic developer has yet initiated formal consultation for centralised marketing authorisation applications (MAA) in the EU, highlighting a significant gap in aligning development programmes with European regulatory frameworks.

While the EMA provides insights on dose-response relationships, effect durability, and concomitant medication management, clear guidelines for Phase III trials remain elusive. As drug regulators, the EMA focuses on the pharmaceutical component rather than the accompanying psychotherapy, creating unique trial design and evaluation challenges. Developers must address uncertainties around individualised dosing strategies and long-term response maintenance, complicated by limited data on interactions with other psychiatric medications.

The Spravato (esketamine) development experience, discussed during the 2024 EMA meeting, ⤴ demonstrated the importance of rigorous site selection, recruitment strategies, and blinded assessments to mitigate expectancy biases. For psychedelics, intense media coverage and public interest magnify these challenges. While regulators like the EMA and MHRA emphasise early dialogue, it is crucial to note that regulatory approval does not guarantee payer acceptance. Although joint regulatory-payer advice is available, these stakeholders often seek different types of evidence, necessitating careful consideration of both perspectives during development.

The pathway to market authorisation involves addressing practical timeline issues. The EMA's centralised evaluation lasts 180 days, but accelerated assessments can potentially reduce it to 120 days (EC, 2023a).[15] Innovative platforms like the PRIME scheme and the Innovation Task Force provide additional engagement opportunities, particularly for therapies that address unmet medical needs. Early regulatory engagement remains crucial for navigating these complex requirements while optimising development strategies for regulatory and subsequent payer success.

Working with Payers and HTA Bodies

Early engagement with payers and HTA bodies guides clinical development strategies for psychedelic therapies. These treatments combine drug and psychotherapeutic components, requiring developers to generate evidence addressing clinical efficacy and economic considerations. Phase II and III trial design should incorporate endpoints that reflect both immediate therapeutic benefits and longer-term health economic outcomes, such as reduced healthcare utilisation and improved quality of life measures.

Developers should consider conducting head-to-head trials against standard treatments (such as SSRIs or psychotherapy alone) during Phase III, as comparative effectiveness data will be crucial for future HTA evaluations. Patient-reported outcomes →

[15] These timelines are the ambition of the European Commission, but should be seen in a context of a historical average of a 400 day average in the past.

should be integrated throughout the clinical development programme, particularly focusing on aspects that matter most to patients and payers, such as functional improvement and sustained remission rates. The experience with developing esketamine (Spravato) demonstrates the importance of selecting appropriate comparators and endpoints that can support regulatory approval and subsequent reimbursement decisions.

Platforms like the EMA's parallel consultations with HTA bodies provide opportunities to align clinical trial designs with regulatory and payer requirements during development. These consultations can help define appropriate patient populations, validate endpoint selection, and ensure evidence-generation plans adequately address future HTA requirements. Early alignment on these aspects can prevent costly protocol amendments or the need for additional studies post-approval.

Involving Patient Advocacy Groups

Patient advocacy groups can provide valuable insights into clinical trial design. Organisations like the Psychedelic Participant Advocacy Network (PsyPAN) and the Psychedelic Access and Research European Alliance (PAREA) bridge the gap between researchers, developers, regulators, and patients. PsyPAN brings together previous trial participants to provide feedback on trial design, safety protocols, and patient communication strategies, while PAREA works to improve access to psychedelic treatments across Europe.

Collaboration with indication-specific advocacy groups offers additional perspectives for clinical development. These groups help refine patient-reported outcome measures and highlight potential barriers to trial participation. Their input helps shape treatment protocols and ensures that trial designs capture meaningful patient outcomes, such as quality-of-life improvements and functional recovery measures. Advocacy groups can also assist in participant recruitment and retention strategies, ensuring diverse representation in clinical studies. ■

5 Payer and Health Technology Assessments

Securing access to psychedelic therapies requires working with payers and health technology assessment (HTA) bodies after regulatory approval. These therapies combine drug treatment with psychotherapeutic support, making them different from standard drug-only medicines and creating unique challenges for reimbursement decisions. Understanding how to work with these bodies is key to making treatments available to patients.

HTA occurs at different levels across Europe. While the European Union conducts Joint Clinical Assessments (JCA) focusing on clinical effectiveness, the most influential assessments occur at the national level. These national HTAs, along with some regional ones, examine both clinical and economic aspects of new treatments. ⤴

Each country has its own process, with different requirements and expectations that developers must understand.

This chapter outlines how to work effectively with payers and HTA bodies. It covers what evidence they need to see, particularly around how well treatments work compared to existing options and whether they provide value for money. The chapter also looks at practical challenges, such as the combined nature of these therapies and whether healthcare systems are ready to deliver them. By understanding these requirements early and planning carefully, developers can improve their chances of securing reimbursement and making treatments available to patients who need them. ■

5.1 Understanding HTA and Payer Evidence Requirements

5.1.1 Clinical Efficacy

Demonstrating Comparative Efficacy

Comparative efficacy evaluation serves as the foundation for reimbursement and pricing decisions. Unlike regulatory approval, which often hinges on placebo-controlled trials, HTAs demand insights into a treatment's performance relative to existing standards of care. The European HTA landscape, guided by Regulation (EU) 2021/2282, emphasises this through EU-led joint clinical assessments (JCAs) while retaining room for national-level customisation.[17]

Direct Comparisons: The Gold Standard

Direct comparison trials are the best way to show how well a new treatment works against existing ones. These trials can compare the benefits and risks of psychedelic therapies with current treatments like antidepressants or talking therapies. No developer has yet started these kinds of trials for psychedelic therapies outside of esketamine (Spravato), even though they are critical.

Running these comparison trials is difficult and expensive, particularly for treatments that include therapy sessions and need special treatment rooms. Despite these challenges, speakers commenting on the HTA evaluation at the EMA 2024 meeting on psychedelics made it clear that these direct comparison trials will be needed to prove how well these new treatments work compared to current options.

Alternative Approaches: Indirect Comparisons

When direct comparison trials are not possible or developers have chosen not to complete such studies, indirect treatment comparisons (ITCs) offer another way to evaluate how well treatments work against each other. This method allows researchers to combine and analyse data from separate clinical trials that share common comparison groups.

Some developers are completing or considering study designs that use neither standard of care nor inert placebo, instead opting for an 'active placebo' compound with dissociative effects. While this approach aims to maintain blinding and demonstrate the clinical effect of the psychedelic arm more clearly, it creates methodological challenges for payer assessment. These challenges extend beyond just the choice of comparator—the presence of psychosocial support across both active and control arms means that even studies with inert placebos may face difficulties in network meta-analyses (NMAs), as the supportive care component differs from trials of standard treatments.

Under the EU's new Joint Clinical Assessment (JCA) procedure, indirect comparisons remain important for demonstrating relative effectiveness when head-to-head trials are unavailable. However, HTA bodies vary widely in how they view ITCs, from Germany's acceptance of ITCs only when sufficient comparability is given (which is rare) to NICE's acceptance of ITCs with appropriate consideration of uncertainty.

These indirect comparisons have important limitations. Common challenges include differences between patient groups across studies, variations in how outcomes are measured, and questions about statistical methods. To address these issues, developers should emphasise the importance of clearly documenting assumptions and conducting sensitivity analyses to test how robust the findings are (van Beekhuizen et al., 2024). NICE's guidelines note that indirect comparisons are particularly vulnerable to systematic bias in networks with few trials, and researchers should consider population adjustment methods when there are imbalances between trials (NICE, 2023).

Researchers should follow established guidelines for choosing appropriate comparison treatments and statistical approaches to make indirect comparisons more credible. NMAs and matching-adjusted indirect comparisons (MAICs) represent commonly used methods, but their success depends on careful attention to methodology and transparent reporting. While the JCA focuses on clinical effectiveness at the EU level, national HTA bodies may have additional requirements for economic evaluations and local decision-making.

Navigating the European Landscape

The JCA process aims to streamline HTA assessments across the EU, while Member States retain autonomy for local decision-making. As the impact of JCAs evolves, developers should plan for EU-level and national requirements. For psychedelic therapies specifically, unique challenges exist around blinding, expectancy effects, and integrating psychotherapeutic components, requiring innovative trial designs and early dialogue with HTA bodies.

Subgroup Analyses

Subgroup analyses help determine how treatments may work differently in distinct patient populations within an approved indication. They are particularly important when a treatment's additional benefit is unclear, when many patients could receive treatment, or when the budget impact is substantial—situations where payers might consider reimbursing treatment for only specific patient groups.

Importance to HTA and Payers

HTA bodies and payers use subgroup analyses to refine their value assessments. NICE (2013; 2023) emphasises the need for subgroup-specific estimates of clinical and cost-effectiveness, particularly when there are biological or clinical reasons to expect different treatment effects. These estimates help target reimbursement to patients most likely to benefit. Different countries handle subgroups differently. For instance, while some might limit reimbursement to specific subgroups, Germany evaluates clinical benefits across all indicated patients, with subgroup results affecting overall pricing discussions.[16]

Methodological Challenges

Good subgroup analyses need careful planning and explicit methods. Groups should be defined before the analysis begins, with clear reasoning based on biological or clinical factors (EC, 2024). While exploratory analyses can generate new ideas, investigators must interpret them carefully to avoid overestimating effects. Statistical tests for interaction can help prove that subgroup differences are real, especially when results are consistent across multiple studies.

Key challenges include maintaining statistical accuracy with smaller patient numbers and managing multiple comparisons. Small subgroups can lead to unreliable results or bias. Testing many subgroups or outcomes requires statistical adjustments to maintain reliable conclusions, using established statistical methods or more advanced modelling approaches.

Practical Considerations for Psychedelics

Subgroup analyses are particularly relevant for psychedelic therapies, given how responses can vary based on demographic, genetic, and psychological factors. For example, comparing outcomes between treatment-resistant depression (TRD) and first-line cases could show different effectiveness levels, helping to build specific value cases for different populations. These analyses can also help elucidate the role of various treatment components, such as the intensity of subjective effects or the strength of therapeutic alliance, in driving outcomes.

By incorporating well-designed subgroup analyses into their evidence generation, developers can better meet HTA and payer expectations, supporting fair and cost-effective access to innovative treatments across diverse patient populations. ■

[17] JCA is a new process, with some EMA-approved therapies being reviewed from January 2025, initially oncology therapies. JCA will ultimately aim to review all newly EMA-approved novel therapies by 2030.

[16] A key characteristic in Germany is that reimbursement always applies to the full indicated patient population, so patient subgroups with low or no clinical benefit will negatively impact the follow-on pricing negotiations.

5.1.2 Cost-Effectiveness

Health Economic Modelling

Health economic models help decision-makers understand whether new treatments provide an effective use of funds where there are limited healthcare resources. These models compare the costs of a treatment with its health benefits, often using a measure called the Incremental Cost-Effectiveness Ratio (ICER). The ICER shows how much extra money is needed to gain one additional year of healthy life (called a Quality-Adjusted Life Year or QALY).

For psychedelic therapies, cost-effectiveness analyses (CEAs) and cost-utility analyses (CUAs) are especially important because they can provide a balanced view on clinical and cost implications over time, including future cost savings, compared to current standard treatments for mental health conditions. While psychedelic therapies involve intensive therapeutic support and medication costs, they may reduce long-term healthcare expenses through fewer hospital stays, reduced relapses, and decreased use of chronic medications. Since psychedelics are new to modern healthcare, these models must carefully consider uncertainties about long-term results and test different scenarios to ensure their conclusions are reliable.

Current Landscape of Psychedelic Cost-Effectiveness Evaluations

Economic modelling for psychedelics is still in its early stages in Europe, with only a few studies providing initial frameworks and evaluating cost-effectiveness compared to a handful of standards of care (various psychological interventions). These studies highlight key challenges around pricing assumptions and data limitations (McCrone et al., 2023; Buiter, 2023). Early work on psilocybin therapy for depression in the UK has shown promising health gains in terms of QALYs. Still, it suggests that achieving cost-effectiveness will require significant reductions in therapist and drug costs (McCrone et al., 2023).

Similar challenges emerge in other European analyses, such as the evaluation of MDMA therapy for PTSD in the Netherlands, where researchers found that while cost-effectiveness ratios could fall within acceptable ranges, this heavily depends on the choice of comparator treatments and key assumptions about therapy delivery and outcomes[18] (Buiter, 2023).

Target Population Selection and Cost-Effectiveness Implications

The selection of target patient populations significantly impacts cost-effectiveness assessments. First-line treatment populations and larger patient groups typically have access to inexpensive standard treatments, such as generic SSRIs costing only pence per day. This low cost of existing treatments creates a challenging cost-effectiveness barrier for novel therapies, regardless of their clinical effectiveness. For psychedelic treatments, the additional costs of therapist time and infrastructure make demonstrating cost-effectiveness in these populations particularly difficult.

Later-line treatments generally have more favourable conditions for cost-effectiveness analyses. These settings often involve higher-cost branded drug comparators, while treatment-resistant populations may already incur substantial healthcare costs or lack effective standard care options. Despite their intensive delivery requirements, these factors can improve the likelihood of demonstrating cost-effectiveness for psychedelic interventions.

Key Components of Health Economic Models

1. **Costs and Resource Use:** Economic models must include all relevant costs, including direct drug acquisition costs, therapy sessions, monitoring, and managing side effects. Economic models almost always include direct medical resource utilisation costs (such as clinical staff and facilities). Indirect costs (such as lost work time and caregiver support) appear in only a small proportion of health economic assessments that make decisions on drug reimbursement.

[18] Across the pond, U.S. projections indicate potential savings from MDMA therapy through lower long-term PTSD management costs (Stanicic et al., 2024). However, these more developed analyses are done in a very different healthcare system.

2. **Clinical and Humanistic Outcomes:** Models calculate health outcomes in natural units (e.g., life years, quality of life) and QALYs, integrating clinical trial data, epidemiological estimates, and long-term projections. Researchers capture the humanistic burden through healthcare utilities, which patients generate through patient-reported outcomes to assess the treatment's impact on their quality of life. These measures can be general (EQ-5D or SF-36) or disease-specific. Analysts often model therapies using decision trees and Markov models to estimate how the disease and treatment effects progress over time.

3. **Time Horizons and Discounting:** Since psychedelic treatments may have long-lasting benefits, existing models typically look 5-10 years ahead to capture effects like fewer relapses or better quality of life. The need to capture these long-term effects requires analysts to extrapolate benefits and validate them with clinical data, expert opinion, or precedence from existing models or expert groups. Analysts adjust future cost savings and clinical benefits downward (by 3-5% per year) to reflect that benefits now are worth more than benefits later.

3. **Sensitivity Analyses:** Models test different scenarios because many factors are uncertain (such as total treatment costs and how well treatments work over time). These sensitivity analyses help decision-makers understand how cost-effectiveness varies under different assumptions and the probability of staying within any pre-specified cost-effectiveness thresholds.

Country-Specific Variations in Economic Evaluations

While EU Regulation 2021/2282 aims to harmonise HTAs in evaluating clinical effectiveness at the EU level, significantly different approaches to economic analysis have developed in individual countries over time and will persist in the future:

- **Germany (IQWiG/G-BA):** Health economics plays no role in the national benefit assessment but can be useful in access discussions with individual health insurance companies.
- **Netherlands (ZiN):** Makes use of cost-effectiveness analysis to inform reimbursement decisionsand can also adopt a societal perspective if these are significant, such as valuing productivity gains and caregiving reductions. Uses flexible thresholds (€20,000 to €80,000 per QALY) linked to disease severity, making it more receptive to therapies with broader benefits.
- **United Kingdom (NICE):** NICE sets clear cost-effectiveness thresholds of £20,000–£30,000 per QALY, primarily focusing on direct healthcare system costs and cost savings. However, NICE can accept higher thresholds in certain cases of higher unmet needs. While supplementary analyses may consider societal benefits, they rarely influence the primary assessment and final reimbursement recommendation.
- **Czech Republic (SÚKL):** Employs a healthcare system perspective that focussed primarily on direct medical costs and resource utilisation. The assessment framework emphasises budget impact and affordability considerations, in addition to cost-effectiveness analysis.

These differences in both HTA methodology and health economic thresholds mean psychedelic therapies may be assessed more favourably in some markets than others, particularly where indirect benefits are valued and higher cost-effectiveness thresholds apply.

Balancing Upfront Costs with Long-Term Savings

Healthcare payers often hesitate when treatments need significant upfront investments, which is particularly true for psychedelic therapies that combine drugs with therapy support. While these treatments hold potential for lasting benefits—like fewer relapses and less need for ongoing medications—proving these long-term savings is difficult without extended patient data.

When making economic cases for psychedelic treatments, it will be important to consider both sides: the initial costs (treatment delivery, facilities, and therapist training) and potential future savings (fewer hospital stays, lower medication costs, and patients returning to work). To help address concerns about high initial costs, flexible payment arrangements could be considered, such as payment by results or phasing in coverage gradually, especially where treatment-resistant patients exist in significant numbers.[20]

Inclusion of Indirect Costs and Benefits

Indirect costs capture health interventions' broader economic and societal impacts beyond direct medical expenses. These costs include productivity losses due to temporary absence from work, reduced working capacity caused by illness or disability, and early death. For psychedelic therapies, which aim to improve mental health conditions such as depression and PTSD, indirect cost savings could be substantial if treatments enable patients to return to work, maintain employment, or reduce reliance on caregivers.

Health economists use two main approaches to calculate indirect costs (Mennini & Gitto, 2022):

- **Human Capital Method:** Estimates lost productivity based on the time individuals cannot work, valuing their absence at average wage rates.
- **Friction Cost Method:** Focuses on the costs of temporarily replacing an employee who can not work, accounting for labour market dynamics and adjustments.

Both approaches offer insights into the economic consequences of untreated mental illness and the potential gains from effective interventions. For psychedelic therapies, which may provide durable benefits after a short treatment period, these frameworks can help illustrate potential long-term value.

[20] Innovative reimbursement arrangements are discussed in section 5.5 and Chapter 10.

National Approaches to Indirect Costs: Divergence Across Europe

European countries differ significantly in their approaches to incorporating indirect costs into health economic evaluations, reflecting broader philosophical and methodological perspectives on healthcare spending (García-Mochoón et al., 2022).

Countries such as England and the Czech Republic primarily adopt a healthcare perspective, focusing on direct medical costs related to treatment and excluding broader economic impacts in base-case analyses. While this perspective simplifies calculations, it may fail to capture the full value of therapies, particularly those with non-traditional delivery models that have the potential to lead to a step-change in outcomes, such as psychedelics.

In contrast, countries including the Netherlands, Sweden, and Denmark may employ a societal perspective, incorporating indirect costs and benefits into primary analyses. For example, the Netherlands explicitly accounts for productivity gains, reduced caregiver burden, and societal contributions, making it more receptive to therapies that promise long-term economic benefits despite high initial costs.

Economists also use hybrid approaches in countries like France and Belgium, where they exclude indirect costs from base-case health economic evaluations but may include them in supplementary analyses. This flexibility allows decision-makers to consider broader impacts without compromising methodological consistency.

5.1.3 Budget Impact

Affordability for Health Systems

Budget impact analyses (BIAs) assess how new treatments affect healthcare spending, typically over 3-5 years. Unlike cost-effectiveness analyses, BIAs focus on practical affordability within existing budgets. They estimate the financial impact on the pharmaceutical drug budget or, potentially, the combined budget impact across the health system related to overall service delivery.

For psychedelic therapies, which have high initial costs but potentially long-term savings, the way analysts conduct BIAs may lead to wildly varying outputs for decision-makers. For example, BIAs that look only at pharmaceutical costs will look very different from those that include infrastructure setup and therapist services. Where decision-makers consider budget impact high, this situation more likely leads to reimbursement restrictions and price negotiations with payers.

European Approaches to Budget Impact

The European and U.S. healthcare systems differ significantly in how they approach affordability and financial planning.[19] In Europe, public healthcare systems often focus on cost containment and equitable access, using centralised negotiations to determine coverage and pricing. BIAs in Europe often emphasise system-level affordability and resource allocation, reflecting broader societal goals.

Most European countries will require budget impact analysis of a new drug's expected national direct drug costs over 3-5 years at a minimum. Some budget analyses stipulate the inclusion of all direct costs to the health system. The Netherlands' ZiN methodology incorporates societal costs into economic models, extending the scope of BIAs beyond direct healthcare spending.

Key Considerations for Psychedelics

Psychedelic treatments present unique budget challenges because their costs are "front-loaded"—concentrated in initial treatment phases rather than spread over time like traditional medications, especially for chronic mental health conditions. Key questions include:

- **Patient Population Size:** How many patients will receive treatment in the first few years? Will eligibility criteria limit uptake?
- **Adoption Rates:** How quickly can treatment centres be established, and how will infrastructure constraints impact rollout?
- **Cost Comparisons:** How do psychedelics compare to conventional treatments (e.g., SSRIs or CBT) in terms of annual costs and resource use? Will payers consider cost comparisons to non-pharmaceutical therapies, which are often more cost-intensive?
- **Cost Offsets:** What savings can health systems expect from quicker hospital discharges, reduced hospitalisations, less emergency care, or reduced long-term medication use?

Target Population Selection and Budget Impact

When developing psychedelic therapies, companies must choose between targeting broader conditions like depression or PTSD or focusing on smaller groups with treatment-resistant conditions. Companies that start with smaller, high-need populations (like TRD) typically combine lower initial total costs with a higher willingness to pay and thus greater payer acceptance while allowing themselves to build evidence through specialised clinics. However, targeting broader conditions could position psychedelics as earlier treatment options, though this will likely raise concerns about overall costs and scalability.

A phased approach, starting with treatment-resistant conditions before expanding to broader populations, often works best to build payer and clinician confidence. This strategy helps prove the treatment's value while managing costs, allowing time to develop infrastructure and gather real-world evidence. Companies can then use this data to support expansion to broader patient groups while giving healthcare systems time to adapt their budgets and resources. ■

[19] In contrast, the U.S. lacks a centralised approach to budget impact assessment. While individual private insurers and pharmacy benefit managers conduct their own analyses, there is no standardised national requirement for BIAs. Medicare, the largest public payer, is legally prohibited from using cost-effectiveness or budget impact considerations in coverage decisions. Instead, pricing and access decisions are largely determined through fragmented negotiations between manufacturers and multiple private payers, leading to significant variability in both coverage and pricing across the healthcare system.

Understanding HTA and Payer Evidence Requirements

Key HTA concept	Definition	Potential impact on HTA outcomes and market access
Comparative effectiveness	Evaluation of a treatment's performance relative to existing standards of care	Direct comparisons preferred by HTAs; lack of head-to-head data may limit access or price potential
Subgroup analyses	Determining how treatments work differently in distinct patient populations	Can refine value assessments and target reimbursement to patients most likely to benefit
Direct vs. indirect benefits	Direct benefits: patient health improvements and cost savings; indirect benefits: productivity, caregiver relief, and societal gains	Countries vary in considering indirect benefits; broader societal perspective may improve value proposition
Cost effectiveness	Comparison of costs versus health benefits, often using ICER/QALY metrics	Expected higher upfront costs of psychedelics necessitates evidence of clear clinical benefits and demonstration of economic benefits over time
Budget impact	Assessment of how new treatments affect healthcare spending over 3-5 years	High initial costs may trigger reimbursement restrictions; smaller patient populations minimise budget concerns

5.2 Engaging with HTA Bodies

HTA bodies evaluate new treatments to ensure they provide good value for healthcare systems. For psychedelic therapies, this evaluation is complex because it must consider both the drug effects and the therapeutic component, including how well these work together and their long-term benefits.

This section examines HTA processes in Germany, the United Kingdom, the Netherlands, and the Czech Republic. Each country has distinct requirements. For instance, Germany focuses on proving any added clinical benefit compared to existing treatments, while the UK emphasises cost-effectiveness thresholds. The Netherlands and Czech Republic pay particular attention to affordability and broader societal benefits. Understanding these differences helps developers plan their evidence generation and effectively engage with HTA bodies to support access to psychedelic therapies.

5.2.1 Understanding HTA Processes in Target Countries

Germany (G-BA and IQWiG)

Germany's HTA process operates under the AMNOG framework (*Arzneimittelmarktneuordnungsgesetz*), a structured system designed to evaluate new therapies' added clinical benefit following their approval (Bundesministerium für Gesundheit, 2010). The Federal Joint Committee (G-BA), which sets the requirements for evaluation, and the Institute for Quality and Efficiency in Healthcare (IQWiG), which conducts the scientific assessments to inform these decisions, oversee this process. Together, these bodies form the backbone of Germany's HTA process. Therapies with orphan drug designation and below a certain annual cost threshold are exempt from the regular benefit assessment procedure as the orphan drug designation is based on a clear unmet need and noted benefit vs. existing medicines.

Initial Submission Process

The AMNOG process begins immediately after a therapy enters the German market. Within three ⤴ months of market entry, IQWIG begins assessing the manufacturer's dossier detailing the therapy's clinical and economic evidence to the G-BA. This dossier includes data on efficacy, safety, and patient-relevant outcomes and comparative evidence against the appropriate comparator therapy determined by the G-BA.

This step introduces complexities for psychedelic therapies, as the combined drug-and-therapy model necessitates data not only on the pharmacological intervention but also on the accompanying psychotherapy if it is part of the indication. Developers must demonstrate the synergy between the two components, clearly outlining how this integrated approach provides superior clinical outcomes compared to existing treatments.

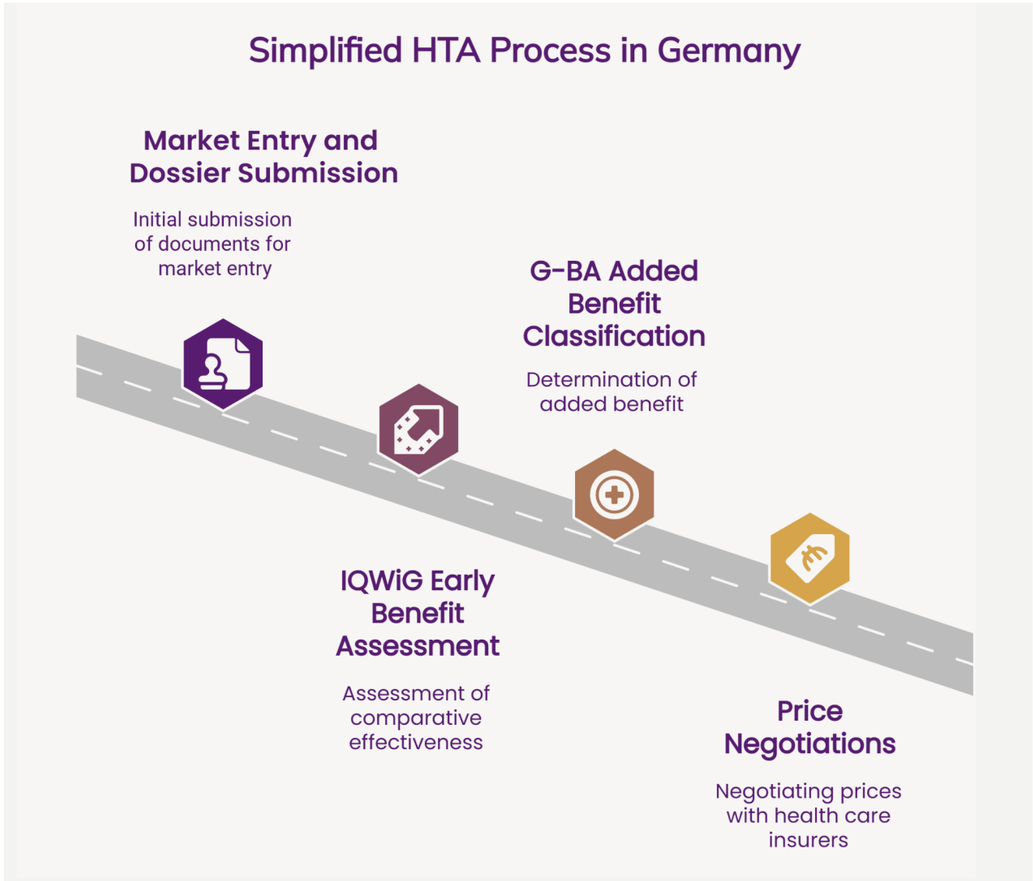
Early Benefit Assessment

Once the dossier is submitted, the G-BA commissions IQWiG to conduct an early benefit assessment (*frühe Nutzenbewertung*). This assessment evaluates the therapy's comparative effectiveness, improvements in patient-relevant outcomes such as mortality, morbidity, quality of life, and safety profiles. IQWiG does not conduct health economic evaluations. However, the IQWiG assessment forms the foundation for G-BA's later pricing negotiations with the manufacturer.

The early benefit assessment focuses heavily on comparative evidence, requiring head-to-head trials wherever possible. When such data are unavailable, developers may need to rely on ITCs, which are scrutinised for methodological rigour and relevance and rarely accepted as adequate.

Benefit Classification and Pricing

Following IQWiG's evaluation, the G-BA reviews the findings and determines whether the therapy offers an added benefit over standard treatments. G-BA categorises the benefits into major, considerable, minor, non-quantifiable, none, or lower benefit, with higher ratings offering more substantial leverage during price negotiations. Of note, therapies with an orphan drug designation (ODD) and under the set →



Key Bodies:

- Federal Joint Committee (G-BA): Sets requirements and makes final decisions
- Institute for Quality and Efficiency in Healthcare (IQWiG): Conducts scientific assessments

Key Features:

- Focus on comparative effectiveness against G-BA-determined comparator
- Head-to-head trials strongly preferred; indirect comparisons scrutinized
- No formal health economic evaluation
- Benefit classification directly impacts price negotiations
- Free pricing for first 6 months after market entry
- G-BA decisions are binding

annual cost threshold must receive, at a minimum, a non-quantifiable benefit from the G-BA.

For psychedelic therapies, demonstrating major or considerable benefit will be critical. Establishing long-term efficacy and durability of response may help to achieve favourable ratings, as therapies that address TRD or PTSD may face additional scrutiny regarding their sustained impact and safety profiles. Notably, Spravato achieved a considerable benefit rating due to its patient-relevant benefits in TRD.

Price Negotiations and Market Access

The G-BA's decision also sets the stage for price negotiations between the manufacturer and Germany's statutory health insurance association (*GKV-Spitzenverband*). During the first 6 months of market entry, manufacturers can set their own prices, but subsequent pricing depends on the G-BA's benefit classification. The GKV typically negotiates therapies rated with no added benefit at parity with or even below existing treatments. In contrast, those demonstrating major or considerable benefit have the potential to achieve higher prices than the existing standard of care.

Post-Marketing Requirements

Beyond the initial assessment, the G-BA may impose post-marketing requirements to monitor long-term outcomes and safety. For psychedelic therapies, this could include Phase IV studies, registry data, and real-world evidence collection to address uncertainties about durability, side effects, and integration protocols. IQWiG's methodological standards emphasise transparency and reproducibility, requiring developers to document assumptions and data sources used in the evaluations. These post-launch obligations reflect broader uncertainties in psychedelic therapy outcomes and highlight the need for ongoing evidence generation to maintain pricing and reimbursement status.

Unique Challenges and System Integration

Despite Germany's well-defined HTA framework, psychedelic therapies pose unique challenges, especially if implemented as a combined drug-plus therapy model. Current billing systems, such as the *Gebührenordnung für Ärzte* (GOÄ) and the *Einheitlicher Bewertungsmaßstab* (EBM), are poorly equipped to capture the costs of intensive psychotherapeutic support sessions that may be required for psychedelic therapies, potentially limiting accessibility and adoption.[21] Developers must also navigate budget constraints imposed on outpatient providers, who may hesitate to prescribe high-cost treatments without explicit reimbursement guarantees from insurers.

The adoption of psychedelic therapies in Germany's healthcare system will likely focus on establishing appropriate funding mechanisms, particularly for outpatient settings, and securing reimbursement for therapist time. While there may be some parallels with esketamine integration, the key challenges appear to centre on developing practical payment pathways that account for the unique delivery model of psychedelic therapy, including longer clinic visits for dosing and psychotherapeutic support.

Germany's HTA system sets a high bar for evidence quality and directly links drug pricing to it. While this presents a challenge for psychedelic therapies, it also provides opportunities to demonstrate their potential as paradigm-shifting treatments for psychiatric disorders. Developers must strategically plan their evidence-generation activities, considering the ability to deliver clinical trials with head-to-head comparative data, the costs and complexity of doing so, and the implications of not doing this on drug pricing in Germany, which is usually an early launch market. ■

[21] The GOÄ is the fee schedule for billing of privately provided medical services. If a service is provided to statutory health insurance patients in the outpatient setting, billing is based on the *„Einheitlicher Bewertungsmaßstab"* (EBM).

United Kingdom (NICE and SMC)

In the United Kingdom, the evaluation and reimbursement of new therapies falls under the jurisdiction of the National Institute for Health and Care Excellence (NICE) in England and Wales, and the Scottish Medicines Consortium (SMC) in Scotland. The NICE process focuses on evidence-based recommendations and ensuring cost-effectiveness for treatments introduced into the National Health Service (NHS) (NICE, 2023).

Unlike many European countries, the UK does not follow the European Medicines Agency (EMA) approval pathway, requiring manufacturers to engage directly with the Medicines and Healthcare products Regulatory Agency (MHRA) for market authorisation before proceeding to NICE evaluations.[22]

NICE Health Technology Assessment Routes

Therapies seeking NHS adoption generally follow one of three routes: NICE Health Technology Appraisals (HTA), NHS clinical policy development, or the Clinical Priorities Advisory Group (CPAG) process.

Among these, the NICE HTA is the most comprehensive and widely applicable route, evaluating clinical and cost-effectiveness and providing binding recommendations on NHS funding and access. The CPAG process, often reserved for rare diseases and highly specialised treatments, may offer a potential alternative for therapies if targeted at small, high-need populations but applies to only a small number of interventions per year. NHS clinical policy development is more relevant for interventions outside NICE's remit, often focusing on service delivery frameworks rather than specific new technologies, although exceptions exist where drug treatment funding has been reviewed.

Topic Selection and Scoping

The NICE process begins with topic selection, initiated by referrals from the Department of Health and Social Care or NHS England. During the scoping phase, NICE defines the key elements of the assessment, including the target population, relevant comparators, and relevant outcomes. For psychedelic therapies, this step would identify unique delivery requirements, such as psychotherapy integration, which may create additional challenges in defining cost-effectiveness models and comparators.

Technology Appraisal Framework

Psychedelic therapies are likely to undergo NICE's Single Technology Appraisal (STA) process, which focuses on assessing one drug for a specific indication. The STA model requires manufacturers to submit detailed dossiers containing clinical trial data, health economic models, and budget impact analyses (BIAs).

Given the therapy-drug combination inherent in psychedelic treatments, submissions must address both pharmacological efficacy and the therapy's delivery framework. NICE evaluates these submissions through independent Evidence Review Groups (ERGs), which appraise the evidence base for clinical and cost-effectiveness.

Appraisal Committees and Consultation

NICE convenes an independent Appraisal Committee to review evidence and hear input from stakeholders. The committee bases decisions on clinical trial data, cost-utility analyses (typically using QALYs), and economic models that address uncertainties through sensitivity analyses.

Particular scrutiny of psychedelic therapies is likely to focus on the duration and resource intensity of treatment protocols, including therapist time and infrastructure needs. NICE's reliance on cost-effectiveness thresholds—commonly £20,000–£30,000 per QALY—poses a significant hurdle for therapies with high upfront costs, reinforcing the importance of modelling long-term cost offsets. ⤴

[22] Although we discuss UK-specific requirements here, the International Recognition Procedure (IRP) enables the MHRA to recognise and use the assessment work and decisions made by trusted regulatory authorities, including the EMA, as part of its evaluation process. This can help to avoid duplication of regulatory efforts while maintaining high standards of medicines evaluation.

In 2022, NICE introduced a severity modifier, allowing the approval of treatments for some severe diseases with a higher cost-effectiveness threshold.

The draft guidance, released as an Appraisal Consultation Document (ACD), is subject to public consultation before the final Appraisal Determination (FAD) is published. Positive recommendations obligate NHS adoption within 90 days, while negative appraisals may lead to developer-triggered appeals or requests for further evidence generation. Therapies 'not recommended' by NICE may struggle to achieve any meaningful access within the NHS.

During the HTA process, manufacturers may refine the requested patient population for reimbursement or amend the position in the care pathway to take account of initial NICE recommendations of UK clinical practice and the likelihood of meeting cost-effectiveness thresholds. Additionally, manufacturers may reduce the therapy's net price to increase the certainty of meeting cost-effectiveness criteria and the likelihood of a positive final HTA recommendation.

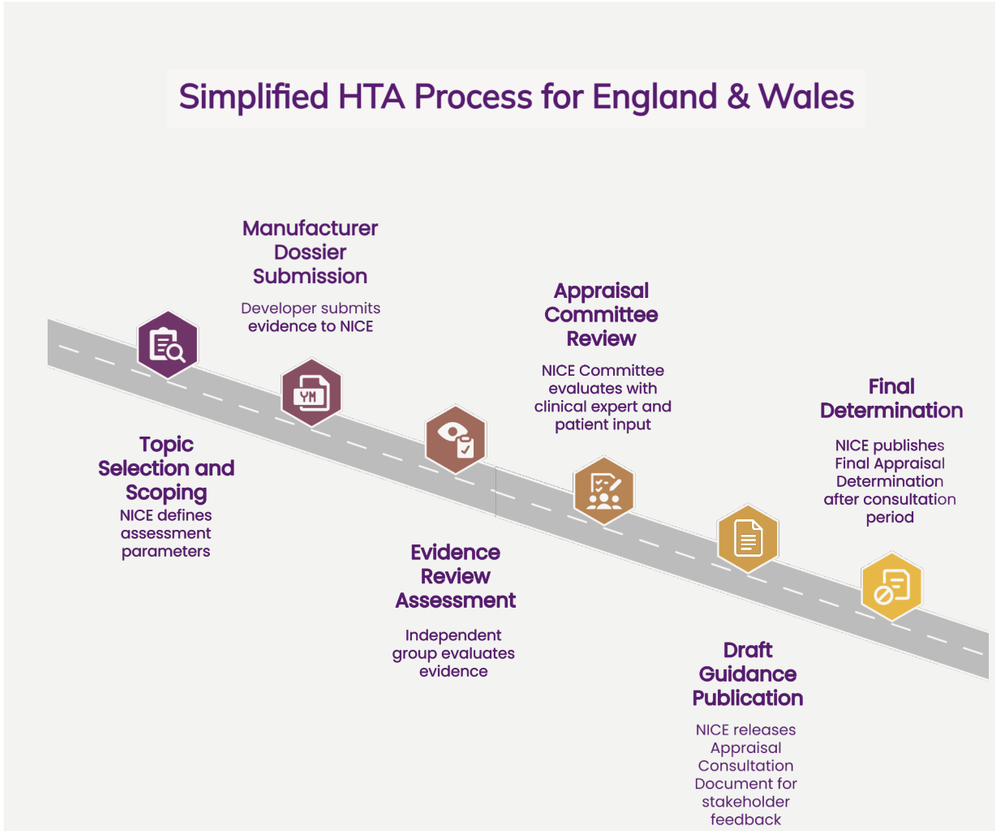
Managed Access and Real-World Evidence

To address novel treatments' uncertainties, NICE may consider Managed Access Agreements (MAAs), which conditionally approve therapies while mandating ongoing data collection. This approach may prove especially useful for psychedelic therapies, where long-term efficacy and economic data will be limited.

The Innovative Medicines Fund (IMF) may provide interim funding for a few therapies while real-world data is collated or longer-term studies are taking place. NICE can later revise recommendations based on this real-world evidence and make a final determination on cost-effectiveness and NHS funding and access.

Regulatory and Implementation Challenges

Despite the rigorous evaluation framework, psychedelic therapies face additional hurdles due to their controlled substance status. Prescribing requirements, storage conditions, and clinical supervision protocols need to be aligned. These factors necessitate collaboration between NICE, the Medicines Value and Access Team (MVAT), and possibly the Home Office, to streamline regulatory and health system implementation. ■



Key Bodies:

- National Institute for Health and Care Excellence (NICE): England and Wales
- NHS England: Oversees implementation of recommendations and manages innovative medicines fund.

Key Features:

- Comprehensive clinical and cost-effectiveness evaluation
- Cost-utility analysis using QALYs with £20,000-£30,000/QALY threshold
- Severity modifier allows higher thresholds for severe conditions
- NHS must implement positive recommendations within 90 days
- Innovative Medicines Fund for conditional approval with data collection

The Netherlands (ZiN)

In the Netherlands, *Zorginstituut Nederland* (ZiN) manages HTAs for new therapies, including psychedelics. ZiN determines whether to recommend a treatment for inclusion in the statutory health insurance (SHI) package (*basispakket*) based on its clinical effectiveness, cost-effectiveness, necessity, and feasibility.

Given the distinct combination of drugs and psychotherapy in psychedelic treatments, the assessment framework must address both pharmacological efficacy and the broader therapeutic context, making this evaluation more complex than for conventional medications.

Regulatory Pathway and Submission Requirements

Following approval by the EMA, manufacturers seeking reimbursement in the Netherlands must submit a dossier to ZiN for evaluation (ZiN, 2024). This dossier must provide comprehensive evidence, including clinical trial data, cost-utility analyses (CUAs), and information on societal impact. ZiN's assesses the submission using "package management criteria" (*pakketbeheercriteria*).

These criteria include effectiveness, cost-effectiveness, necessity, and feasibility. Clinical outcomes, such as improvements in symptoms or quality of life, supported by evidence from randomised controlled trials (RCTs) or real-world data, demonstrate effectiveness. ZiN evaluates cost-effectiveness using incremental cost-effectiveness ratios (ICERs) and quality-adjusted life years (QALYs) to determine whether the therapy provides sufficient value for its cost compared to existing treatments. Necessity focuses on whether the therapy addresses a significant unmet medical need. At the same time, feasibility examines whether providers can integrate it practically into the Dutch healthcare system, considering infrastructure requirements and professional training.

The "Lock" (Sluis) Process for High-Cost Therapies

The Netherlands employs an additional review process known as the "lock" (*sluis*) for therapies with high costs or significant projected budget impacts. This process applies to treatments exceeding €50,000 per patient and €10 million annually in projected costs. It involves more stringent assessments of cost-effectiveness and affordability, often requiring additional data collection post-launch.

Psychedelic treatments will likely avoid this pathway. However, if a therapy enters the lock, it faces further negotiations and may only receive conditional approval, contingent upon collecting long-term evidence to address remaining uncertainties.

Decision-Making and Reimbursement

ZiN compiles its recommendations into an advisory report for the Minister of Health, Welfare, and Sport, who ultimately decides whether to include the therapy in the basic health insurance package. The advisory report evaluates whether the treatment meets the four key criteria and may propose conditions for reimbursement, such as limiting use to specific patient populations or requiring providers to participate in registries to track long-term outcomes.

For example, psychedelic therapies could be approved only for patients who have not responded to multiple lines of treatment, reflecting a cautious approach similar to that taken with esketamine for TRD. Price negotiations may also follow, particularly for high-cost therapies, with managed entry agreements and risk-sharing arrangements used to balance payer concerns with patient access.

If the Minister approves the therapy, they list it in the *Geneesmiddelenvergoedingssysteem* (GVS), which governs reimbursement categories. The Minister may place therapies in Appendix 1A for full reimbursement without restrictions or Appendix 1B for conditional reimbursement, which often includes eligibility criteria or other usage constraints. For psychedelic therapies, the Minister will likely place them in Appendix 1B, particularly in the early stages, as clinicians integrate them into clinical practice and collect additional data.

Cost-Utility Modelling and Indirect Benefits

A key feature of the Dutch HTA process is its emphasis on cost-utility modelling and societal perspectives. The process includes indirect costs and benefits, such as productivity gains and reduced caregiver burden, in its economic evaluations. The Dutch broader perspective aligns well with the potential long-term benefits of psychedelic therapies, particularly for conditions like PTSD and TRD.

However, developers must provide robust data to support these claims, as ZiN applies a sliding scale for willingness-to-pay thresholds based on disease severity and burden. A critical challenge often underestimated by developers is the need to document and substantiate disease severity and burden thoroughly. Historical HTA submissions across various therapeutic areas show that approximately 80% struggle to adequately demonstrate these aspects, potentially limiting their ability to justify higher willingness-to-pay thresholds and secure favourable reimbursement decisions.

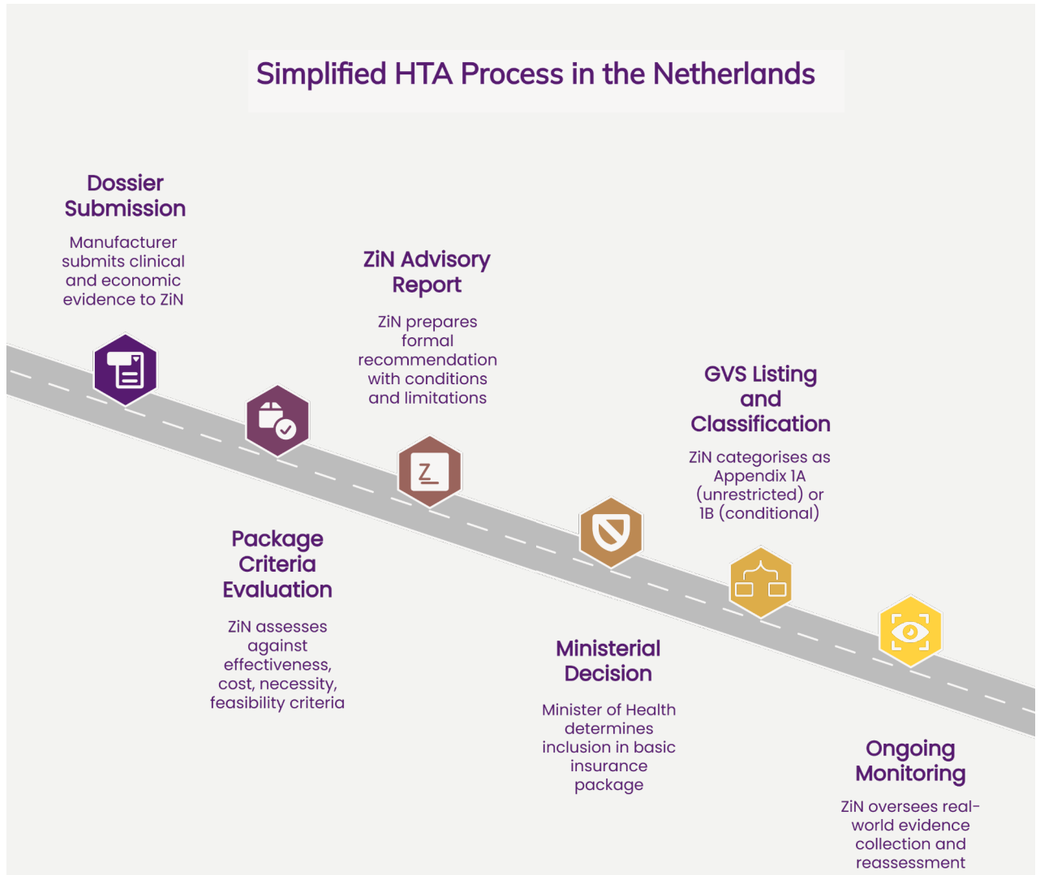
Ongoing Monitoring and Real-World Evidence

Conditional approvals often require post-marketing surveillance and ongoing data collection to address uncertainties. Psychedelic therapies may be subject to additional scrutiny, with requirements to participate in registries or conduct Phase IV trials to verify long-term safety and effectiveness. ZiN can also re-evaluate therapies as new evidence emerges, adjusting reimbursement conditions or withdrawing coverage if expectations are unmet.

Challenges for Psychedelic Therapies

While the combination of drug administration and therapeutic support in psychedelic treatments presents a novel evaluation scenario, existing healthcare codes and care pathways may provide useful frameworks for assessing the psychotherapeutic components. The challenge lies primarily in adapting these established structures to this emerging treatment paradigm.

For new treatments like psychedelics, ZiN maintains high standards for evidence quality and cost-effectiveness modelling, including careful evaluation of treatment comparisons. While this presents certain hurdles, the Dutch system's mechanisms for managed entry agreements and conditional approvals provide a structured but adaptable pathway for integrating novel therapies into standard care, particularly when direct comparative evidence may be limited. ■



Key Bodies:

- Zorginstituut Nederland (ZiN): Manages HTAs
- Minister of Health, Welfare, and Sport: Makes final decisions

Key Features:

- Evaluation based on effectiveness, cost-effectiveness, necessity, and feasibility
- Societal perspective including indirect costs/benefits
- Sliding scale for willingness-to-pay thresholds based on disease severity
- Appendix 1A (full reimbursement) or 1B (conditional reimbursement)
- Focus on both clinical and economic evidence
- Minister makes final decision based on ZiN recommendations

Czech Republic (SÚKL)

In the Czech Republic, new therapies undergo a structured HTA process managed by the State Institute for Drug Control (SÚKL). This evaluation focuses on clinical effectiveness, cost-effectiveness, and budgetary impact to determine eligibility for inclusion in the public health insurance system. Most new drugs, particularly innovative therapies like psychedelics, secure centralised marketing authorisation through the EMA. Once the EMA grants approval, it applies across EU Member States, including the Czech Republic, streamlining the initial regulatory phase.

A national authorisation route through SÚKL remains an option for less complex therapies, although developers rarely pursue this route for innovative treatments. Instead, developers of psychedelic therapies are more likely to rely on EMA approval and direct their efforts toward addressing the Czech Republic's economic and logistical requirements for reimbursement. This approach reduces duplication of scientific evaluations and positions EMA approval as a baseline for local pricing and coverage discussions.

Dossier Submission and HTA Evaluation

Following EMA authorisation, manufacturers submit a detailed dossier to SÚKL to request registration and inclusion in the public health insurance system. The dossier comprises clinical data, economic models, and budget impact analyses tailored to the Czech healthcare landscape. Clinical evidence is typically derived from the EMA's centralised assessment, minimising the need for re-evaluation. However, pharmacoeconomic models must be customised to demonstrate cost-effectiveness in the Czech context.

SÚKL applies strict requirements for proving therapeutic value and cost-efficiency. Submissions must quantify health gains using incremental cost-effectiveness ratios (ICERs) and quality-adjusted life years (QALYs) metrics. The agency also requires budget impact analyses to estimate the financial consequences of adopting the therapy, accounting for patient numbers, pricing, and resource use. For psychedelic therapies, this means addressing both drug costs and the logistical requirements of therapist-led sessions and specialised treatment environments.

Pricing and Reimbursement Decisions

A key component of the national pricing and reimbursement process is determining the maximum ex-factory price, known as the "*maximální cena výrobce*." SÚKL relies on international reference pricing, comparing costs across EU Member States. Typically, prices from a basket of selected countries cannot exceed the average of the three lowest country prices. This external price benchmarking approach helps control drug pricing and drug costs, but would not manage non-drug costs associated with supervised administration and psychotherapy requirements.

Reimbursement decisions classify drugs into different categories, ranging from full coverage to partial reimbursement with restrictions. Expensive or novel therapies are often subject to conditional reimbursement agreements, particularly if long-term effectiveness data are still emerging. For psychedelics, these agreements may limit coverage to specific subgroups, such as patients with TRD, or require prescribing within specialised clinics to ensure safety and protocol adherence.

Budget Impact Analysis and Economic Modeling

Budget impact analyses (BIAs) address the broader financial implications of adding new therapies to the public health system. Payers scrutinise whether the treatment's costs are sustainable under existing budgets. If projected costs exceed predefined thresholds, manufacturers may be required to negotiate risk-sharing agreements, such as budget caps or outcomes-based pricing models, to control expenditures.

Economic models for psychedelic therapies must account for drug prices and associated costs, such as therapy preparation, monitoring, and post-treatment integration sessions. To offset initial expenses, it is crucial to demonstrate long-term savings through reduced healthcare spending,

such as hospitalisations and lower medication use. Conditional reimbursement pathways often include periodic reassessments to verify these projected savings over time.

Implementation and Real-World Monitoring

Once a therapy is approved for reimbursement, SÚKL lists it in the Czech "List of Reimbursed Medicinal Products," which details pricing, reimbursement levels, and prescribing conditions. Physicians and pharmacists must follow these prescribing conditions when prescribing and dispensing, particularly for therapies requiring controlled environments or specialised training, such as psychedelics. SÚKL monitors treatment outcomes through pharmacovigilance programs, ensuring continued safety and efficacy.

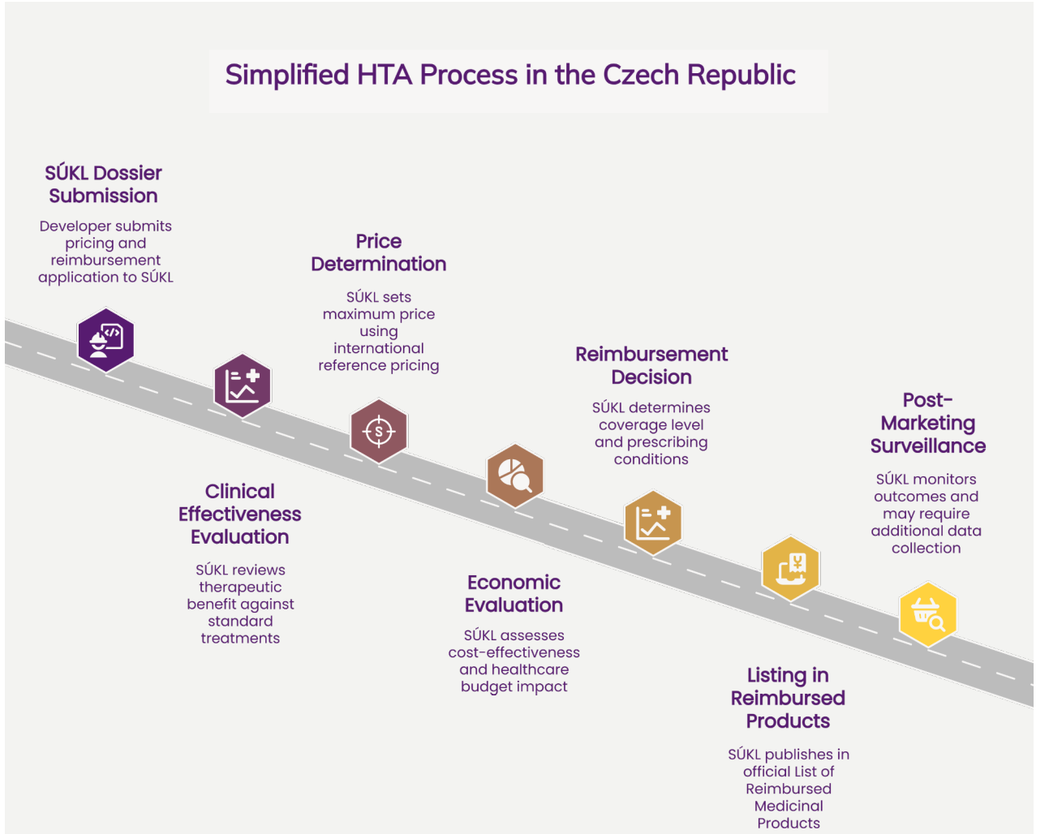
Given the novel nature of psychedelic therapies, SÚKL is likely to recommend conditional reimbursement. This designation allows temporary coverage while mandating additional data collection through patient registries or post-marketing studies. This evidence supports future reassessments, enabling SÚKL to refine reimbursement terms or expand coverage based on updated findings.

Therapies that fail to meet expectations during follow-up evaluations may face restrictions or removal from reimbursement lists. Conversely, positive real-world outcomes can justify broader use, reinforcing the importance of robust initial data submissions and ongoing evidence generation for psychedelic therapies.

Special Considerations for Psychedelic Therapies

Psychedelic therapies present unique challenges for HTA evaluations due to their combined drug-and-therapy approach. SÚKL must assess the pharmacological component and the psychotherapy elements, which complicates economic modelling. Evaluators consider the costs of training therapists, maintaining treatment facilities, and ensuring regulatory compliance, which differ significantly from standard pharmaceutical interventions.

Psychedelics also face additional scrutiny under the Czech Republic's narcotics regulations. Controlled substances require licensing and oversight, adding administrative and legal hurdles to their implementation. Societal attitudes and ethical debates may further influence policymakers, highlighting the need for stakeholder engagement and transparent communication about therapeutic benefits and safeguards. ■



Key Body:

- State Institute for Drug Control (SÚKL): Manages HTAs and makes reimbursement recommendations

Key Features:

- International reference pricing across EU countries
- Budget impact analysis central to decision-making
- Conditional reimbursement common for novel therapies
- Post-marketing surveillance and data collection requirements
- Focus on affordability and sustainability within health system
- SÚKL decisions are binding for reimbursement

5.2.2 Preparing HTA Submissions

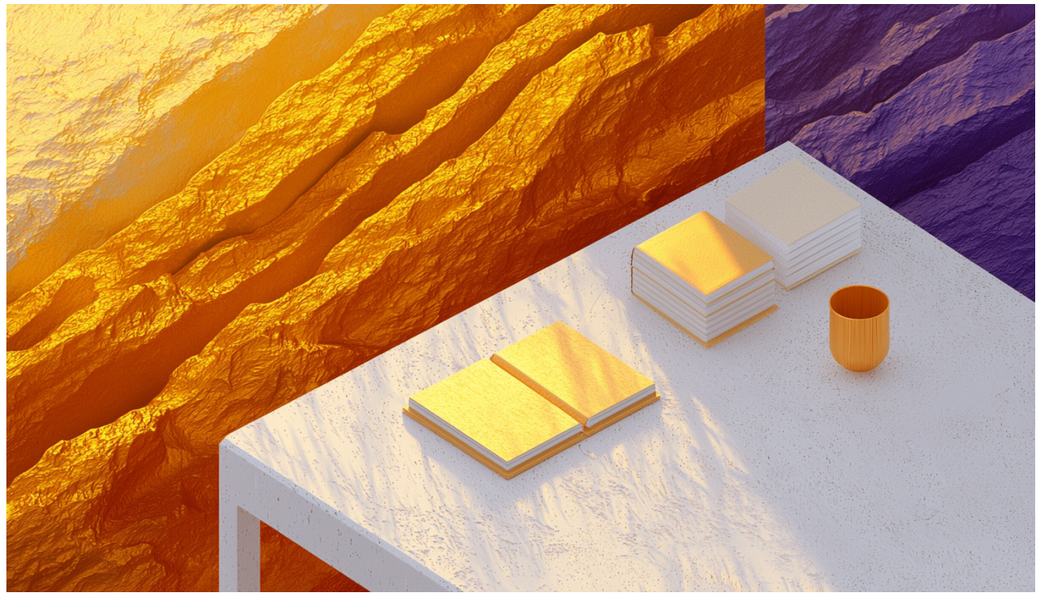
Preparing submissions for HTA bodies requires combining evidence about a treatment's effectiveness and value. This combination is complex for psychedelic therapies because submissions must cover both the drug effects and therapy components, showing how they work together to help patients.

Submissions must include clinical trial results, comparisons with existing treatments, economic analysis, and budget impacts. Although making these comparisons can be challenging, it is important to show how psychedelics compare to current treatments. Economic analysis must consider all costs—including therapist time, facilities, and follow-up care—while highlighting potential long-term savings and patient life improvements.

Since psychedelic therapies are new, HTA bodies will question their long-term effects. Developers can address these concerns by testing different scenarios in their economic models, suggesting ways to collect more data as clinicians roll out treatments, and being transparent about what researchers know and do not know.

Submissions often benefit from input from doctors, patients, and advocacy groups during the HTA process. Doctors can explain why new treatments are needed, while patients can describe how conditions or specific treatments affect their lives. These perspectives will help demonstrate the broader benefits of psychedelic therapies and increase the chances of approval.

The most effective approach in preparing for HTA submission is to use early advice or early engagement meetings wherever possible. HTA bodies offer these opportunities, ranging from informal discussions with broad-ranging advice to extremely structured processes where reviewers answer specific questions or validate evidence-generation plans. Developers should understand that some advice is binding, while other advice is only guidance, requiring developers to clearly understand the process before initiating engagement. ■



5.3 Innovative Reimbursement Models

Innovative reimbursement models represent a dynamic interface between manufacturers and payers, offering mechanisms to manage uncertainties while enabling access to promising therapies. These models may be particularly relevant for psychedelic treatments, where long-term outcomes and durability of effect remain areas of active investigation. Given the novelty and complexity of these therapies, which combine pharmacological and psychotherapeutic elements, standard pricing and reimbursement approaches may prove limiting, and they could benefit from considering the following approaches.

Outcomes-Based Agreements / Performance Agreements

One potential approach is performance-linked reimbursement, where payers tie payments to predefined patient outcomes. For psychedelic therapies, these outcomes could include sustained remission rates, reductions in hospitalisations, or improvements in quality-of-life metrics. Such agreements reduce financial risk for payers by ensuring that payments reflect real-world effectiveness rather than relying solely on clinical trial data. However, developers must address challenges in defining appropriate metrics and establishing mechanisms for long-term data collection early in the negotiation process.

Managed Entry Agreements

Conditional coverage arrangements, also known as managed entry agreements, allow therapies to enter the market while additional evidence is collected. These models are particularly useful when early clinical data shows promise, but gaps remain regarding long-term efficacy or safety. For psychedelics, this approach could help balance the urgency of treating patients with severe conditions against the need for ongoing evidence generation.

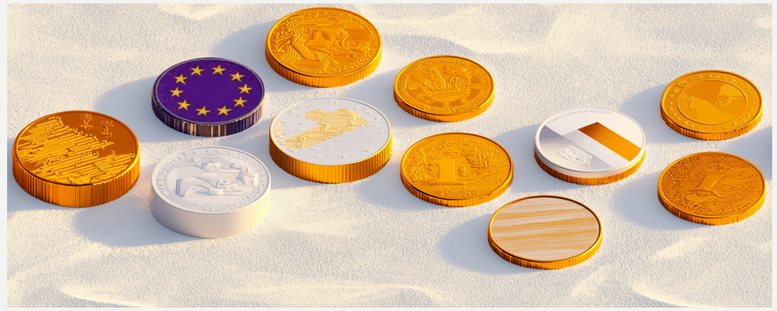
Value-Based Pricing

Another option for psychedelic therapies is flexible pricing strategies based on therapeutic benefits. Value-based pricing aligns costs with demonstrated clinical and economic value, reflecting the therapy's impact on patient outcomes and healthcare resource utilisation. For psychedelics, this might involve accounting for indirect cost savings, such as productivity gains and reduced caregiver burden, to justify higher upfront costs. However, implementing value-based pricing requires robust health economic modelling and transparent agreements on how value is measured over time, and some payer groups have considered and then abandoned this approach in the past.

A particular challenge for psychedelic therapies in value-based models is the cost structure of delivery. Unlike traditional pharmaceuticals, where manufacturers minimise production costs and maintain pricing flexibility within their margin, psychedelic treatments include substantial fixed costs for therapist time and monitoring that must be paid immediately, regardless of long-term outcomes. The immediate payment requirement for substantial fixed costs creates practical constraints on implementing value-based pricing that are not present with conventional drug-only interventions.

While these models will be explored in greater depth in Chapter 10, they offer a framework for addressing the uncertainties common in psychedelic therapies. Innovative reimbursement models can bridge gaps between clinical promise and payer requirements by combining evidence development with flexible payment structures, supporting long-term access to these groundbreaking treatments. ■

6 Reimbursement Landscape in Europe



In Europe, while the European Medicines Agency (EMA) handles drug approvals centrally for most countries, each country makes its own decisions about medicine reimbursement. This separate national decision-making process means developers must work with different systems and requirements across countries.

Most European countries fund medicines through public health systems, but with varying approaches—from Germany's statutory health insurance with national reimbursement decisions, to England's tax-funded NHS, to multi-payer systems like in the Czech Republic and the regulated private insurance model in the Netherlands. Even with national systems, private insurance sometimes supplements coverage for additional treatments.

The overall timing for drug evaluation by payers varies significantly, as does the evaluation method. These differences affect how long it takes to get medicines approved and what evidence countries need. Psychedelic therapies face unique challenges because they combine drugs with psychotherapeutic support. Unlike regular medication, they may require payment systems that cover both the drug and the therapist's time and possibly funding for local infrastructure.

This chapter explains how each country's funding system works, the challenges across markets, and what this means for psychedelic treatments.

6.1 General Reimbursement Pathways for Pharmaceuticals

6.1.1 Overview of European Reimbursement Systems

European healthcare systems all aim to provide universal health coverage but differ in how they balance public and private healthcare delivery. These differences affect how new treatments, including psychedelics, get paid for and delivered. European healthcare systems can be grouped by how much they rely on private versus public providers.

Germany, the Netherlands, and Belgium have significant private sector involvement, with over 60% of hospitals privately owned (Montagu, 2021). These countries use statutory health insurance (SHI), where everyone must contribute to healthcare funding, but private providers can deliver services within regulated frameworks. This framework creates a competitive market while maintaining universal coverage.

The UK, Denmark, and Sweden mainly use public healthcare systems, known as Beveridge models, funded through taxation and run by governments. The UK's NHS is a prime example, providing comprehensive healthcare free at the point of need. However, private insurance may supplement coverage for faster access to elective treatments or additional services, even within public-dominant systems.

France, Italy, and Spain use mixed systems. About 40-60% of their hospitals are private but get public funding. This approach tries to balance efficiency with fair access to healthcare, combining public funding with private service delivery to optimise healthcare provision. ■

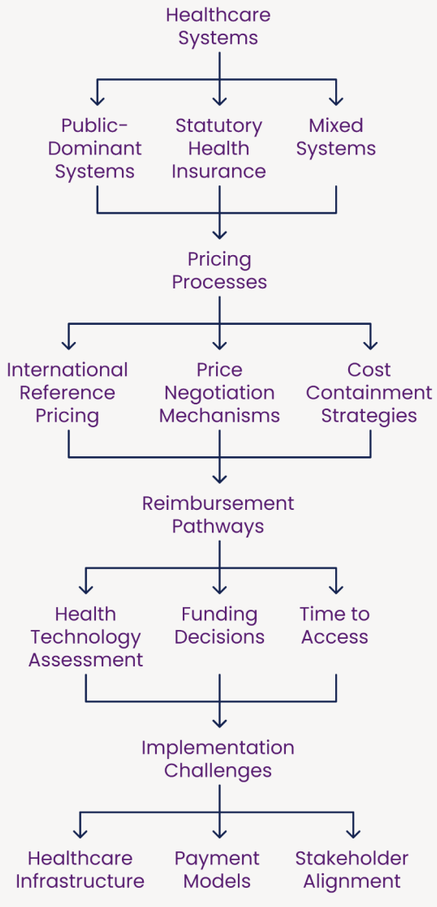
6.1.2 Common Elements Across Countries

Pricing Regulations and Affordability Frameworks

A key goal across Europe is making medicines affordable while maintaining sustainable healthcare systems. The European Commission's pharmaceutical strategy aims to balance innovation with accessibility. While EU countries have different systems, all must follow the EU Transparency Directive, which requires clear pricing decisions while letting countries set their own prices (EP, 1988).

Most European countries use international reference pricing (IRP) to compare medicine prices across countries. Germany uses IRP in price negotiations after its AMNOG (*Arzneimittelmarkt-Neuordnungsgesetz*) benefit assessment. Meanwhile, the Czech Republic sets maximum prices based on the average of the three lowest prices in reference countries. This price referencing system helps control costs but can delay access if companies postpone launches in lower-priced markets to protect prices elsewhere.

European Reimbursement Landscape for Psychedelics



Countries also consider existing treatment prices (internal price benchmarking) and use health economic modelling to assess value. This health economic evaluation often involves measuring quality-adjusted life years (QALYs). The UK's NICE typically allows £20,000-£30,000 per QALY, with flexibility for exceptional cases. The Netherlands uses sliding thresholds based on disease severity. While this approach focuses on health outcomes, it can be challenging for therapies like psychedelics that lack long-term data.

Cost-Containment Strategies and Budgetary Pressures

Countries use various strategies to manage the costs of new medicines. Many use managed entry agreements (MEAs), where payment depends on collecting more evidence or meeting performance targets. Germany allows risk-sharing agreements after benefit assessments, while the Netherlands uses financial risk-sharing for expensive treatments with uncertain long-term effects.

Budget impact analyses (BIAs) help estimate the cost of adopting new treatments across the healthcare system. The Czech Republic and the Netherlands require these analyses to check if treatments are affordable within national budgets. BIAs are particularly important for psychedelic therapies, which often have high upfront costs and might need a gradual introduction with real-world data collection.

Convergence and Flexibility in Policy Frameworks

While countries control their own pricing and reimbursement, the European pharmaceutical strategy promotes cooperation through shared best practices. The EU Joint Clinical Assessment (JCA) aims to standardise clinical evaluations across countries, speeding up market access and reducing duplicate work (EP, 2021). Economic evaluations and pricing negotiations remain under national control to address local needs and budgets.

The EU supports affordability through initiatives like the EURIPID project, which tracks medicine prices across countries. This initiative helps countries make informed decisions while maintaining flexibility in their approaches. ■

6.1.3 Time to Market Access

Variability in Access Timelines Across Europe

Patients' access to new medicines varies widely across Europe, showing problems in how treatments reach the market. It takes an average of 511 days for new treatments to get coverage in the EU and EEA countries (EFPIA, 2022; EFPIA, 2024a). This significant time delay ranges from 126 days in Germany to 804 in Poland.

Germany leads in quick access because it allows most medicines to be prescribed and reimbursed right after EMA approval, with payment details worked out later. Countries like Spain and Poland often take longer because they need multiple reviews at different levels. This disparity in access timing means patients in some countries can get new treatments much earlier than others, showing ongoing problems in creating a more unified European medicines market.

For psychedelic therapies, these differences create extra challenges. The unique treatment approach—including the potential for combining drugs with therapy—may take longer to get approved for payment. They might also need special agreements to track how well they work over time, which adds more steps to the process.

Factors Contributing to Delays

Several interconnected factors contribute to access delays. According to a London School of Economics study, lengthy marketing authorisation procedures, duplicative HTAs, and fragmented pricing negotiations create bottlenecks (Kamphuis et al., 2021). Even after EMA approval, most countries require additional national-level evaluations. Additionally, countries with regional HTA systems, such as Spain and Italy, frequently face delays due to decentralised decision-making processes.

Price-setting approaches, particularly international reference pricing (IRP), further exacerbate delays. Manufacturers may stagger market launches to prevent lower prices in certain countries from influencing pricing negotiations in higher-income markets. This "sequenced launch" approach deprioritises countries with a lower willingness to pay, often based on lower income, compounding inequalities in access.

Pricing and reimbursement complexities are particularly relevant to psychedelics. These therapies will likely have high upfront costs due to clinician time, infrastructure needs, and multiple therapy sessions. The need for flexible pricing and reimbursement models, such as value-based or outcomes-based pricing, could introduce additional delays on top of the existing negotiations over HTA recommendations and determining cost-effectiveness.

Potential Solutions and Policy Initiatives

The EU and some individual countries are trying to speed up access to new medicines. The European Commission's Transparency Directive requires countries to make pricing and reimbursement decisions within 180 days, but this is not necessarily followed (EC, n.d.). The recent EU pharmaceutical legislation package incentivises companies to seek broader and faster launches across EU Member States. Also, the introduction of an EU HTA process, the Joint Clinical Assessment (JCA), aims to eliminate the need for multiple national assessments.

At a country level, innovative payment models, such as MEAs and outcomes-based contracts, offer potential mechanisms to facilitate faster adoption while addressing uncertainty. These payment models can help treatments reach patients faster while controlling costs and reducing financial risks. Still, payers and drug developers have mixed views on the desire to implement these more commonly. ■

6.2 Comparative Analysis of Target Countries

After HTAs or national reimbursement evaluations, the path to getting treatments paid for and used varies between European countries. While HTAs evaluate how well treatments may work and their value for money, the following steps—such as agreeing on prices and adding treatments to healthcare systems—depend on each country's rules and systems.

This section examines how four countries—Germany, the United Kingdom, the Netherlands, and the Czech Republic—handle these steps after HTA. It shows the challenges that new treatments like psychedelics face when trying to enter these markets.

6.2.1 Germany

Germany's rigorous HTA process under the AMNOG framework defines its reimbursement landscape, followed by price negotiations and integration into statutory and private insurance systems. While the HTA establishes comparative clinical value, the implementation phase determines how therapies—particularly innovative ones like psychedelics—are reimbursed and accessed within the healthcare system. This phase hinges on negotiated pricing, physician willingness to prescribe, clarity in billing arrangements with insurers, and adherence to treatment protocols.

Final Steps After the AMNOG Procedure

Following a positive or conditional HTA outcome, the focus shifts to translating the assessment into practical pricing and prescription. Once the Federal Joint Committee (G-BA) determines the therapy's added benefit, the manufacturer directly negotiates with the National Association of Statutory Health Insurance Funds (GKV-SV) to set a new price. This negotiated price applies universally to all statutory health insurers (GKV).

After agreeing to a price, statutory insurers reimburse the therapy based on the specified treatment conditions. Although outcome-based agreements ⤴ are rare in Germany, there is growing interest in piloting such models for therapies with limited long-term data, allowing payers to link reimbursement to measurable patient outcomes.

Differences Between Statutory and Private Insurance

Germany's dual insurance system—statutory (SHI/GKV) and private (PHI/PKV)—introduces variations in reimbursement flexibility. SHI covers roughly 90% of the population and adheres strictly to G-BA guidelines and negotiated prices. Physicians treating patients follow standardised reimbursement rates set by the Uniform Value Scale (EBM), which prioritises cost containment. For therapies without a demonstrated added benefit, SHI coverage may still apply but at reference price levels, limiting reimbursement to the cost of existing therapies.

Private insurance, by contrast, may offer broader access to new treatments and higher compensation rates for physicians under the *Gebührenordnung für Ärzte* (GOÄ) fee schedule. These insurers may adopt therapies even without full AMNOG endorsement, provided evidence supports efficacy and safety. As a result, private patients often face fewer access barriers but may encounter higher out-of-pocket expenses if coverage terms are less restrictive. For psychedelic therapies, private insurance may be more accommodating in covering both the drug and the accompanying psychotherapy.

Incentives for Physicians and Providers

Reimbursement mechanisms influence prescribing behaviours, particularly under SHI. Physicians must operate within regional budget caps when treating SHI patients and can only prescribe high-cost therapies when meeting specific budget and compensation conditions. This budget pressure may make prescribers hesitant to adopt psychedelic treatments, especially if they require prolonged therapy sessions or integration with psychotherapy.

Private insurance generally offers higher compensation rates for physicians, incentivising them to prioritise private patients for novel therapies. When developers roll out treatments in specialised, →

centres, practitioners may also benefit from reputational gains, positioning themselves as leaders in emerging therapeutic fields. This dynamic creates an interplay between reimbursement systems that could shape the early adoption of psychedelics, particularly within private settings.

Specific Challenges for Psychedelic Therapies

Innovative therapies like psychedelics face significant challenges in Germany's reimbursement model. Where psychedelics combine pharmacological effects with psychotherapy, this will require payers to evaluate the therapy as a unified intervention rather than as separate components. The unified treatment approach may necessitate adjustments to coverage frameworks to ensure reasonable reimbursement for drug administration and therapy delivery.

Infrastructure readiness is another hurdle, as clinics require the capacity to safely administer psychedelics, including appropriate monitoring environments and trained professionals. Without an established infrastructure, payers may impose stricter conditions, such as limiting access to designated treatment centres.

Long-term evidence requirements also remain a concern. While initial reimbursement may be granted based on short-term efficacy data, German payers may demand real-world evidence to confirm sustained effectiveness. Psychedelic therapies, which may lack long-term data at launch, could face post-marketing surveillance obligations or conditional reimbursement agreements requiring ongoing data collection to maintain coverage. ■

6.2.2 United Kingdom

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) establishes the reimbursement framework through authoritative evaluations of treatments' clinical and cost-effectiveness in England and Wales. Meanwhile, Scotland relies on its Scottish Medicines Consortium (SMC) for health technology assessments. Following a positive recommendation from either body, the NHS and devolved administrations are responsible for determining how to integrate and fund these therapies within existing care structures.

Post-HTA Implementation in England and Wales

In England and Wales, a positive NICE recommendation carries legal weight, obligating the NHS to fund the treatment within 90 days of publication (The National Archives, 2013). This "funding mandate" applies to all NHS Trusts and Integrated Care Systems (ICSs). Implementation often involves operational adjustments, especially for therapies requiring complex delivery models.

NICE typically separates drug costs from non-drug costs, the latter defined under standard NHS service frameworks. For psychedelics, this could mean fragmentation in funding. NICE may recommend the drug for reimbursement based on incremental cost-effectiveness ratios (ICERs), while other NHS commissioners may take responsibility for decision-making and managing the funding of the associated non-drug services through separate budgets and funding pathways.

This compartmentalised approach can reduce the perceived cost of therapy to any one payer type. However, it also shifts the burden of decision-making for funding non-drug elements onto local NHS groups, potentially delaying full implementation if resources are constrained.

When NICE finds uncertainty in clinical evidence, like limited long-term data on psychedelic therapies, it can recommend conditional funding through Managed Access Agreements (MAAs) or Data Collection Arrangements. These agreements introduce a limited number of treatments while gathering additional real-world evidence.

Scotland's Distinct Pathway

The Scottish Medicines Consortium (SMC) conducts evaluations separately from NICE in Scotland, though it often relies on similar evidence submissions. Unlike NICE, the SMC does not impose a national funding mandate. Instead, Health Boards decide whether ⤴

to adopt recommendations, leading to potential regional variation in access.

The SMC prioritises therapies with clear evidence of added benefit and cost-effectiveness, applying similar willingness-to-pay thresholds as NICE (typically £20,000–£30,000 per QALY). However, Scotland's smaller size and more centralised approach to health governance often facilitate faster implementation, particularly in cases of unmet need.

Northern Ireland and Wales

Northern Ireland generally follows NICE guidance through an "automatic endorsement" process. Wales aligns closely, with the All Wales Medicines Strategy Group (AWMSG) occasionally supplementing evaluations for drugs not reviewed by NICE.

Implementation timelines in these regions mirror England's, with a 90-day funding requirement. However, local differences in service capacity may affect the pace of the rollout, particularly for therapies requiring specialised infrastructure or staffing. For psychedelics, this could result in phased adoption, starting with major population centres before expanding to smaller or rural areas.

Infrastructure and Service Integration Challenges

For complex therapies like psychedelics, reimbursement in the UK depends heavily on service readiness. The NHS must evaluate whether existing clinics can accommodate the therapy's unique requirements, including supervised administration and integration sessions. Early adopters may face higher costs when establishing these services, while later entrants benefit from pre-existing infrastructure.

Developers must also account for NHS cost-containment measures. NICE's focus on ICER thresholds means manufacturers may need to price therapies competitively, factoring in non-drug costs that the NHS could attribute to standard care. In cases where services are entirely new—such as therapy clinics tailored to psychedelics—developers may need to absorb NHS set up costs within their cost-effectiveness calculation. ■

6.2.3 The Netherlands

The reimbursement process in the Netherlands begins after a therapy successfully clears the HTA conducted by *Zorginstituut Nederland* (ZiN). Once the Minister of Health, Welfare, and Sport approves the treatment for inclusion in the national benefits package, the focus shifts to practical implementation, pricing negotiations, and insurer adoption. This process, while structured, allows for flexibility in how insurers manage and contract reimbursement agreements.

Inclusion in the Medicine Reimbursement System (GVS)

ZiN places approved therapies into the *Geneesmiddelenvergoedingssysteem* (GVS), the Dutch Medicine Reimbursement System. The GVS categorises treatments under Appendix 1A for full reimbursement without restrictions or Appendix 1B for specific conditions or limitations.

Complex therapies like psychedelics typically qualify for Appendix 1B placement. Appendix 1B listing requires clear protocols around eligibility criteria, patient monitoring, and evidence collection. These conditions can lead to phased rollouts, focusing initially on specialised centres or pilot programs before broader adoption. While listing in the GVS legally mandates insurers to provide coverage, national-level negotiations determine pricing and conditions, which then apply across all insurers. These negotiations influence how and when patients ultimately gain access to treatment.

Negotiations on Pricing and Reimbursement Conditions

Healthcare providers, particularly specialised clinics offering psychedelic treatments, negotiate service delivery and reimbursement terms with insurers. While ZiN sets the framework, insurers retain flexibility in tailoring contracts with these providers. These negotiations often centre on bundled payments, which cover the entire course of care—including diagnostics, drug administration, and therapy—over a defined period (e.g., 120 days or one year). This framework is primarily relevant for clinics and →

healthcare providers, as pharmaceutical manufacturers negotiate separate national-level pricing.

Insurers may separate costs into drug and non-drug elements for therapies combining pharmacological and psychotherapeutic components. This separation can lead to variability in how therapy components, such as integration sessions, are reimbursed. The variation in coverage rates—from nearly 100% with some contracts to as low as 45% without a contract—impacts patient access and influences the eligible population that clinics can effectively serve.[23] Understanding these coverage variations is crucial for healthcare providers planning to establish specialised treatment centres.

For clinics and care providers offering psychedelic therapies, insurer negotiations often focus on demonstrating value through measurable outcomes and efficient care delivery. These providers must structure their service offerings and demonstrate benefits within existing healthcare codes and reimbursement mechanisms. Care service delivery follows rules different from drug components, which operate under separate national pricing and reimbursement pathways.

Role of Insurers and Pilots

Four major insurers—Achmea (operating under brands like Zilveren Kruis, FBTO, and De Friesland), VGZ, CZ, and Menzis—dominate the insurance market in the Netherlands. Collectively, these insurers cover the majority of the population. While competition exists, insurers often adopt similar approaches to reimbursement decisions, particularly for high-profile therapies.

Pilot programs are a key mechanism for introducing innovative therapies in the Netherlands. Providers and insurers frequently collaborate on small-scale pilots to test new treatments, evaluate outcomes, and refine implementation models. These pilots allow insurers to de-risk adoption by gathering real-world evidence before committing to broader coverage. For psychedelic therapies, pilots could demonstrate efficacy and scalability, providing insurers with the data needed to support broader reimbursement.

Value-based arrangements are emerging in Dutch healthcare, historically driven by collaborations between hospitals and provider networks rather than directly with insurers. These provider-led models have achieved measurable improvements in patient outcomes by sharing data and best practices. While performance-linked payments do exist in theory—for example, to reduce hospital admissions in chronic conditions like COPD—the administrative burden of implementing full outcome-based contracts often limits their use.

These arrangements might influence the adoption of psychedelic therapies by healthcare institutions, though likely through simplified financial structures rather than complex outcome-based mechanisms. The focus typically remains on demonstrating value through established care pathways and reimbursement mechanisms, with healthcare institutions as the key partners in implementation.

Political and Advocacy Influence

While ZiN's decisions are grounded in clinical evidence and cost-effectiveness, political lobbying and advocacy efforts can significantly influence outcomes, particularly when highlighting disease severity and societal burden. High-impact therapies often attract media attention and patient advocacy, pushing policymakers to accelerate access.

For psychedelic therapies, patient advocacy groups (PAGs) can be crucial in demonstrating the significant burden of mental health conditions, their societal costs, and the critical need for innovation in treatment options. These patient advocates are especially impactful in the mental health space, where both ⤴

[23] The reimbursement rates vary significantly between contracted and non-contracted mental healthcare providers. Contracted providers typically receive 75-100% of the standard rates set by the Dutch Healthcare Authority (NZa), with larger integrated institutions often receiving 95-100%. In these cases, patients only pay their annual deductible (eigen risico) of €385-885, depending on their policy. Non-contracted providers receive substantially lower reimbursements (45-70%) and may charge additional out-of-pocket fees beyond the annual deductible, potentially creating financial barriers to access.

the severity of conditions and the historical lack of innovation can be powerful drivers for securing reimbursement and reducing stigma.

Political considerations may also affect budget allocations for mental health services, particularly as policymakers respond to growing awareness of unmet needs in areas like treatment-resistant depression (TRD) and PTSD. Developers should remain proactive in engaging with policymakers, framing psychedelic therapies as solutions to pressing public health challenges rather than niche treatments.

Infrastructure Readiness and Provider Networks

Reimbursement decisions must also account for infrastructure and provider readiness. Although the Netherlands' clinical infrastructure is known as one of the best in the world, psychedelic therapies require dedicated treatment rooms, trained therapists, and monitoring protocols, raising questions about how quickly existing mental health services can adapt. Providers negotiate directly with insurers to establish service packages, and prices may vary based on regional capacity and expertise.

For example, some providers already operate under bundled payment models, offering comprehensive care packages for depression and anxiety disorders. Providers can adapt these frameworks for psychedelic therapies by integrating drug administration with therapy sessions into a single reimbursable unit. However, insurers may initially limit coverage to centres of excellence or pilot programs, requiring providers to scale up gradually as demand grows.

With infrastructure development, political advocacy, and pilot programs playing pivotal roles, the Netherlands represents a fertile but complex market for psychedelic therapies. Successful adoption will depend on proactive engagement with insurers, robust evidence generation, and scalable delivery models that align with existing healthcare frameworks. ■

6.2.4 Czech Republic

The reimbursement process in the Czech Republic builds upon the HTA evaluation conducted by the State Institute for Drug Control (SÚKL). After a favourable decision by SÚKL, the focus shifts to pricing agreements, insurance coverage, and implementation within the healthcare system. While the Czech system receives public funding through SHI, private insurers supplement coverage, especially for innovative therapies. The pathway for psychedelic therapies draws from prior experiences with novel treatments, such as esketamine and medicinal cannabis, indicating both openness to innovation and the need for structured reimbursement frameworks.

Implementation After SÚKL Approval

SÚKL's approval requires therapies to enter the Czech reimbursement system under the Act on Public Health Insurance. First, officials set the highest allowed price and establish payment methods. They base prices primarily on EU cost comparisons, specifically selecting the three lowest prices from a designated basket.

Specific indications and protocols determine reimbursement eligibility. For example, the 2022 agreement on esketamine (Spravato) stipulated that reimbursement applies only when administered in exceptional cases in specialised centres for TRD. At the end of 2024, Spravato gained standard reimbursement. Similar conditions are likely to govern psychedelics, particularly their combination with psychotherapy, which demands infrastructure and trained staff.

Insurance coverage typically follows the SÚKL decision, but insurers can impose additional conditions, particularly for therapies with high upfront costs or uncertain long-term outcomes. Budget impact analyses play a critical role, with insurers demanding evidence of economic sustainability. If the projected costs exceed predefined thresholds, risk-sharing agreements—such as price-volume arrangements or rebates—may be required to limit financial exposure.

Role of Health Insurance Providers

The Czech Republic's healthcare system operates through SHI, with the General Health Insurance Company (VZP) covering most of the population and several smaller insurers providing additional options. Public insurers must follow SÚKL recommendations, but they retain some discretion in defining reimbursement conditions. For instance, the agreement on esketamine required joint approval from the Czech Psychiatric Society and insurers.

While SHI covers most psychiatric and psychotherapy services, innovative treatments such as ketamine therapy have often required partial reimbursement models. Patients may face co-payments, particularly for ancillary services, such as therapy sessions accompanying pharmacological interventions. Some clinics address affordability gaps by offering grant programs or leveraging partnerships with multiple insurers to create flexible financing options.

Although less dominant, private insurers can provide quicker access to therapies through performance-based reimbursement models. These agreements tie payments to outcomes, enabling insurers to manage uncertainty while incentivising high-quality care. Psychedelic therapies may benefit from such models, especially if early pilots demonstrate measurable improvements in patient outcomes.

Regional Variability and Infrastructure Challenges

Although the Czech Republic has a centralised reimbursement framework, implementation can vary regionally, particularly for therapies requiring specialised infrastructure. Psychedelic therapies are likely to be limited initially to centres of excellence or university hospitals equipped with trained staff and monitoring facilities. Clinics offering ketamine psychotherapy already provide a precedent, operating within regulatory guidelines while negotiating tailored agreements with insurers.

Expanding access will depend on creating reimbursable codes for psychedelic therapy, which currently lacks standardised billing mechanisms. To enable broader adoption, stakeholders, including providers and advocacy groups, may need to push for legislative or administrative updates. Early engagement with insurers and policymakers is critical to streamlining this process and addressing gaps in existing frameworks.

Lessons from Ketamine and Cannabis Adoption

The Czech Republic's experience with medicinal cannabis and esketamine shows how psychedelic therapies might navigate reimbursement. Medicinal cannabis, legalised in 2013, required coordination between regulators, prescribers, and insurers to establish prescribing protocols and pricing. Similarly, partially reimbursed ketamine therapy highlights the need for unified payment models covering both drug and therapeutic aspects.

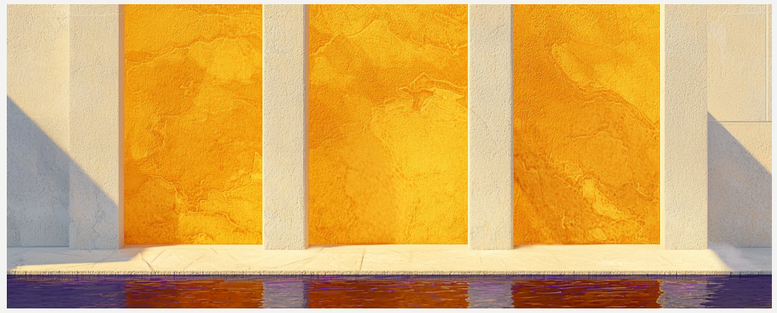
These precedents suggest that psychedelic therapies could face stepwise adoption, starting with pilot programs in specialised centres before scaling more broadly. Such pilots demonstrate feasibility and generate real-world evidence to support reimbursement negotiations. They also allow insurers to test value-based agreements, tying payments to metrics like patient remission rates or reductions in hospital admissions. ■

Comparison of Market Access Systems Between Case Study Countries

Country	Medicine Evaluation & Access Pathway	Value Assessment Framework	Evidence Requirements for HTA	Pricing Mechanism & Negotiation Process	Funding & Reimbursement System
Germany	Centralised via *Gemeinsamer Bundesausschuss* (G-BA), including rigorous AMNOG-based HTA evaluation conducted by *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (IQWiG)	Assessment of additional linical benefit compared to appropriate comparator therapy	Comparative head-to-head RCTs against standard of care generally required; focus on patient-relevant outcomes and mortality, morbidity, quality of life	Initial free pricing for first six months, followed by centralised price negotiated between manufacturer and *GKV-Spitzenverband* (National Association of Statutory Health Insurance Funds); agreed price applies to all statutory insurers (GKV)	Predominantly statutory health insurers (GKV) covering about 90% of population; private insurance (PKV) more flexible, particularly for innovative therapies; drugs with no added benefit priced at level of comparator therapy
United Kingdom	NICE HTA in England & Wales; SMC HTA in Scotland; AWMSG for some medicines in Wales	Cost-effectiveness evaluation with £20,000-£30,000/QALY threshold (higher for end-of-life care and rare diseases)	Evidence on patient quality of life impact; preference for head-to-head RCT comparisons against standard care, but indirect comparisons accepted; patient and clinical expert testimony considered	List price set by manufacturer; net pricing influenced during HTA evaluation, using patient access schemes	NHS funded; mandatory local funding for NICE approved products within 90 days of decision; some Managed Access Agreements with centralised funding
Netherlands	Centralised via *Zorginstituut Nederland* (ZiN), with initial marketing authorization from *College ter Beoordeling van Geneesmiddelen* (CBG/MEB)	Cost effectiveness and therapeutic value assessment	Comparative clinical effectiveness evidence; may accept pragmatic, real world evidence; incorporation of societal benefits	Initial pricing set by manufacturers; ZiN advises the Ministry of Health, Welfare and Sport (VWS), which may conduct price negotiations for expensive medications; insurers can further negotiate prices for reimbursed products	Health insurers implement ZiN recommendations; ZiN-approved medicines included in national benefits package (GVS) - mandatory insurer coverage with potential for preferred medicine policies by insurers
Czech Republic	State Institute for Drug Control (SÚKL) oversees HTAs for medicines seeking national reimbursement	Cost-effectiveness, budget impact, and therapeutic value	Comparative clinical effectiveness evidence; pharmacoeconomic models demonstrating incremental cost-effectiveness ratios (ICERs) and quality-adjusted life years (QALYs); international reference pricing comparisons	Maximum pricing set via international reference pricing (based on lowest prices in reference countries); net pricing influenced through price-volume agreements and risk-sharing schemes	Statutory Health Insurance (SHI) with health insurance funds; partial reimbursement or co-payments common for many therapies; highly innovative products may receive temporary reimbursement (VILP) for up to three years

Challenges and Barriers to Reimbursement

7



Getting psychedelic therapies approved and paid for by healthcare systems is challenging. While these treatments show promise for mental health conditions, their unique approach—combining drugs with psychotherapeutic support—creates hurdles not seen with regular medicines. This chapter consolidates and summarises key challenges from earlier chapters, setting up the solutions discussed in Chapter 8.

Interviews with regulators, insurance companies, healthcare providers, and industry experts reveal key barriers at every stage, from clinical trials and proving effectiveness to securing reimbursement and insurance coverage. The hybrid nature of psychedelic therapies, combining pharmacological & psychotherapeutic components, adds particular complexity. Healthcare systems typically evaluate and fund drugs or therapy services separately, not together. As a result, systems may undervalue these treatments or delay access because their frameworks cannot effectively assess and implement these unique combined features.

This chapter examines clinical evidence challenges, economic barriers around costs and benefits, regulatory hurdles across different countries, healthcare system implementation issues, social and ethical concerns, public perception, and resistance from various stakeholders with conflicting goals. Understanding these challenges is essential for developing effective solutions that can help psychedelic therapies reach patients who need them while ensuring they are used safely and cost-effectively within modern healthcare systems. ■

7.1 Clinical Evidence Challenges

Providing solid evidence for psychedelic therapies is more complicated than for regular medicines. These treatments combine powerful drugs with psychotherapeutic support, making it harder to design objective clinical trials and track how well therapies perform. There are several significant hurdles: studies often include only certain types of patients, it is difficult to blind participants on whether they received the active drug or not, and comparing these treatments to existing options is not straightforward.

Another significant challenge is understanding how well these treatments work over extended periods of time. Most studies only follow patients for a few weeks or months, which is insufficient to determine whether the benefits persist or what kind of ongoing care people might need. Research must also demonstrate how these treatments perform in real-world healthcare settings, not just in carefully controlled research studies. These evidence gaps make it harder for health authorities to decide whether to approve and pay for these treatments.

7.1.1 Trial Design Limitations

Small Samples and Selection Bias

Many early psychedelic trials have relied on small, highly selective patient groups, raising concerns about their generalisability to broader populations. Participants in these studies are often highly motivated, well-educated, and financially stable—factors that enable them to take time off work, travel to trial sites and commit to time-consuming treatments.

These participants may not reflect the demographics of patients most in need of treatment in real-world settings, where barriers such as socioeconomic limitations, geographic isolation, and coexisting health conditions are more prevalent. As a result, the efficacy observed in controlled trials may be difficult to replicate in routine clinical practice.

Another issue is that most data on psychedelics comes from the United States, where healthcare systems and cultural views differ from those in Europe. Some studies suggest that European patients might not respond as strongly to psychedelic therapies as American patients, possibly due to different expectations, social settings, or how treatments are delivered.

Blinding and Psychedelic-Induced Effects

Blinding—keeping patients and doctors from knowing who received the actual drug—is especially challenging in psychedelic research because these substances cause noticeable mental effects. Unlike regular medicines, psychedelics create clear changes in thinking and perception, making it more likely that participants and therapists will correctly identify whether they received the actual drug or a placebo.

While other treatments with noticeable effects, like sedatives, face similar issues, the problem is more prominent with psychedelics because their effects are so intense. This challenge requires creative approaches to trial design, but creating these new methods complicates achieving regulatory approval. Researchers have tried to mitigate unblinding by using active placebos or lower doses of the active drug. However, this raises concerns because even these control conditions can produce meaningful therapeutic effects, complicating the interpretation of results.

Comparator Selection and Cost Constraints

Choosing appropriate comparison treatments is another major challenge in psychedelic trials. European regulators usually require new treatments to have at least a comparable risk-benefit ratio as existing ones, and payers also want to be able to evaluate comparative effectiveness. For psychedelics, which often treat resistant conditions and combine drug effects with psychotherapeutic support, identifying appropriate comparators can be difficult.

The unique mechanisms of psychedelics, combining pharmacological effects with psychotherapeutic support, make them difficult to compare against →

traditional monotherapies. The comparison challenge has led some stakeholders to propose hybrid models that assess both components independently, though such approaches risk oversimplifying the treatment model and missing its synergistic effects.

The situation is made more challenging by high costs. Comparative trials with combination therapies are expensive and take longer to complete. Developers may lack the money or willingness to run such trials. These financial and practical challenges slow evidence generation and make it harder to prove value to payers.

Regulatory Expectations and Novel Trial Designs

The EMA and other regulators have not yet created clear rules or guidance for evaluating psychedelic therapies as a class, which further complicates trial design. Current requirements follow traditional drug testing models, focusing on standard dosing and symptom reduction. While these conventional approaches are important, they may not fully capture the unique therapeutic mechanisms and outcomes of psychedelic treatments, including improvements in overall well-being and quality of life.

With no previous psychedelic approvals in Europe outside of esketamine (Spravato), regulators might demand comprehensive evidence, including multiple large trials and long-term follow-up. This regulatory uncertainty has significant implications beyond just market approval. Even if regulators accept novel trial designs, such as the use of active placebos, the lack of formal guidance means that country payers may reject these studies for not meeting their established assessment criteria. This dual challenge of regulatory and reimbursement uncertainty has led some companies to focus on markets with clearer paths, like the U.S., instead of Europe. ■

7.1.2 Limited Long-Term Data

Gaps in Long-Term Follow-Up

One of the most pressing challenges for psychedelic therapies is likely to be the scarcity of data to determine their longer-term efficacy. While early trials, including small-scale academic studies and Phase II clinical trials, have shown promising short-term results, they often lack the extended follow-up periods necessary to capture the durability of effect and potential adverse outcomes.

Most psychedelic trials report outcomes measured in weeks or months, leaving uncertainties about whether the initial gains—such as reductions in depressive symptoms or post-traumatic stress—persist over years. This absence of longer-term data raises uncertainties for regulators and payers, who require robust evidence to justify reimbursement, especially where treatment costs are higher, and investment to support long-term adoption in healthcare systems.

Adding to this issue is the nature of psychedelic treatments, which often involve profound subjective experiences and a degree of psychological restructuring. These effects may vary in stability, with some patients experiencing relapses or requiring ongoing psychotherapy to maintain benefits. Whether long-term improvements hinge on repeated dosing, booster sessions, or continued psychological support remains largely unresolved.

Without this information, it becomes difficult to estimate the true cost-effectiveness of psychedelic interventions, particularly for health systems that operate under budgetary constraints.

Challenges of Real-World Evidence Collection

Even when studies track patients long-term, the results can be inconclusive. Many participants in early psychedelic trials are highly motivated and may seek additional treatments outside the trial, like joining support groups or using psychedelics on their own. These outside activities make it difficult to isolate the effects of the initial treatment.

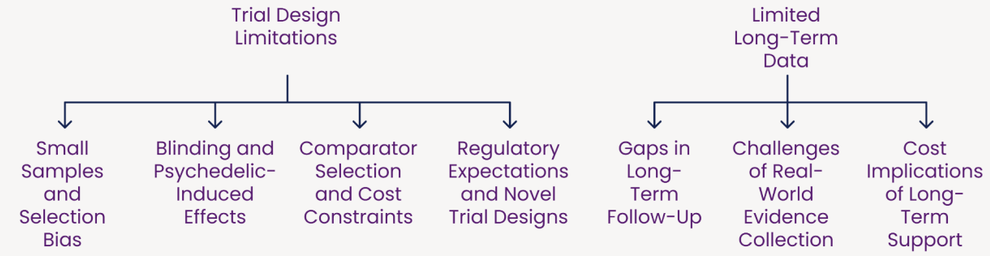
Real-world results migh also be different to those seen in carefully controlled trials. While research studies have highly motivated patients and experienced therapists, regular medical practice differs. Patients might not follow treatment plans strictly, therapists might have less training, and people might be less engaged overall.

Cost Implications of Long-Term Support

The full long-term costs of psychedelic therapies remain unknown. While these treatments often involve just a few intensive sessions over several weeks, patients might need ongoing support. The extended care could include follow-up therapy sessions, support groups, or additional doses to maintain benefits. The uncertainty around extra costs complicates calculations of true treatment costs and widespread implementation potential.

For instance, many patients join support groups after treatment, but these groups operate outside regular healthcare systems. The informal nature of support groups makes it hard to track their effectiveness or determine whether patients need more formal care. Insurance companies and health authorities might be reluctant to cover psychedelic treatments without a better understanding of these ongoing needs, especially since the cost argument for these therapies relies heavily on their long-term benefits. ■

Clinical Evidence Challenges in Psychedelic Trials



7.2 Economic Evaluation Challenges

Working out whether psychedelic therapies provide good value for money is particularly challenging. These treatments have high upfront costs—not just for the drugs themselves but also for the therapy sessions, infrastructure use, and trained staff needed to deliver them safely. While supporters argue these treatments could save money in the long run by helping people recover from severe mental health problems, proving these savings is difficult without long-term evidence.

Another challenge is measuring how these treatments might benefit society. While it is relatively easy to count direct savings like reduced hospital stays or less medication use, it is much harder to put a value on indirect benefits. These could include people being able to return to work, families spending less time caring for ill relatives, or reduced societal costs from problems like addiction. Different European countries also have different ways of measuring these benefits and deciding what makes a treatment worth paying for, complicating things further.

7.2.1 High Upfront Costs of Combined Treatment

High Costs of Psychedelic Drugs

The cost of psychedelic therapies is likely to be a significant challenge. While manufacturing these drugs might be relatively cheap, developers rationalise higher drug prices based on the argument that they need to cover development and approval costs, cover costs of other failed medicines, and continually invest in pharmacovigilance and evidence generation even after launching a medicine. For example, Spravato (esketamine) costs thousands of euros per treatment course, indicating that psychedelic drugs might cost similar amounts per course of treatment.

Health authorities evaluate whether treatments are worth the cost. If drug prices are too high, reimbursement might only be granted for certain patients or under specific conditions. The price negotiations create tension between companies that aim for higher prices and payers and insurers that try to control costs, especially for treatments that might help hard-to-treat conditions but lack long-term evidence.

Psychotherapy and Resource-Intensive Delivery

Beyond drug costs, psychedelic treatments might require substantial therapeutic support. While the dosing sessions can last several hours and need continuous healthcare provider oversight, there is ongoing debate about the optimal amount of preparation and integration therapy. Some proponents advocate for intensive psychotherapy to achieve the best outcomes, while others suggest a more minimal approach focused on ensuring patient safety.

For example, MDMA therapy protocols can involve up to 100 hours of therapist time. Based on cost modelling from U.S. studies, these resource requirements could lead to total treatment costs of €15,000 to €40,000 per patient, reflecting the drug price and extensive therapeutic support needed.

Current systems frequently assess drugs or therapy separately for reimbursement, not both together. Since psychedelic drugs and psychotherapeutic support may require use together, any attempts to separate out their effects complicates value-for-money calculations. The interconnected nature of drugs and psychotherapeutic support creates uncertainty in defining value and appropriate cost for the drug-only part of therapy and justifying reimbursement at higher price points.

Short-Term Costs vs. Long-Term Benefits

These treatments must balance high initial costs against possible but uncertain long-term health outcomes and savings. While they might reduce future spending on medications, hospital stays, and lost work time, there is currently not enough long-term evidence to prove these savings. When health systems focus on short-term budgets, expensive treatments often face resistance, even if they might save money later.

The cost-benefit uncertainty could lead to limited reimbursement and insurer coverage, such as coverage only for patients who have not responded to a set number of other treatments. Finding ways to consider long-term benefits while managing current costs remains a key challenge. ■

7.2.2 Measuring Indirect Benefits

Quantifying Societal and Economic Gains

Distinguishing Direct and Indirect Benefits

The direct economic benefits of psychedelic treatments are easy to measure—things like fewer hospital stays and less medication use. When a patient recovers from depression or PTSD using psychedelics, we can capture how much less they use health services. These savings can be estimated using standard methods.

However, the indirect socioeconomic benefits are more challenging to measure but just as important. These benefits include people being able to work better, needing less help from family, and having better relationships. Mental health problems often make it hard for people to work and live normally. Fixing these issues can benefit society broadly, but it is harder to put numbers on these benefits.

Challenges in Valuing Productivity Gains

One big challenge is measuring how many more people can work after treatment. While patients might return to work or do better at their jobs, it is hard to capture how much of this improvement comes from the treatment versus other factors like the economy or education.

There are different ways to calculate these work benefits. One method considers all the money someone might earn over time, while another only counts short-term gains since others eventually fill ⤴

jobs. Neither method is perfect—one might show too much benefit while the other might show too little. The calculation differences make it hard to agree on the value of these treatments.

Reducing Caregiver Burden and Improving Quality of Life

Beyond individual productivity, psychedelic therapies may alleviate burdens placed on caregivers—family members and friends who often provide unpaid support to individuals struggling with mental illness and may have had to give up full-time employment due to the demands of caregiving. Patients often require lots of support from others, who might have to help with daily tasks and provide emotional support. Good treatment can reduce this burden, letting caregivers work more and live better lives.

However, measuring these benefits is even more challenging than measuring productivity gains. Current methods are not good at putting a monetary value on things like caregiving, even though they are crucial for families and society.

Addressing Long-Term Societal Impacts

It is also hard to measure long-term benefits. While psychedelic treatments might help people for many years or decades, most calculations only look at short-term savings. These short-term evaluations might undervalue these treatments, especially when considering fewer disability payments and less need for government help.

For instance, addiction disorders generate significant public costs through increased criminality, violence, and social care interventions. Successful treatments could reduce these substantial societal burdens, along with decreasing disability payments and the need for ongoing government support.

Real-world results might differ from expectations. Support groups might improve treatments, but calculations rarely consider these benefits. Limited access to follow-up care might also reduce long-term benefits. These factors complicate predictions of the treatments' actual economic value.

Cost Implications of Long-Term Support

The full long-term costs of psychedelic therapies remain unknown. While these treatments often involve just a few intensive sessions over several weeks, patients might need ongoing support. The extended care could include follow-up therapy sessions, support groups, or additional doses to maintain benefits. The uncertainty around extra costs complicates calculations of true treatment costs and widespread implementation potential.

For instance, many patients join support groups after treatment, but these groups operate outside regular healthcare systems. The informal nature of support groups makes it hard to track their effectiveness or determine whether patients need more formal care. Insurance companies and health authorities might be reluctant to cover psychedelic treatments without a better understanding of these ongoing needs, especially since the cost argument for these therapies relies heavily on their long-term benefits.

Variability in Health Economic Standards

Different Countries, Different Rules

European countries have different ways of deciding whether to pay for new treatments. Some countries like the Netherlands and Sweden may consider all benefits, including helping people return to work and reducing family burdens. Others, like Germany, prioritise patient-relevant outcomes with no formal economic analysis. This disparity means that developers must make different arguments for each country.

In countries that consider wider benefits, psychedelic treatments might have a better chance of demonstrating value to payers and securing favourable pricing and broader reimbursement. However, demonstrating payer-accepted value will be more challenging in countries that only look at direct healthcare costs, even if they help patients and society in other ways.

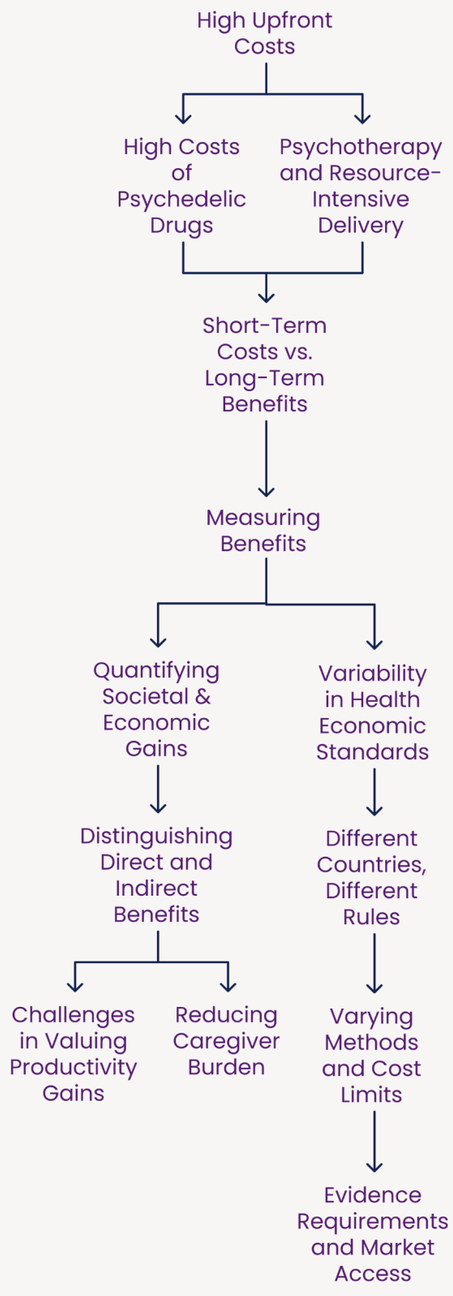
Varying Methods and Cost Limits

Countries also use different methods to calculate benefits and have different limits for what they will pay. The UK usually will not pay more than £30,000 per year of healthy life gained, while the Netherlands allows higher costs for more serious conditions. Germany takes a different approach, negotiating prices case by case without set limits.

E*vidence Requirements and Market Access*

Countries handle uncertainty about new treatments differently. Some approve treatments while gathering more evidence about long-term effects, while others wait for complete proof, which can delay access to treatment. These differences make it hard to get psychedelic treatments approved across Europe. Companies usually focus on countries with larger populations first, which means smaller countries wait longer. The prioritisation of larger markets creates an unequal system in which access to these potentially valuable treatments varies widely depending on where patients live. ■

Economic Evaluation Challenges in Psychedelic Treatments



7.3 Regulatory and Policy Barriers

Getting psychedelic therapies approved and regulated presents unique challenges because most countries classify these substances as Schedule 1 drugs with no accepted medical use. Developers must overcome hurdles beyond the usual medicine approval process by dealing with drug control authorities and health regulators. While some controlled substances like esketamine have successfully become approved medicines for depression, complex and expensive requirements create barriers through special permits, secure storage, and strict safety measures.

Different countries' varying approaches to these treatments complicate the approval process. Countries maintain individual rules about controlled substances and different systems for funding new treatments. The regulatory and payment variations impede the widespread availability of psychedelic therapies, especially since most healthcare systems lack frameworks specifically designed for combined drug-therapy treatments. The multiple requirements create a complex web that developers must navigate, often delaying patient access in some countries.

7.3.1 Controlled Substance Regulations

Legal Restrictions and Scheduling

Current Legal Status

International law classifies most psychedelics like psilocybin, MDMA, and LSD as Schedule I drugs. The Schedule I status labels them as highly dangerous with no medical use. The restrictive classification makes treatment and research challenging. Anyone working with these drugs needs special permits, secure storage, and strict safety measures. The strict requirements make operations more expensive and complicated, deterring many hospitals and researchers from working with psychedelics.

Examples of Change

Some controlled drugs have successfully become medical treatments, showing that change is possible. Medical professionals first used ketamine as an anaesthetic, but now regulators have approved a form of it (esketamine) to treat depression. Doctors prescribe GHB (sodium oxybate), another controlled drug, to treat sleep disorders under the brand names Xyrem and Xywav.

However, getting approval for psychedelics will likely take longer and be more difficult. Regulators want extensive evidence that these drugs are safe and work well, especially since the treatment includes therapeutic support along with the drugs. They often require ongoing studies even after approval to keep checking safety, which adds more costs and complexity to the process.

Practical Challenges

Rescheduling psychedelics from Schedule I to a lower schedule creates a significant hurdle before doctors can prescribe them in health systems. The rescheduling process demands extra effort, delays patient access, and increases uncertainty around market entry.

Even after rescheduling, substantial practical challenges remain. Healthcare facilities will likely need special storage arrangements and maintain detailed prescribing records, which adds costs and administrative burdens. Additionally, healthcare providers will need specific training and certification to use these drugs, but no recognised training programs are available yet.

This shortage of qualified providers could become a significant bottleneck, limiting access to treatment even if the drugs become legally approved. These regulatory requirements, high handling costs, and limited training opportunities make it harder for healthcare systems to adopt these treatments, even if they prove effective.

Complex Approval Processes

Extra Regulatory Steps

Getting approval for psychedelic treatments is more complicated than for regular medicines. These →

treatments need two types of approval: one as a medical treatment and another because they are controlled substances. The dual approval process requires coordination with both health authorities and drug control agencies. Each step needs lots of paperwork, safety checks, and facility inspections. The combination of drugs with psychotherapeutic support adds complexity. Regulators evaluate the drug components and therapy elements separately, making it difficult to demonstrate the treatment's overall effectiveness.

Higher Costs and Longer Timelines

These extra steps make developing psychedelic treatments more expensive and time-consuming. Companies must follow both medical and drug control rules, which means more paperwork and longer waiting times. A prolonged process is especially challenging for smaller companies developing psychedelic treatments, as they often have limited money and time compared to big pharmaceutical companies. When regulators ask for more long-term safety data or extra trials, it increases costs and delays.

Different Views on Approval

There is a debate about how psychedelics should be approved. Drug companies focus on getting approval for their specific versions, like Compass' COMP360 for psilocybin. Nevertheless, some supporters want broader changes to make all forms of psychedelics available, including natural ones. These opposing views create a challenge. Specific drug approvals keep tight controls but limit access and keep costs high. In contrast, broader access might make treatments cheaper but more challenging to control for quality and safety, and for use only in appropriate patients.

Implications for Market Access

These complex approval processes affect how quickly treatments become available. Treatment centres might wait to invest in facilities and staff training until they know regulations and payment systems. The lengthy approval process also slows down the development of support systems needed to ⤴ provide these treatments widely. All these challenges make it more complex and more expensive to bring psychedelic treatments to patients who need them and create more significant uncertainties for return on investment, which is important for commercial drug developers. ■

7.3.2 Lack of Established Reimbursement Pathways

Novelty of Combined Therapies

Challenges in Integrating Drug and Therapy Models

Psychedelic therapy is different from most medical treatments because it combines drugs with psychotherapeutic support sessions. The therapeutic part potentially involves long sessions with trained professionals, special facilities, and follow-up care, which adds significant costs beyond just the drug itself. Healthcare systems may find it difficult to define whether this should be considered one complete treatment or separate parts that need different kinds of payment. Treatment periods and therapy quantities vary significantly depending on the condition and psychedelic type, making healthcare providers unable to define 'complete care packages' upfront.

National health systems face a particular challenge because they often divide funding among different parts of the system. Healthcare systems will have to choose between treating psychedelic therapy as one complete treatment or breaking it into separate parts. When broken into parts, the drug might be paid for through typical drug payment systems, while the therapy sessions are paid through separate mental health budgets.

This split approach causes problems because it might not recognise how the drug and therapy work together to help patients. It could also mean insufficient money is available for either part of the treatment, making it harder for patients to access the complete treatment they need. In contrast, insurer-based reimbursement systems might be better equipped to handle combined treatment approaches as a single package.

Creating New Payment Systems

Healthcare systems need to develop new ways to pay for these combined treatments. Some possible solutions include "bundled payments" covering everything in one package or performance-based payments based on the treatment's effectiveness. However, changing payment systems is complicated and takes time. Countries must also decide whether to pay for these treatments based on their mental health or drug budgets. Mental health budgets are often stretched, which could limit access, while drug budgets might struggle with the extra therapy costs.

Questions About Long-Term Value

Another challenge is proving that these treatments are worth their cost in the long run. Early research suggests they might save money by reducing the need for other healthcare services and helping people return to work. However, without long-term evidence, insurance companies and healthcare systems might hesitate to pay the high upfront costs. Developers will need to keep collecting evidence even after approval, which adds more costs.

Implications for Market Access

These payment challenges affect how quickly treatments become available. Healthcare systems might start with small trial programs to test different payment methods. However, this careful approach could mean that treatments take longer to become widely available. Making these treatments part of regular healthcare will require new systems for selecting appropriate patients, delivering treatment, and monitoring results. Healthcare systems, insurance companies, other payer groups, and developers need to work together to create payment systems that are fair and sustainable.

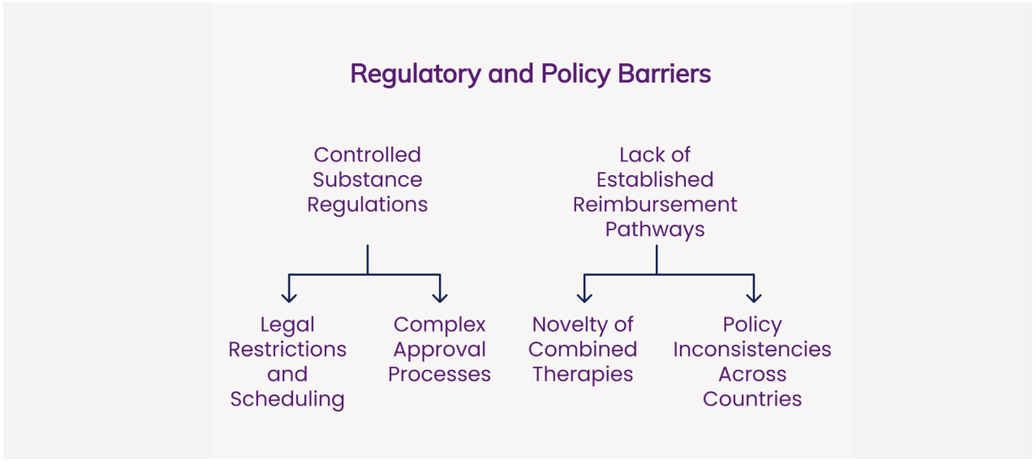
Policy Inconsistencies Across Countries

Fragmented Regulatory and Reimbursement Frameworks

Countries will handle the approval and payment for psychedelic therapies in very different ways. This fragmentation complicates the process for developers to getting approval and reimbursement in multiple countries. Each country has its own system for deciding if treatments are worth paying for and how much they should cost.

Examples of Country Differences

Germany has one national system (AMNOG) for evaluating treatments and negotiating prices, with insurers directly involved in pricing decisions. The UK has separate systems for England and Wales, Scotland, and Northern Ireland, each making its recommendations for the local health services providers to implement. The Netherlands evaluates treatments nationally through ZiN, but insurance →



companies can still make their own rules about payment. The Czech Republic uses SÚKL for national assessments but lets insurers add more requirements.

Regional Differences Within Countries

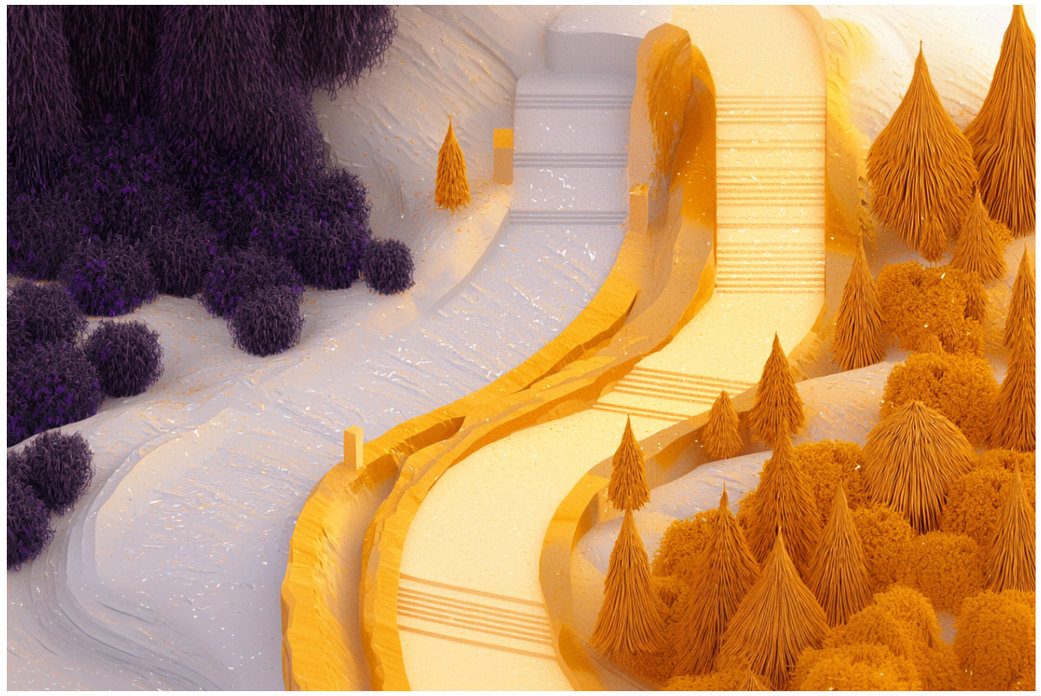
Even within countries, access to treatments can vary by region. In Spain and Italy, different regions can make their own decisions about funding treatments. While public health insurance follows one system in Germany, private insurance companies can make other choices around the provision of care. Regional differences and insurance types determine whether patients can access specific treatments.

Costs for Drug Developers

Drug manufacturers must prepare separate pricing and reimbursement applications for each country, which requires expertise, time, and money. They must create documents that comply with each country's specific rules about evidence and analyses, provide a clear pricing rationale, and prove that the treatment will be effective in the local health system.

The combined drug-therapy nature of psychedelic treatments forces companies to provide complex explanations about their interdependence. Small biotech companies, which make up most psychedelic drug developers, face additional difficulties due to their limited resources and expertise in navigating Europe's complex HTA processes. Smaller countries might have to wait longer for these treatments because companies focus first on larger markets where they can reach the most patients with their first reimbursement applications.

These differences between countries make it harder to make all treatments widely available in a timely matter, and this is especially true for innovative therapies such as psychedelics. Some efforts—such as the Joint Clinical Assessment—have been made to make parts of the process similar across EU countries over time. However, developers still need to deal with many different systems for now. ■



7.4 Infrastructure and Implementation Challenges

Even if psychedelic therapies get approved and funded, healthcare systems face significant practical challenges in actually delivering these treatments. These treatments need facilities with dedicated rooms for long sessions, secure drug storage, and specially trained therapists who might work with just a few patients each week. Hospitals and clinics may lack the setup required for this kind of care, and there are not enough trained professionals to provide it. Without established professional networks to help develop guidelines and training programs, individual facilities must independently figure out these complex requirements, making it harder to implement these treatments widely and effectively.

7.4.1 Limited Clinical Infrastructure

Facility Requirements and Physical Space Limitations

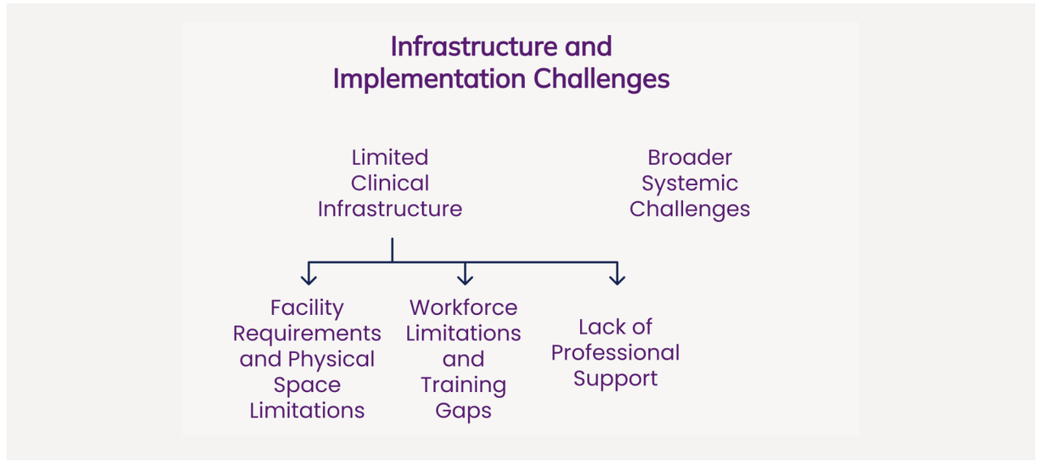
Psychedelic therapy requires dedicated spaces that most hospitals and clinics do not currently have available. While the physical setup requirements are relatively modest—requiring mainly a comfortable reclining chair or bed, soft lighting, calming decor, and a quiet environment—the main challenge lies in dedicating these spaces for extended periods. Treatment sessions lasting 6-8 hours mean these rooms are occupied for long stretches, significantly reducing the number of patients that can be treated compared to regular outpatient services. This extended room occupation could impact cost-effectiveness and limit a facility's ability to provide other treatments.

The availability of appropriate space is likely to be the primary infrastructure challenge, particularly affecting access patterns. Finding and dedicating suitable rooms may be especially difficult for small clinics and those in rural areas. Additionally, facilities need special secure drug storage following strict regulations. As a result, psychedelic treatments are likely to be concentrated in larger urban facilities, particularly in inpatient and acute care settings, at least initially. This concentration in bigger cities could create significant access barriers for people in other areas.

Workforce Limitations and Training Gaps

Another big problem is finding enough trained therapists. Psychedelic therapy needs special training beyond regular therapy skills.[24] Therapists must know how to help patients through intense experiences and handle any challenging reactions, and they need to learn about the pharmaceutical characteristics of these novel treatments. Requiring two therapists per session, as in trials, would further strain the limited workforce.

[24] Currently, it is unclear which prerequisites a facilitator of the psychedelic session itself needs to have. This could be limited to psychiatrists, psychologists, nurses or might involve other healthcare professionals.



Currently, there are no recognised training programs, and it is uncertain whether the certification of current programmes will be retrospectively recognised. This uncertainty creates a tricky situation: Therapists do not want to get training if they are not sure they will find work, but clinics cannot offer treatments without trained therapists. Since each treatment might include many intense hours, even trained therapists can only work with one to a few patients weekly.

Another significant challenge is creating sufficient financial incentives for established therapy providers to transition to psychedelic therapies, given the time commitment and additional training requirements compared to conventional therapeutic or drug-based approaches.

Lack of Professional Support

A further challenge is that advocacy groups and professional networks dedicated to supporting the implementation of psychedelic therapies are still in their early stages and relatively fragmented. While other fields, such as oncology or cardiology, benefit from highly organised professional societies that lobby for funding, develop clinical guidelines, and promote public awareness, psychedelic therapies have not yet developed this level of institutional presence and coordination.

The limited presence of established patient and professional advocacy groups hinders securing funding, creating treatment guidelines, and educating the public. Their absence reduces pressure on healthcare systems to include these treatments and weakens support for policy changes and funding for training programs.

Broader Systemic Challenges

Many healthcare systems in Europe already struggle with long waiting lists for mental healthcare. A lack of coordination between different types of care providers and small behavioural health budgets compounds this. Psychedelic therapy needs different healthcare providers to work together well, which is challenging in these disconnected systems. Also, many healthcare providers are used to prescribing medicine and might resist treatments that combine drugs with psychotherapeutic support. Changing these attitudes will take time and education. ■

7.5 Societal and Ethical Challenges

Using psychedelics as medical treatments raises complex social and ethical issues that go beyond typical healthcare concerns. These substances carry significant stigma from their history of recreational use and previous legal restrictions, which can make both the public and healthcare providers wary.

At the same time, serious ethical questions remain about patient safety, informed consent, and fair access to treatment. Since these therapies can powerfully affect how people think and feel, protecting vulnerable patients and providing treatments safely and equitably, rather than just to those who can afford private care, remains a critical priority.

7.5.1 Stigma and Public Perception

Past Problems with Image

Psychedelics have a complicated history that affects how people view them today. In the 1960s and 70s, protest movements and illegal drug use became associated with these substances. Media coverage emphasised dangerous experiences and mental health risks, leading governments to ban these drugs. The ban halted medical research for many years and created fears that still exist today.

Many older people and decision-makers still remember the warnings about these drugs from that time. Even though science now shows these substances might help treat mental health problems, many people still see them as dangerous illegal drugs. This old reputation makes it harder to get treatments approved and funded. Some healthcare providers might also worry about offering these treatments because they do not want to damage their professional reputations.

News Coverage Today

While recent media coverage has become more balanced, highlighting both therapeutic potential and safety concerns, public perception remains volatile. The media serves a dual role—raising awareness of therapeutic benefits while also providing important public safety oversight by reporting on adverse events or misuse. However, individual negative incidents can still overshadow scientific progress and reignite historical concerns.

Impact on Policy and Reimbursement Decisions

How society views psychedelics affects political and funding decisions. When people are scared of these substances, decision-makers might be too careful, making it harder to get treatments approved or funded. On the other hand, when media coverage makes these treatments sound like miracle cures, it can create unrealistic hopes. People might lose trust when the treatments do not live up to these high expectations.

Developers of psychedelic treatments need to find a balance between addressing old fears and avoiding overselling the benefits. Finding this balance requires careful communication with the public and ongoing conversations between scientists, healthcare providers, and government officials. Scientists, healthcare providers, and government officials must base their decisions on facts rather than fears or hype.

7.5.2 Ethical Considerations

Patient Safety and Informed Consent

Keeping patients safe during psychedelic therapy presents unique challenges. Unlike regular treatments, patients cannot fully know what to expect because these treatments change how they think and feel. The unpredictable nature of subjective response makes it difficult for patients to understand what they agree to. These uncertainties raise questions about whether patients can give informed consent.

Moreover, many patients may have valid reasons for not wanting to experience these altered states, whether due to personal preferences, cultural beliefs, past experiences, or other concerns. Healthcare providers must respect these preferences and carefully consider them during initial patient selection and consent discussions.

Treatment centres need strict safety rules to protect patients. These include careful education before treatment, clear explanations of risks, and the right to stop treatment if necessary. Patients are often more easily influenced during treatment, which could make them vulnerable to manipulation. Cases of therapists misbehaving—both in conventional therapeutic settings and specifically within psychedelic trials and treatments—have shown why strict rules about professional behaviour and special training for therapists are needed.

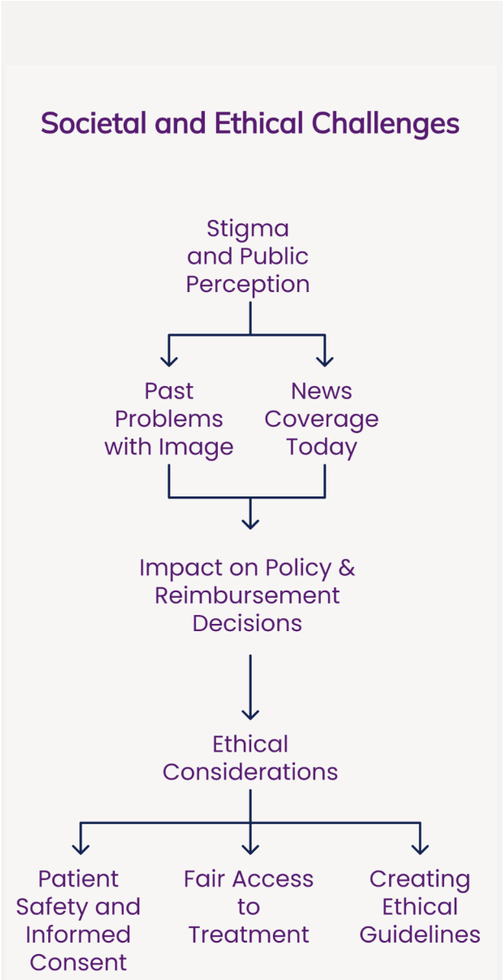
Fair Access to Treatment

Cost is a major ethical concern. Psychedelic therapy can cost anywhere from a few thousand euros to well into the five figures per treatment course, which means only wealthy people might be able to afford it privately. While European countries will likely fully or partially pay for treatment through their healthcare systems, access restrictions mean that many people still might not be able to get these treatments.

This problem is worse for people who already have trouble getting healthcare. People in rural areas or from minority communities often have less access to mental healthcare. If psychedelic therapy is only available in big cities or specific regions, this makes the problem worse. Also, some communities might not trust these treatments, especially if few therapists are from their cultural backgrounds.

Creating Ethical Guidelines

Healthcare systems need clear rules for providing these treatments fairly and safely. This includes setting professional standards, ensuring therapists are adequately trained, and having ways to hold people accountable if something goes wrong.



While this section highlights key ethical challenges, equitable access and fairness issues require deeper exploration. In Chapter 9, we will examine strategies to promote accessibility, reduce disparities, and create sustainable pathways for implementation across diverse populations. This analysis will include recommendations for policy reforms and practical initiatives so that psychedelic therapies fulfil their transformative potential without reinforcing existing inequities.

7.6 Stakeholder Resistance and Misalignment

Making psychedelic therapies work in healthcare systems requires collaboration between many different groups, but these groups often have conflicting priorities and concerns. Healthcare payers worry about high costs and uncertain benefits, while developers need to cover their research expenses and satisfy investors. Regulators want extensive safety data, but patients and advocacy groups push for quicker treatment access. Healthcare providers have practical concerns about facilities and training, while insurance companies focus on immediate costs rather than potential long-term savings.

These different goals and priorities create significant barriers to implementing these treatments effectively, especially since many companies developing them are smaller startups without established relationships in healthcare systems.

7.6.1 Payer Reluctance

Concerns About Risk and Uncertainty

Healthcare payers are likely to demonstrate significant hesitation towards psychedelic therapy due to its limited track record in modern clinical settings. The relative novelty of these treatments, combined with a scarcity of longitudinal data regarding efficacy and safety outcomes, will likely create substantial barriers to widespread coverage approval.

These interventions present unique challenges beyond traditional pharmacological treatments, requiring specialised infrastructure, therapeutic support, and prolonged treatment sessions. This complexity introduces variables that make risk assessment and cost projection particularly challenging for payers.

Despite improving public sentiment towards psychedelics, isolated adverse events or misuse incidents can significantly influence coverage decisions. Healthcare payers remain hesitant to approve coverage, and the lack of coordinated advocacy from healthcare professionals creates little institutional pressure for implementation.

Budget Constraints and Competing Priorities

Healthcare systems face increasingly constrained budgets, and psychedelic therapy presents substantial upfront costs. While proponents argue for potential long-term cost reductions through decreased hospitalisation rates and reduced conventional treatment needs, these projected savings remain largely theoretical, pending longitudinal economic data.

In resource allocation decisions, HTAs and payers typically prioritise interventions with more immediate and quantifiable outcomes, particularly for acute or life-threatening conditions. While psychedelic therapy shows promise for achieving significant short-term health gains in areas like depression, suicidal ideation, anxiety, addiction, and eating disorders, key challenges remain. Success will depend not only on the cost-effectiveness of these treatments but also on the ability to deploy or reassign existing resources in these already resource-constrained areas of healthcare.

Systemic Evaluation Framework Limitations

Current HTA frameworks present structural obstacles to evaluating psychedelic therapies effectively. These systems, optimised for conventional pharmaceutical interventions, may struggle to adequately assess treatments with more subjective outcome measures and complex therapeutic components. The inability to properly evaluate the synergistic effects of combined drug-therapy interventions can result in fragmented assessments that may undervalue the comprehensive benefits of psychedelic therapy.

The absence of appropriate reimbursement categories for integrated treatment modalities forces evaluation through traditional pharmaceutical assessment pathways, potentially leading to unfavourable determinations that do not accurately reflect the treatment's full therapeutic value. ■

7.6.2 Divergent Stakeholder Objectives

Different Goals Among Key Stakeholders

The development of psychedelic therapy involves stakeholders with differing priorities. Commercial developers focus on proving efficacy, securing regulatory approval, and delivering financial returns to offset research costs and satisfy investors. These pressures can drive efforts to accelerate approval, reduce the psychotherapy component, and cut costs.

HTAs and regulators take a careful approach, requiring strong evidence of safety and effectiveness. They often want extensive long-term data before reimbursing new treatments. Insurance companies and healthcare systems primarily worry about immediate costs, which can clash with companies promoting expensive treatments that might only save money years later.

Healthcare providers have concerns about practical issues like facilities, training, and payment. Meanwhile, patients and advocacy groups often want these treatments available as quickly as possible, even before all the evidence is available. These different priorities create tension and make it harder to implement these treatments effectively.

Communication Problems and System Barriers

Many companies developing psychedelic treatments are smaller startups that lack established relationships with regulators and insurance companies.[25] While this independence can promote innovation, it also makes it more challenging for them to understand and work within existing healthcare systems.

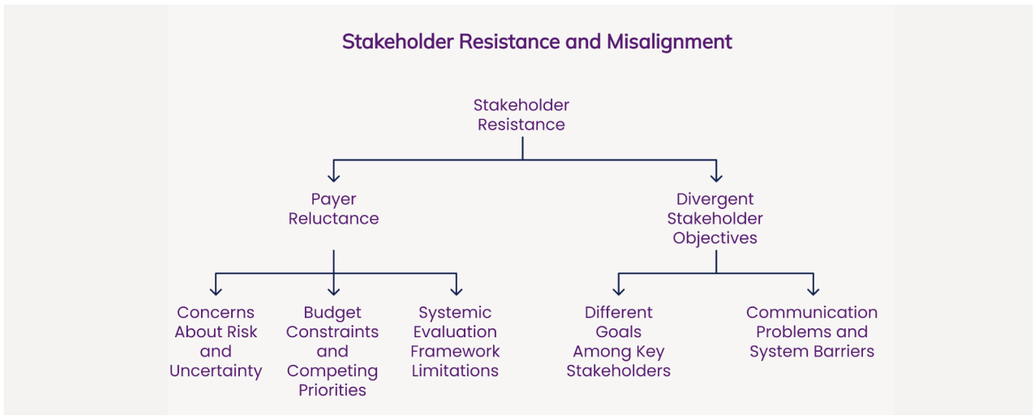
The lack of coordination between different groups causes other problems. Assessment agencies might focus too narrowly on the drug aspect, missing the importance of therapy and specialised treatment settings. Insurance companies might look at costs without fully considering the broader benefits that drug developers emphasise.

Working Towards Better Cooperation

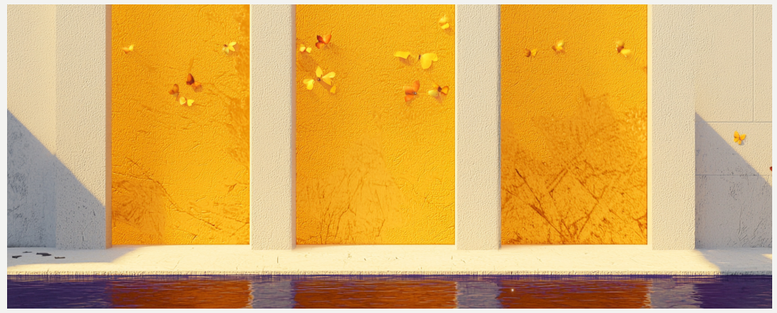
These challenges are not unique to psychedelic therapy, but they are more pronounced because these treatments are new and complex. Solving these problems requires new ways for different groups to work together while maintaining appropriate safety standards and cost controls. Early discussions between groups and flexible payment agreements could help bridge some of these gaps.

The implementation of psychedelic therapy confronts multiple barriers spanning scientific, clinical, economic, regulatory, and social dimensions. The next chapter will explore potential solutions and opportunities to overcome these obstacles and expand these treatments' applications and availability within healthcare systems. ■

[25] The combined market capitalisation of major psychedelic startups is approximately $3 billion, whereas the top 10 pharmaceutical companies collectively hold a market cap of $2.6 trillion.



8 Solutions and Recommendations



This chapter explores practical solutions for integrating psychedelic therapies into European healthcare systems. Building on the previous chapter's discussion of challenges—from regulatory issues and trial limitations to economic concerns—we now focus on concrete steps forward. Our recommendations draw from extensive stakeholder interviews and emerging trends in healthcare innovation.

Our solutions address interconnected areas: strengthening clinical evidence, enhancing economic evaluation methods, improving regulatory processes, and building treatment infrastructure. Each recommendation considers multiple stakeholder perspectives—from treatment developers and healthcare providers to regulators, insurers, and patients.

Psychedelic therapy represents a fundamental shift in mental health treatment, combining drug treatment with psychotherapeutic support in ways that challenge traditional frameworks. Integrating these novel treatments demands new approaches to healthcare coverage, regulation, and delivery systems. How can healthcare systems can adapt while maintaining efficiency and delivering quality care?

These treatments are still developing, and our recommendations support both their initial implementation and long-term success. With appropriate systems and policies in place, psychedelic therapy could significantly improve mental healthcare options. The solutions balance rapid progress with carefully considering effectiveness, safety, and sustainable integration. ■

8.1 Clinical Evidence Recommendations

8.1.1 For Drug Developers

Key recommendations:

- Consider trial designs using active placebos and crossover studies to support robust blinding and efficient data collection.
- Implement extended follow-up periods of at least 6-12 months to track relapse rates, ongoing treatment needs, and resource use, supplemented by patient registries for long-term data collection.
- Wherever possible, compare psychedelic treatments directly against the existing standard of care (especially for the German market) to show their relative benefits and costs.
- Launch pilot programs in receptive countries like the Netherlands and the Czech Republic to generate complementary real-world evidence alongside Phase III clinical studies.
- Use validated metrics for functional recovery and quality of life while tracking broader benefits like improved work productivity, reduced hospital stays, and decreased caregiver burden to demonstrate value to healthcare systems and beyond.
- Engage with regulators and payer assessment bodies (HTA groups) during Phases II and III to align evidence collection and analyses with requirements.

Pre-Market Authorisation Trials

Drug developers must design substantial, credible trials to satisfy regulators and evaluators. Using active placebos (like low doses of the study drug) helps maintain proper blinding. Compass Pathways has already used this approach, setting a helpful example. Developers should continue the dialogue with the EMA to agree on acceptable active placebos, even though this makes trials more complex and potentially more expensive.

Crossover studies, where participants receive both treatment and placebo at different times, can be an effective trial design. These studies are efficient because each person acts as their own control. However, developers must carefully consider how long psychedelic effects last when planning these trials.

Adaptive trial designs that allow changes based on early results can save time and resources. While not yet common in psychedelic research, these designs can speed up approval by pre-agreeing potential changes with regulators. Supplementing traditional confirmatory trials with pragmatic trials and real-world data initiatives to better understand optimal treatment protocols could be particularly valuable in the early stages of psychedelic therapy development, helping to prevent suboptimal parameters from becoming regulatory standards and supporting more sustainable development of these treatments.

Trial designs should delineate and measure the contributions of both the pharmaceutical intervention and the psychotherapeutic support provided. While academic researchers may better investigate different therapeutic approaches post-approval, developers should ensure their trials can demonstrate the specific impact of their pharmaceutical intervention within their chosen treatment protocol. Lykos's recent difficulties with the FDA over their MDMA therapy for PTSD illustrate the importance of this clarity in assessing both clinical benefits and costs.

Real-world pilots—especially in countries like the Netherlands and the Czech Republic, where regulatory environments support innovation—can complement traditional clinical trials. When conducted in partnership with regulators, healthcare providers, and other stakeholders, these pilots could potentially serve as an alternative to local Phase III trials. They can generate valuable additional data on cost-effectiveness and treatment scalability while offering insights to payers and policymakers to support approval and adoption.

Post-Market Authorisation Evidence Generation

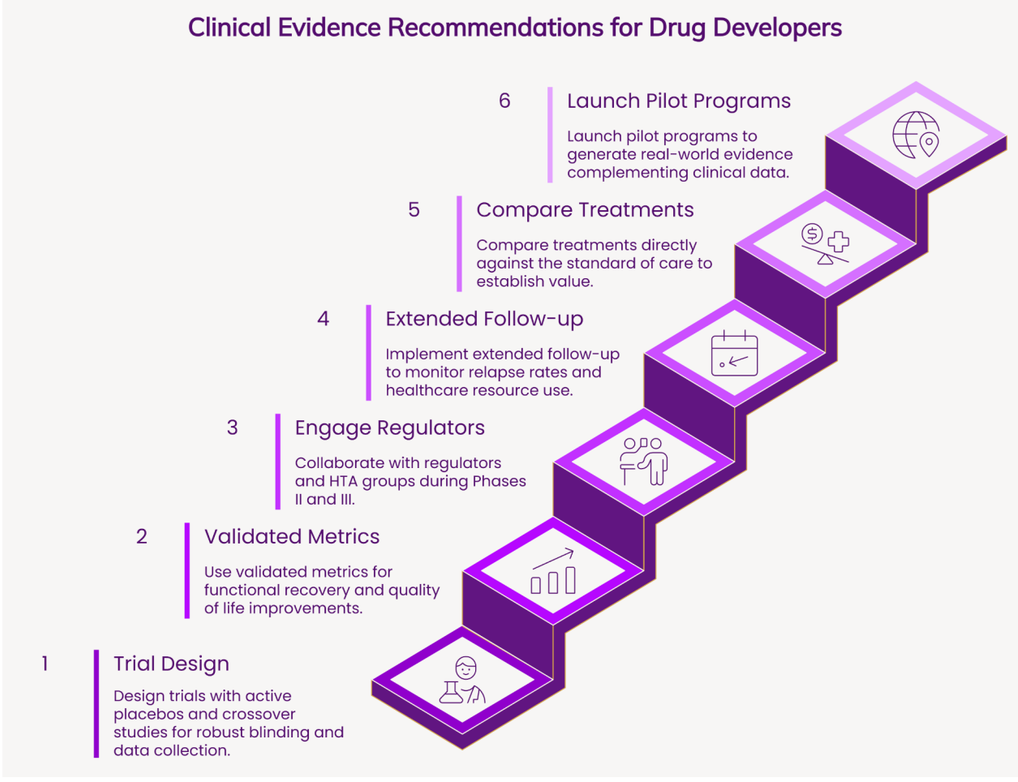
Developers need to show that treatments work both initially and over time. Clinical trials should track key outcomes like depression scores for 6-12 months after treatment. However, understanding the full impact on healthcare systems requires real-world data collection after treatments become available. Real-world data collection includes tracking relapse rates, ongoing treatment needs, and healthcare resource use in clinical practice. The resulting real-world evidence is crucial for proving value to healthcare systems, particularly in markets with strict budget constraints.

Developers should consider registry-based studies to track real-world and long-term outcomes after market entry. These studies can provide real-world evidence to supplement clinical trials, particularly for countries like Germany that may require ongoing reassessment.

Addressing Evidence Gaps for Regulators and Evaluators

Developers need to focus on evidence that aligns with HTA expectations, using validated metrics for quality of life, functional recovery, and symptom reduction rather than creating new tools. Their economic models should also capture indirect benefits like productivity gains, reduced caregiver burden, and lower hospitalisation rates. These factors are especially important in countries like the Netherlands, which may take a broader view of value. Early engagement with payers through scientific advice programs can help identify the most relevant metrics and prevent conflicting requirements between regulatory approvals and reimbursement criteria.

For many markets, particularly Germany (the largest EU pharmaceutical market), comparing new treatments to existing ones like SSRIs, augmentation therapies, or ketamine for depression is crucial for achieving reimbursement and more favourable drug pricing. Where direct comparisons aren't possible, developers must justify alternative approaches. The need for proper blinding in regulatory trials often moves study designs away from payer expectations around comparative effectiveness. Developers should engage with payers and HTA groups early to explain why true placebos or standard-of-care



comparators might not be feasible, and work together to find pragmatic solutions for generating comparative effectiveness evidence. These discussions should happen during Phase II or early Phase III to avoid costly delays or rejections and to ensure trial designs meet local requirements.

For therapies with high uncertainty, conditional reimbursement or managed entry agreements that link reimbursement to real-world performance can help address payer concerns while providing earlier patient access. Starting with pilot submissions in smaller markets can help test and refine evidence packages before targeting larger countries. ■

8.1.2 For Regulators and Evaluators

Key Recommendations:

- Provide more precise guidance on trial design requirements while offering early consultation opportunities to help developers effectively plan their evidence collection.
- Support the development of standardised patient registries and outcome measures across Europe to improve the efficiency of data collection and comparison.
- Coordinate between European regulatory and reimbursement evaluation bodies to harmonise requirements and reduce duplicate work for treatment developers.
- Establish clear incentive frameworks for mental health treatments similar to successful models used for orphan drugs and paediatric medicines.

Improving Guidance and Support

Regulators and payers must provide clear, consistent guidance about the evidence they require to evaluate psychedelics. While assessment frameworks exist at both European (Joint Clinical Assessment) and national levels, with published methodological guidance, these frameworks would need updating to handle the unique aspects of psychedelic treatments, which often combine pharmaceutical interventions with specialised therapeutic protocols. Better guidance on acceptable trial designs and standards for real-world data collection will help developers plan more effectively.

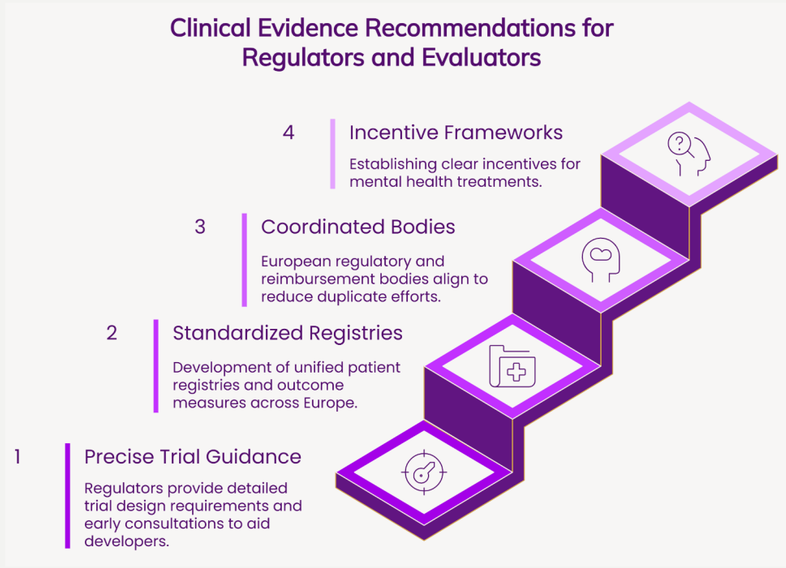
A critical component is establishing clear definitions of unmet needs that recognise the significant societal burden of mental health conditions and their decades-long innovation stagnation. Following successful models used for orphan and paediatric medicines, these definitions should serve as prerequisites for accessing development incentives such as PRIME designation, accelerated assessment, conditional marketing authorisation, and additional data protection periods.

Regulators should expand early consultation opportunities, allowing developers to discuss their plans before starting patient trials. These consultations should address practical challenges like maintaining proper blinding and selecting appropriate comparators. To help more organisations participate, regulators should make these consultations more affordable or free for smaller developers. Regulators should also specify country-specific comparators, so developers can align studies with national standards of care.

Supporting Evidence Generation and Methods

Regulators and reimbursement evaluators should consider innovative trial designs, such as crossover and hybrid models, that effectively test drug-therapy combinations while addressing blinding and placebo concerns. These approaches can better evaluate individual treatment components and reduce inconclusive results. Long-term follow-ups through national or EU-level registries are essential to track treatment durability while providing real-world evidence across diverse populations.

Harmonised metrics across countries would reduce duplicate studies and facilitate data comparison. Regulators must balance flexibility in assessment with clear standards for data transparency and post-marketing surveillance. Success will require collaboration between regulators, developers, and other stakeholders to establish practical guidelines for evidence generation and create sustainable pathways that appropriately incentivise innovation in mental health treatments. ■



8.2 Economic Evaluation Strategies

The economic evaluation of psychedelic therapies presents unique challenges for both developers and health technology assessment (HTA) bodies in Europe. These novel treatments combine drug interventions with psychotherapy sessions, creating more complex cost structures than existing care models with higher upfront investments but with the potential for rapid clinical efficacy, medium to long-term clinical outcomes and additional societal benefits.

Success requires developers to build compelling economic models that demonstrate value within established HTA frameworks. Assessment bodies must also consider how to evaluate and reimburse these innovative treatment approaches. These parallel challenges create a shared responsibility: Developers must provide robust cost-effectiveness estimates, while HTAs must adjust their assessment frameworks to accommodate for the uncertainty arising from evidence gaps present at market entry, e.g. longer term outcomes and comparative effectiveness.

While HTA bodies may not incorporate societal benefits in their core cost-effectiveness analyses, developers should be allowed to present supplementary analyses that demonstrate these wider benefits. Including supplementary analyses would enable stakeholders to understand the full value proposition of these treatments, even if such benefits can not directly influence reimbursement decisions under current assessment frameworks.

8.2.1 For Drug Developers

Key Recommendations:

- Develop comprehensive economic models incorporating direct and indirect benefits to demonstrate the full set of value provided by therapies.
- Create market-specific economic models that align with national requirements and use validated metrics, particularly for markets using health economics for price and reimbursement decision-making, such as the UK and the Netherlands.
- Include scenario analyses and sensitivity testing to address treatment effects and adoption rate uncertainties.

- Evaluate market viability early by analysing each market's specific HTA requirements, cost-effectiveness thresholds, and which economic benefits (like workplace productivity) are included in reimbursement decisions.
- Engage with HTA bodies during development so that economic models meet requirements and prevent costly adjustments later.

Building Comprehensive Economic Models

Economic models for psychedelic therapies must capture both immediate and long-term impacts within European HTA methodologies. These models should include direct costs such as drug pricing, therapist fees, and facility investments, as well as exploring other benefits like productivity gains, reduced caregiver burden, and fewer hospitalisations. Quality-adjusted life years (QALYs) remain the dominant approach, requiring validated mental health metrics that HTA bodies already accept. Comprehensive scenario and sensitivity analyses are essential to explore varying assumptions about treatment effects and uptake rates.

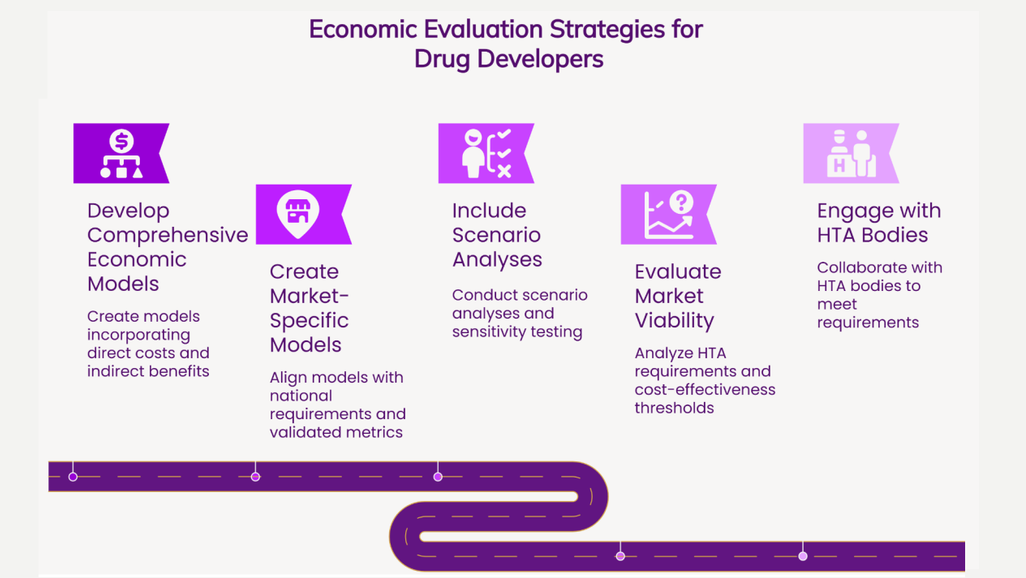
Navigating Market-Specific Economic Requirements

Developers must tailor their economic modeling approaches to different markets to support payer engagement and decision-making. The UK's NICE has very specific guidance on the preferred cost-effectiveness modelling methodology and makes decisions based on cost per QALY thresholds. NICE does not include caregiver or societal benefits to calculate cost-effectiveness, although modifiers for acceptable CE thresholds exist for some conditions. The Netherlands may accept more real-world evidence and registry data and accommodate broader value into its cost-effectiveness evaluations, including work productivity.

For some markets, budget impact will be the main focus of the economic evaluation, which may include drug cost only, drug plus therapy, or all costs associated with care provision.

Strategic Planning and Engagement

Developers should evaluate each market's specific requirements and thresholds early in development to determine where reimbursement is feasible. This assessment must consider whether excluded benefits—such as workplace productivity improvements—or country-specific CE thresholds significantly impact the economic argument for treatment. Early engagement with HTA bodies can help align economic models with evaluation criteria and prevent costly redesigns later in development. ■



8.2.2 For HTA Evaluators and Payers

Key Recommendations:

- HTA groups should develop frameworks for evaluating combined drug-therapy treatments, considering long-term cost savings and societal benefits.
- To manage upfront costs and uncertainties, payers must explore innovative payment models like bundled payments and performance-based contracts.
- HTA groups and payers should collaborate early with developers to align on evidence requirements and acceptable economic models.
- HTA groups should create standardised approaches for tracking and evaluating real-world performance across European healthcare systems.

Adapting Evaluation Frameworks

To properly assess psychedelic therapies, HTAs should ensure their evaluation frameworks accommodate both drug and therapy components. Standardised methods should be developed to evaluate combined treatments, while maintaining flexibility for national requirements. HTAs can incorporate broader societal benefits by adapting existing tools for measuring indirect effects and creating new metrics tailored to mental health outcomes.

Implementing Sustainable Payment Models

For payers, we recommend exploring bundled payment systems that combine drug and therapy costs into single reimbursement packages. Performance-based contracts can help manage uncertainty by linking payment to patient outcomes. To address higher upfront costs, consider implementing staged payment models that spread costs over time while guaranteeing long-term value.

Strengthening Collaboration

Strengthen formal channels for early dialogue between HTAs, payers, and developers. These channels should include regular stakeholder meetings to align evidence requirements with practical reimbursement solutions. Creating shared outcome measures and monitoring systems will help track treatment effectiveness consistently across different healthcare systems.

Building the Evidence Base

Both HTA groups and payers should support the development of real-world evidence programs. Such programs can include creating standardised data collection protocols and establishing partnerships with academic institutions to evaluate real-world and comparative treatment effectiveness. The resulting evidence can inform future assessment criteria and refine payment models over time. ■

8.3 Regulatory Pathways and Policy Reforms

The successful integration of psychedelic therapies into European healthcare systems calls for a significant evolution in regulatory frameworks and policies. Current regulations, designed primarily for traditional pharmaceuticals, are likely to struggle to accommodate treatments that combine controlled substances with structured therapy sessions. These unique treatment characteristics create a complex landscape where existing rules may need updating while maintaining essential safety standards.

Addressing these challenges requires coordinated action across multiple fronts: Developers must navigate existing pathways while advocating for appropriate reforms, regulators must adapt frameworks while protecting patient safety, and policymakers must balance innovation with public health concerns. Progress depends on finding practical solutions that uphold rigorous standards while enabling access to these potentially transformative treatments.

8.3.1 For Drug Developers

Key Recommendations:

- Use expedited pathways like EMA's PRIME and MHRA's ILAP, and pursue conditional approvals to speed up the regulatory process while collecting real-world evidence.
- Consider decentralised approval approaches through national authorities before broader European expansion.
- Start early dialogue with regulators to align on trial designs and evidence requirements for these novel treatments.
- Build comprehensive data collection systems that address both regulatory and HTA requirements from the start.

Leveraging Accelerated Regulatory Pathways

Developers should prioritise expedited regulatory pathways such as EMA's PRIME and MHRA's ILAP, which offer faster evaluations and early feedback. These programs, combined with conditional marketing authorisations, can accelerate approvals while maintaining rigorous standards through post-launch evidence collection. Traditional pre-marketing authorisation early access programs may not be feasible for psychedelic therapies due to legal restrictions on prescribing scheduled substances. This limitation makes post-marketing authorisation access programs with robust data collection particularly crucial for generating real-world evidence and supporting broader adoption.

Leveraging Multiple Regulatory Pathways

Developers should consider both centralised and decentralised approval strategies. While the centralised EMA procedure offers broad market access, the decentralised procedure (DCP) or mutual recognition procedure (MRP) may provide alternative routes. Under these approaches, developers can obtain approval in one EU reference member state and use this as a basis for recognition in other countries. This strategy might be particularly valuable for psychedelic therapies where some countries may be more receptive to novel treatment approaches.

Enhancing Dialogue with Regulators

Regular communication with regulators through scientific advice meetings—such as the EMA's Scientific Advice Working Party (SAWP)—helps prevent delays and align expectations. Early engagement clarifies trial designs and evidence needs, especially regarding unique challenges like placebo controls and therapy protocols. This dialogue should extend to both European and national regulators to navigate varying requirements effectively.

Beyond standard requirements, developers should prepare comprehensive safety monitoring systems specific to controlled substances. The monitoring frameworks should include detailed risk mitigation plans, therapist training protocols, and robust adverse event monitoring. These elements demonstrate a commitment to patient safety while building confidence among regulators and healthcare providers.

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While meeting regulatory requirements remains the priority, developers can advance their understanding of implementing psychedelic therapies through strategic stakeholder engagement. Effective engagement includes evidence-based briefing sessions and collaborations with patient groups. Such efforts help create an environment conducive to regulatory innovation while maintaining a focus on scientific rigour and patient benefit. ■

8.3.2 For Regulators

Key Recommendations:

- Consider bifurcated scheduling models that enable medical use while maintaining controls for recreational use.
- Develop clear frameworks for post-approval evidence collection and conditional marketing authorisations.
- Strengthen coordination between national authorities to facilitate efficient mutual recognition procedures for psychedelic therapies.
- Strengthen collaboration between regulators, HTA groups, and international agencies to streamline development.

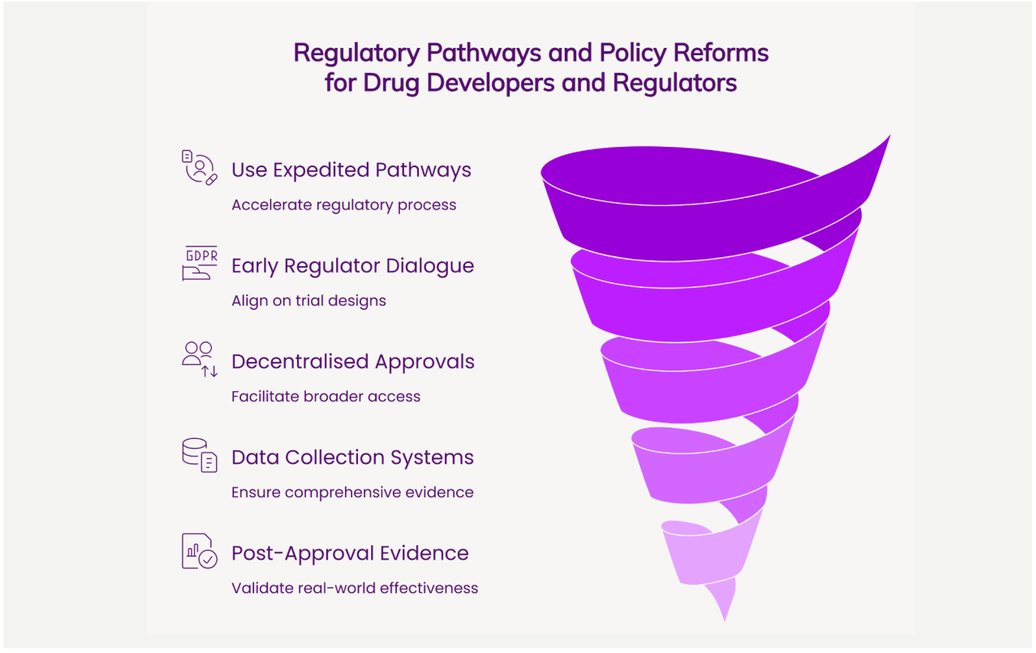
Scheduling and Access

The classification of psychedelics as Schedule I substances presents a key barrier to development. Regulators may create a bifurcated model that maintains controls while enabling medical access, similar to frameworks for ketamine and GHB (sodium oxybate, Xyrem). Explicit criteria for reclassification would give developers the confidence to invest in research while maintaining appropriate safeguards.

Additionally, regulators should consider creating specific exemptions from Schedule I requirements for researchers, as discussed in the UK, to reduce bureaucratic barriers and make it easier to conduct vital research while maintaining appropriate oversight. Such exemptions could significantly expand research capabilities without requiring full rescheduling.

Post-Approval Evidence Generation

Given the scheduling restrictions that limit pre-approval access programs, regulators should focus on developing robust frameworks for post-approval evidence collection. Conditional marketing →



approvals, similar to those used for oncology treatments, can enable market entry while ensuring continued evidence generation through well-designed post-marketing studies. These frameworks should clearly specify requirements for real-world evidence collection, safety monitoring, and effectiveness demonstration.

Harmonising National Approaches

While maintaining sovereign decision-making authority, regulators should work to harmonise evaluation criteria and post-approval requirements across European countries. Harmonisation supports the efficient use of decentralised and mutual recognition procedures while ensuring consistent safety standards. Regular communication between national authorities can help share early experiences with psychedelic therapy approval and monitoring, building collective expertise while respecting different national contexts.

Regulatory-HTA Collaboration

Close alignment between regulators and HTAs helps developers meet both safety and reimbursement requirements efficiently. Dedicated contact points within agencies and template protocols for combination therapies can streamline development. Joint scientific advice meetings allow developers to address regulatory and economic requirements early.

International Coordination

Collaboration between European regulators, the FDA, Health Canada, and other regulators can reduce duplicate work and speed development. This coordination should cover data sharing, evaluation methods, and post-approval monitoring. Supporting research through targeted incentives and establishing research networks can accelerate evidence generation while promoting knowledge sharing across regions. ■

8.4 Infrastructure and Implementation Approaches

The successful integration of psychedelic therapies into European healthcare systems requires substantial changes to existing infrastructure and implementation approaches. While clinical evidence and regulatory frameworks are crucial, the practical considerations of delivering these treatments safely and effectively at scale are equally important. This section examines the key challenges and opportunities across three stakeholder groups: healthcare systems, therapists and providers, payers, and drug developers.

The implementation challenges vary significantly across European countries due to differences in healthcare systems, existing infrastructure, and professional training requirements. However, common themes emerge around the need for dedicated facilities, trained professionals, and sustainable funding models. Addressing these challenges requires coordinated efforts between public and private stakeholders and innovative resource allocation and service delivery approaches.

8.4.1 Healthcare Systems and Providers

Key Recommendations:

- Create dedicated treatment rooms with calming environments and proper safety features to support extended psychedelic therapy sessions.
- Establish partnerships between public healthcare systems, private investors, and insurers to fund facility upgrades and expansion.
- Develop plans to meet growing patient demand, including staffing needs and scheduling systems for longer sessions.
- Join existing professional networks and training programs while advocating for more accessible certification options.
- Create clear patient screening and aftercare procedures, working closely with other mental health professionals.
- Develop unified European standards for therapy delivery and therapist qualifications.
- Build relationships with local mental health ⤴ services to ensure proper patient referrals and emergency support when needed.
- Document outcomes and share experiences with other providers to help develop best practices and improve treatment standards.
- Participate in multi-disciplinary working groups to define optimal and minimum acceptable care package standards.
- Support research into alternative treatment delivery models, including group therapy and other resource optimisation approaches.

Infrastructure Development

Most mental health facilities currently lack spaces suitable for extended psychedelic therapy sessions. These sessions require carefully designed non-clinical environments where patients feel safe and supported during treatments lasting several hours.

Funding and partnerships play crucial roles in infrastructure development. Working with insurance companies, government agencies, and private investors can help fund these changes without overstretching public budgets. Integrating therapy rooms into existing mental health centres improves patient access while maximising current resources. Healthcare providers can strengthen the financial case by documenting improved outcomes and reduced hospital admissions.

Treatment Package Standards

Multi-disciplinary working groups should define both optimal and minimally acceptable care package requirements. The specifications should cover treatment rooms, the therapist's involvement in preparation and integration sessions, and dosing session support. These standards ensure consistent quality while providing implementation flexibility.

Healthcare systems should also invest in research examining different therapy delivery models, such as group sessions for integration or simultaneous dosing of multiple patients in shared spaces. These studies can help identify more cost-effective approaches than those used in clinical trials while maintaining treatment effectiveness.

Training and Professional Development

The availability of trained therapists represents a critical challenge for scaling psychedelic therapy. While several training programmes exist, none are currently recognised or accredited by national healthcare systems, creating uncertainty for both practitioners and healthcare providers. Existing programmes often have limited capacity and high costs, creating additional barriers to entry. Healthcare systems should develop standardised, accredited training programmes that combine online learning with practical experience, making certification more accessible while maintaining quality standards.

Professional development pathways need clear structure and support. Essential components include establishing supervision networks, continuing education requirements, and opportunities for specialisation. Financial support for training, such as subsidies or tax incentives, can help build workforce capacity more quickly.

Clinical Operations and Quality Assurance

Successful implementation requires careful attention to clinical operations and standardisation. Healthcare providers need clear protocols for patient screening, risk assessment, and contraindication checking. Treatment delivery must be standardised while allowing flexibility for individual patient needs.

European healthcare systems should establish unified standards for psychedelic therapy delivery, including protocols for dosing, therapy structures, and risk management. These should specify therapists' professional requirements, including qualifications, training, and ongoing education requirements. Such standards would support safe delivery while building confidence among healthcare providers and patients.

Quality assurance systems should monitor outcomes, track adverse events, and identify improvement areas. The monitoring framework should include regular protocol reviews, therapist supervision, and documentation of patient experiences. Professional networks facilitate knowledge sharing and best practice development.

Integration and Scale-up Planning

Healthcare systems must plan carefully for service expansion. Effective planning requires coordinating between different types of providers, managing referral pathways, and ensuring adequate emergency support. Medicine management systems must meet strict regulatory requirements while remaining practical for clinical use.

Scale-up planning should consider both immediate needs and long-term sustainability. Key planning elements include workforce development, facility expansion, and financial planning. Regular evaluation of outcomes and costs helps demonstrate value to stakeholders and supports continued investment in service development. ■

8.4.2 For Payers

Key Recommendations:

- Develop billing codes and payment structures that accommodate extended therapy sessions combined with novel drug treatments, following examples like the U.S. CPT codes for psychedelic therapy.
- Create outcome-based payment models linking reimbursement to clinical improvements and reduced healthcare utilisation.
- Establish commercial access programs with real-world monitoring to evaluate cost-effectiveness before full implementation.
- Partner with providers to develop standardised outcome measures and documentation requirements for reimbursement.

Payment Structure Development

Payers must create new reimbursement frameworks for psychedelic therapy's unique combination of drug treatment and extended therapy sessions. In the U.S., drug developers have made progress by working with the American Medical Association (AMA) to establish specific Current Procedural Terminology (CPT) codes for psychedelic therapy administration and monitoring. These codes recognise the distinct requirements of psychedelic treatments, including continuous in-person monitoring during therapy.

Building on such examples, bundled payment models, covering both medication and therapy costs, could simplify administration and provide clarity for providers. Performance-based contracts that tie reimbursement to treatment outcomes may help manage uncertainty around long-term effectiveness.

Cost Management Approaches

Given substantial upfront costs, payers should explore flexible pricing models that balance access with sustainability. Potential approaches include staged payments based on treatment milestones or outcome-based pricing tied to specific clinical improvements. Early collaboration with providers and drug developers can help design practical payment structures that work for all parties.

Implementation Programs

Pilot programs offer opportunities to evaluate real-world effectiveness and refine payment models before broader implementation. These pilots can inform the development of standardised and more permanent reimbursement and documentation requirement approaches.

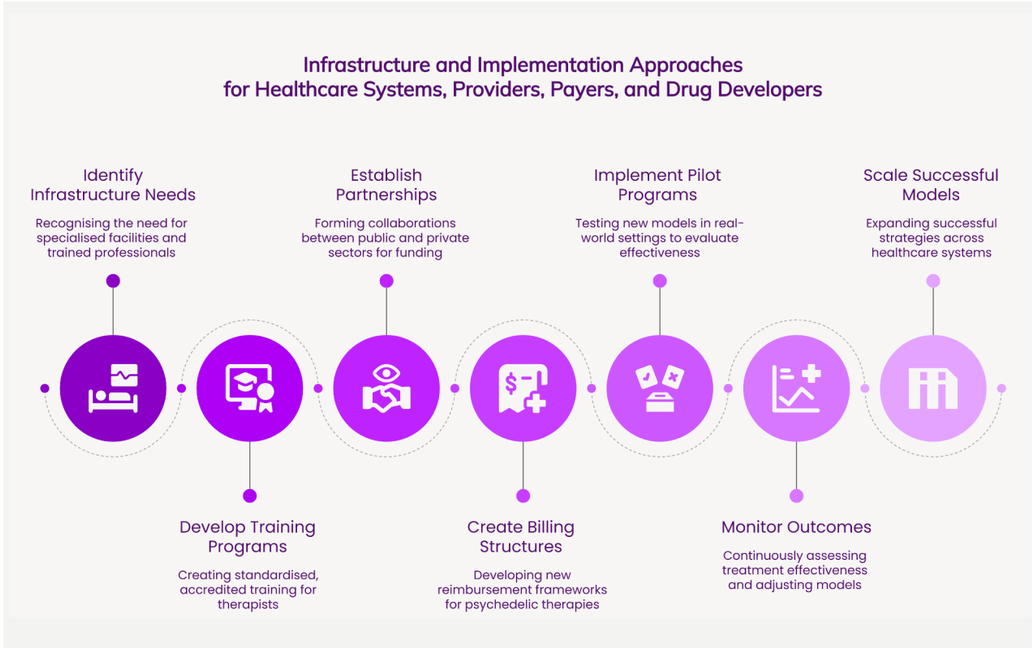
Quality Assurance and Monitoring

Payers should establish transparent systems for tracking outcomes and evaluating treatment effectiveness. The monitoring system should include standard outcome measures, documentation requirements, and monitoring protocols. Regular assessment of clinical results and healthcare utilisation patterns can help refine payment models and demonstrate value. ■

8.4.3 Drug Developers

Key Recommendations:

- Focus on developing clear, practical service specifications in partnership with healthcare stakeholders, which are specific enough to reassure healthcare systems but flexible enough to allow local adaptation.
- Avoid over-engineering treatment requirements beyond regulatory mandates.
- Support retrofitting of existing healthcare facilities rather than creating separate centers of excellence.
- Maintain clear boundaries between drug development responsibilities and healthcare system implementation.



Infrastructure Support

Drug developers should resist the temptation to solve all implementation challenges themselves. Instead of creating dedicated centres of excellence, developers should provide clear guidance for adapting existing healthcare facilities. Practical guidance should include basic specifications for treatment rooms that hospitals, clinics, and mental health facilities can retrofit into their existing spaces, similar to how facilities integrate ECT suites. Using existing healthcare infrastructure will create more scalable and cost-effective solutions than building separate specialised centres.

Treatment Requirements

When designing treatment protocols, developers should avoid over-specifying requirements for therapist qualifications or treatment settings beyond what regulators explicitly mandate. A flexible approach allows for the natural evolution of treatment approaches based on real-world experience and local healthcare system capabilities.

Taking cues from other mental health treatments like opioid use disorder therapy, where psychosocial support requirements remain broadly defined, developers should provide framework guidance while allowing flexibility in implementation.

Market Development

The most effective role for developers in market development is to create clear, practical service specifications that healthcare systems can readily adapt. These specifications should define essential safety and monitoring requirements, outline basic facility needs for treatment delivery, provide guidance on staff training and qualifications, and allow for regional variation in implementation approaches. By focusing on these core elements while avoiding overprescribing specific approaches, developers can support sustainable market development without creating unnecessary barriers to implementation.

Professional Support

Drug developers should maintain appropriate boundaries in professional training and support. While they can provide essential information about their specific treatments, healthcare systems and professional bodies should lead broader therapy training and certification. Developers could provide joint funding for independent groups to develop and deliver training and certification programs. Such collaborative funding maintains the necessary separation while accelerating ecosystem development. The system-led approach ensures sustainable development of the treatment ecosystem. ■

8.5 Societal and Ethical Initiatives

Making psychedelic therapies work in European healthcare systems requires more than clinical evidence and proper facilities—it also means addressing broader social and ethical issues. This section looks at how healthcare providers and policymakers can help build public trust, establish ethical treatment delivery, and make these therapies available to all who need them. While earlier sections covered technical and practical matters, this section focuses on the social aspects and ethical guidelines necessary for long-term success.

Meeting these challenges requires effective collaboration among different groups. Healthcare providers must develop clear ethical guidelines and safety measures. Policymakers are important in making treatments accessible and creating supportive rules and regulations.

8.5.1 For Healthcare Providers

Key Recommendations:

- Develop specialised informed consent protocols that address altered states and psychological vulnerability during treatment sessions.
- Create clear boundaries and safety guidelines for therapist-patient relationships before, during and after psychedelic sessions.
- Establish real-time reporting systems for psychological adverse events and integration challenges.
- Build support networks for providers to share experiences and develop best practices for ethical challenges.

Ethical Guidelines for Altered States

Healthcare providers must develop specific protocols for working with patients under the influence of psychedelics. The protocols should include detailed informed consent procedures that explain the unique psychological risks and experiences patients may encounter. Providers must give special consideration to vulnerable populations, particularly those with trauma histories or past substance use issues.

Healthcare providers should establish comprehensive pre-treatment procedures, including thorough psychological screening and risk assessment protocols. During sessions, providers need clear guidelines for real-time monitoring of psychological states and emergency response protocols for psychological distress. Detailed documentation requirements for altered state experiences and post-session integration support planning form essential components of these protocols.

Therapeutic Boundaries and Integration

While standard medical practice defines clear professional boundaries, psychedelic therapy presents novel situations that require additional guidance. Healthcare providers need specific protocols that address appropriate therapist-patient boundaries during altered states and integration periods. These should build upon existing ethical guidelines whilst providing clear direction for physical presence, emotional support, and post-session contact. Healthcare providers should establish structured integration support systems that maintain professional boundaries while meeting patients' emotional needs following powerful experiences.

These additional ethical considerations require ongoing provider discussion to establish best practices that complement existing medical ethics frameworks. Professional networks can help providers navigate these challenges while maintaining high ethical standards. ■

8.5.2 For Policymakers

Key Recommendations:

- Create funding mechanisms to support treatment access in rural areas and for economically disadvantaged populations.
- Develop initiatives to diversify the therapist workforce and provide culturally appropriate care.
- Build decentralised care networks to reach underserved communities.
- Mandate collection of demographic data to track and address treatment access disparities.

Geographic and Economic Access

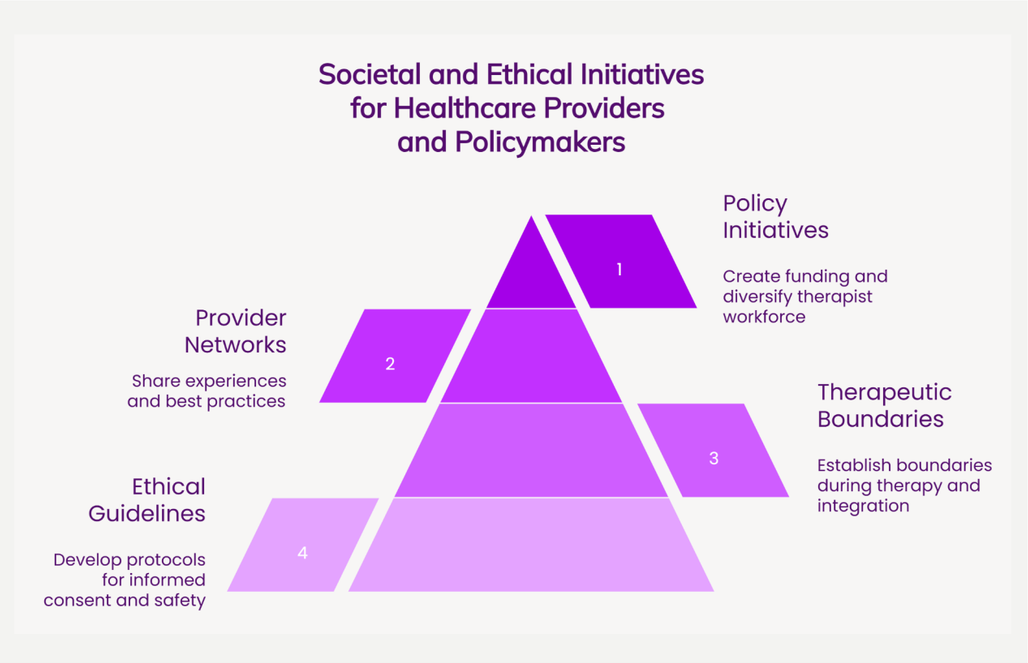
Policymakers should focus on making psychedelic therapies available beyond wealthy urban areas. Expanding access means supporting decentralised care networks that can reach different communities. Regional treatment centres can help serve more areas, following successful models used in cancer care networks across Europe.

Cultural Competency and Workforce Diversity

Making healthcare fair means addressing cultural barriers and building a diverse treatment workforce. Healthcare providers should create training programs that attract therapists from different backgrounds and develop treatment approaches that respect various cultural perspectives. Programs should include community outreach and support for multilingual services.

Data Collection and Monitoring

Good policy needs good data. Tracking who receives treatment and their outcomes helps show where services are lacking and what needs to be improved. Regular reports on demographic patterns can guide programs toward better serving all communities. ■



8.6 Country-Level Perspectives and Best Practices

8.6.1 Germany

Professional and Cultural Adoption

Despite growing interest in psychedelic therapies, conservative attitudes within Germany's psychiatric community may present barriers to adoption. Developers should launch targeted education campaigns highlighting the clinical evidence supporting psychedelics and emphasising safety profiles to address scepticism.

Engaging professional organisations like the German Psychiatric Association to co-develop guidelines and best practices will further legitimise the therapies and reduce prescriber liability concerns. Developers should also focus on building relationships with early adopters in academic and clinical settings to serve as champions for psychedelic treatments.

The positioning of psychedelics as natural compounds, particularly psilocybin, may resonate with German preferences for nature-based therapies. Developers can use this narrative while maintaining rigorous scientific messaging to gain public and professional trust.

Key Recommendations for Germany

- **Strengthen Early Payer Engagement:** Developers should engage with G-BA and IQWiG early to align on clinical trial endpoints, and particularly an appropriate comparator choice.
- **Demonstrate Additional Therapeutic Benefit:** Developers must provide robust evidence to the G-BA and IQWiG of improved patient outcomes compared to appropriate comparators in the German healthcare context.
- **Implement Risk-Sharing Agreements:** Developers and payers should consider using managed entry agreements tied to real-world performance metrics to address insurer concerns, particularly around high upfront costs.
- **Focus on Hospital-Based Rollouts:** Developers should consider prioritising the initial adoption of psychedelics within hospital inpatient and outpatient centres, where healthcare infrastructure, staffing, and funding arrangements better support high-cost, complex therapies.
- **Address Infrastructure Needs:** Healthcare facilities and hospitals should prepare dedicated therapy rooms and protocols to meet regulatory requirements for safety and supervision.
- **Pilot Real-World Evidence Programs:** Developers should develop and validate registry-based studies or post-launch monitoring programs to provide long-term data on outcomes and cost savings.
- **Invest in Workforce Training and Certification:** Clinical and psychiatric associations should prepare therapist training programs aligned with German standards to prepare for implementation.
- **Promote Cultural and Professional Adoption:** Collaborations, including psychiatric and psychotherapy associations, should develop care guidelines and professional advocates are required for psychedelic therapies.
- **Develop Public-Private Partnerships:** Government and private stakeholders should consider collaborations to share the financial burden of infrastructure expansion and workforce scaling.

Regulatory Framework and Clinical Pathways

Germany's regulatory framework, overseen by the Federal Institute for Drugs and Medical Devices (BfArM), provides a structured but demanding environment for psychedelic therapies. To align with Germany's rigorous HTA standards, developers must prioritise engagement with the Federal Joint Committee (G-BA) and IQWiG early in the process. Trials should incorporate comparative effectiveness studies using SSRIs, cognitive behavioural therapy (CBT), or other appropriate comparator treatments recognised by the G-BA. Developers should also invest in naturalistic trials that reflect real-world conditions to complement RCT data and address German regulators' emphasis on real-world applicability.

In addition, developers should anticipate and address requirements for long-term data, such as the durability of therapeutic effects and ongoing safety monitoring, which are critical for showing long-term benefits. Implementing flexible trial designs like adaptive trials and hybrid therapy models can streamline approvals while reducing uncertainty.

Evidence Generation and Monitoring Programs

Germany's health technology assessment process, led by G-BA and IQWiG, requires robust Phase III randomised controlled trial data demonstrating clear added therapeutic benefit compared to existing treatments. This comparative effectiveness evidence forms the foundation for reimbursement and pricing decisions under the AMNOG process.

While real-world evidence—such as post-launch monitoring and registry-based studies—cannot replace high-quality Phase III RCTs, it plays a vital complementary role. These studies are especially useful for tracking long-term safety, evaluating durability of effect, and supporting broader implementation efforts. Developers should prioritise generating decisive comparative trial data while planning real-world studies that extend evidence beyond the initial assessment window.

Significant government funding initiatives demonstrate Germany's commitment to advancing psychedelic research. The Federal Ministry of Education and Research (BMBF) has invested nearly €5 million in the EPIsoDE study investigating psilocybin for treatment-resistant depression (TRD), led by the Central Institute for Mental Health in Mannheim. This government backing extends beyond clinical trials, including acceptance studies and broader implementation research.

The upcoming Dimension Study, supported by the Federal Agency for Disruptive Innovation (SPRIN-D), exemplifies Germany's strategic approach to generating robust evidence through public-private partnerships. Other European governments and research institutions can adopt these partnership models for evidence generation and stakeholder engagement in their markets.

Reimbursement Strategies and Financial Modelling

Germany's statutory health insurance (GKV) mandates that therapies must demonstrate added benefit compared to standard treatments to achieve a price premium over the standard of care. Demonstrating added benefit will be important given that the standard of care for many mental health conditions will be low-cost generic drugs, and a higher price will be required for commercial feasibility. Given the higher costs associated with psychedelic therapy, robust pharmacoeconomic analyses showing long-term cost savings, such as fewer inpatient admissions and lower relapse rates, may be helpful for argumentation with payers.

Risk-sharing agreements and managed entry models may offer opportunities to address payer concerns about initial costs. These agreements tie reimbursement to observed outcomes, enabling developers to negate uncertainties while ⤴ demonstrating value. To strengthen economic arguments, developers may also highlight potential reductions in other treatment usage and hospitalisations, an example being the reduction in ECT use and readmission rates observed with esketamine for TRD patients in German hospitals.

Adoption within outpatient departments associated with specialist psychiatric hospitals is a pragmatic entry point, as hospitals have established funding mechanisms for managing high-cost therapies. These settings also allow for controlled implementation, rigorous data collection, and alignment with clinical protocols. Over time, this approach can pave the way for broader outpatient adoption. However, it is important to recognise that the funding and reimbursement model for the private physician-led outpatient clinics in Germany is extremely cost-constrained. Specific arrangements will need to be set up with insurers to allow private outpatient clinics to receive predictable reimbursement for the combination of a high-cost drug, extended therapist time, and the initial patient evaluation and management.

Workforce Development and Infrastructure

Scaling psychedelic therapies in Germany may require significant investments in workforce training and infrastructure. Clinical and psychiatric associations should lead the establishment of certification programs for therapists, with developers participating in these discussions to ensure alignment with treatment protocols while maintaining German clinical standards. Competency-based training modules, modelled after frameworks used for CAR-T therapies, could accelerate adoption while maintaining quality.

Addressing infrastructure gaps is equally important. Developers, health system stakeholders and policymakers may wish to collaborate to design and fund dedicated therapy rooms that meet regulatory safety, privacy, and supervision standards. Pilot programs demonstrating scalable facility designs could serve as models for larger rollouts.

Given the lengthy session times required for psychedelic treatments, healthcare providers must explore alternative delivery models to optimise resource use. Approaches such as group therapy settings or multi-patient supervision could help mitigate workforce constraints and improve cost-efficiency. Healthcare administrators should evaluate these options while maintaining safety and therapeutic effectiveness.

Public-Private Collaboration and Policy Support

Developers should pursue public-private partnerships with insurers, government bodies, and private investors to overcome infrastructure and funding barriers. These collaborations can support facility upgrades, training programs, and data collection efforts while sharing financial risks.

Policymakers should be encouraged to provide subsidies or tax incentives for infrastructure investments, similar to initiatives used for oncology and rare disease therapies. Engaging progressive political groups could help build momentum for policy reforms and funding support. ■

8.6.2 United Kingdom

Regulatory and Policy Engagement

The UK's regulatory framework, particularly the Innovative Licensing and Access Pathway (ILAP), aims to help accelerate market approvals and market access for promising therapies. Developers should actively pursue an ILAP designation, as five[26] developers have successfully done, to gain early dialogue with health system stakeholders and optimise the clinical programme to improve the likelihood of regulatory approval. Through ILAP, developers can meet with NHS and NICE representatives to plan how to integrate their innovative products into the existing UK health system and establish new treatment services. Engagement with NICE and NHS England is equally critical. Developers should seek early NICE advice to align clinical trial designs and economic models with the stringent evaluation methods. NICE's scientific advice services offer valuable opportunities to clarify evidence requirements and ensure trial designs capture payer-relevant outcomes.

[26] Small Pharma, Eleusis, Compass Pathways, MAPS/Lykos, and Mindmed.

Key Recommendations for the United Kingdom (UK)

- **Leverage Accelerated Regulatory Pathways:** Developers should utilise the Innovative Licensing and Access Pathway (ILAP) to allow for accelerated alignment with regulatory and NHS bodies.
- **Engage Early with NICE and NHS England:** Developers should initiate early dialogues with NICE and the SMC to clarify evidence requirements, cost-effectiveness modelling acceptability, and HTA expectations, ensuring alignment with payer priorities.
- **Utilise the Innovative Medicines Fund (IMF):** Where relevant, NHS England and developers should explore the potential for temporary reimbursement mechanisms through the IMF to enable early patient access while gathering additional real-world evidence to address uncertainties in longer term outcomes.
- **Demonstrate Comparative Effectiveness and Cost Effectiveness:** Developers should conduct head-to-head trials where feasible to compare psychedelic therapies with standard-of-care treatments to meet NICE and SMC preferences for direct comparisons and incremental cost-effectiveness analyses.
- **Incorporate Long-Term Follow-Up Studies:** Developers, in collaboration with NHS research networks, should build robust longitudinal datasets to address uncertainties about the durability of effects and economic sustainability over time.
- **Develop Flexible Reimbursement Models:** NHS England and developers should collaborate on outcome-based pricing and risk-sharing agreements to alleviate payer concerns about high upfront costs and scalability.
- **Invest in Infrastructure and Workforce Development:** NHS trusts should lead the retrofitting of facilities and creation of dedicated therapy rooms, while professional bodies should establish appropriate training programs for therapists and clinicians.
- **Pilot Scalable Delivery Models:** NHS trusts and clinical networks should evaluate alternative approaches, such as group therapy or hybrid treatment protocols, to manage costs and address capacity constraints.
- **Build Partnerships for Implementation** Pilots: NHS trusts, in collaboration with developers, should launch pilot programs to refine care pathways, inform economic models, and demonstrate real-world effectiveness before national rollouts.

The NHS's Innovative Medicines Fund (IMF) presents an opportunity for developers to secure conditional market access while collecting further data. Entry is limited to products demonstrating potential for significant clinical value and potential for cost-effectiveness, with NICE and NHS England gatekeepers to this funding pathway. Policymakers should consider expanding similar mechanisms to accommodate psychedelic therapies, particularly for conditions with high unmet needs like PTSD and TRD.

Clinical Trial Design and Evidence Generation

To secure reimbursement in the UK, psychedelic therapies must demonstrate comparative effectiveness. Developers should focus on head-to-head trials against existing treatments where feasible, aligning with NICE's preference for incremental cost-effectiveness analysis. If this is not feasible, ensure trial designs allow indirect treatment comparisons that meet NICE's expectations. Trials should also prioritise endpoints that reflect real-world patient outcomes, such as reduced hospitalisations, improved quality of life, and lower caregiver burdens. Long-term follow-up studies are essential to address concerns about the sustainability of benefits. Developers should design longitudinal studies to capture data on relapse rates, continued medication use, and healthcare resource utilisation over time.

Real-world evidence generation can also support HTA evaluations by validating trial outcomes in clinical settings. Registry-based studies conducted within NHS trusts could provide additional insights into scalability and cost-effectiveness. Policymakers should incentivise such initiatives to build confidence in these therapies.

Economic Modelling and Reimbursement Strategies

NICE's strict cost-effectiveness thresholds pose challenges for psychedelic therapies, which may have high upfront costs, including new healthcare infrastructure. Developers should create economic models that capture clinical benefits and estimate any possible direct healthcare savings. The relatively low cost of generic ketamine (<£3 per vial) presents a significant advantage compared to proprietary treatments (e.g. Spravato), potentially allowing for cost-effective implementation when infrastructure and staffing requirements are addressed.

Developers should propose outcome-based and pay-for-performance reimbursement models to NHS payers to alleviate payer concerns and allow a shared risk approach to the roll-out of psychedelic therapies. These agreements tie reimbursement to demonstrated outcomes, ensuring the NHS only pays for therapies that deliver measurable benefits. Developers should propose Managed Access Agreements (MAAs) as a transitional solution to enable early adoption while generating supporting data.

Policymakers can facilitate integration by considering if greater use of bundled payment structures can be implemented that combine drug and therapy costs, simplifying reimbursement and enabling scalable implementation.

Infrastructure and Workforce Development

Expanding the NHS's capacity for psychedelic therapies requires investments in infrastructure and workforce training. NHS facilities may need to retrofit existing mental health facilities to include therapy-specific rooms and monitoring environments. Developers should partner with the NHS to develop a service specification for their therapy. NHS trusts should consider collaborating with developers to determine the most cost-efficient way to prepare rooms and potentially consider 3rd party providers to ensure scalability.

Workforce development is equally important. Training institutions should expand certification programs to train therapists in psychedelic protocols, including safety monitoring and integration sessions. Continuing education programs can update practitioners on emerging best practices and regulatory changes.

Alternative delivery models like group therapy and hybrid approaches could improve accessibility while reducing costs. Pilot programs should evaluate these strategies within NHS settings before broader rollouts.

Next Steps for Implementation

NHS trusts should launch pilot programs to integrate psychedelic therapies, refine care pathways, confirm clinical outcomes in real-world settings, and validate economic models. These pilots can assess scalability, cost-effectiveness, and patient outcomes, providing the foundation for national adoption.

The Ketamine Clinical Treatment Pilot in England at Central and North West London NHS Foundation Trust provides an informative example of how to integrate new treatments into existing care pathways while minimising infrastructure and implementation challenges. This pilot utilises standard NHS mental health outcome measures (including PHQ-9, GAD-7, and Work and Social Adjustment Scale) to track patient progress, using existing NHS data systems and facilitating comparative effectiveness analysis. The program's approach of providing 5-7 ketamine doses, when patients are already receiving talking therapy, offers a structured treatment protocol that can be evaluated for both clinical efficacy and cost-effectiveness within the NHS framework.

Policymakers should prioritise legislative reforms to simplify licensing and controlled substance requirements for psychedelics with approved marketing authorisations, enabling broader clinical use. Collaboration between developers, researchers, and payers will be essential to building sustainable frameworks for these treatments. ■

Ketamine Clinical Treatment Service Pilot in England

A new NHS pilot programme launching in 2025 will test how ketamine treatment can help people with severe depression that hasn't responded to standard treatments. Led by Dr. David Erritzoe, this programme aims to offer a new option for patients while working alongside existing NHS mental health services.

The pilot will identify patients through the NHS Talking Therapies programme—a nationwide service helping people with depression and anxiety. Patients who haven't improved after multiple treatments will be considered for ketamine therapy while continuing their regular talking therapy sessions.

Treatment will take place at the CIPPRes Clinic and Central and North West London (CNWL) NHS Trust. Patients will receive five weekly injections of ketamine, each costing the NHS approximately £3. Each treatment session will likely last about 90 minutes, including preparation time, the 40-minute ketamine experience, and a short recovery period.

What makes this approach promising is how it fits into existing NHS care. Patients won't need to navigate a completely new system—they'll continue working with their talking therapist while receiving ketamine treatment from NHS psychiatrists. Their regular therapist will help prepare them for the ketamine sessions and support them afterwards, sharing information with the ketamine clinic team.

The pilot avoids creating expensive new infrastructure by using existing NHS Talking Therapies services for ongoing patient support, standard mental health questionnaires already used by the NHS to track progress, and a straightforward pathway from community care to ketamine treatment and back to GP care. This integrated approach keeps administrative overheads low while maintaining continuity of care.

If successful, this model could potentially be scaled across England, offering a new treatment option for people with treatment-resistant depression while minimising costs and changes to existing services. By keeping patients connected to community-based care and using affordable generic ketamine, the pilot aims to test whether this treatment can be both effective and practical within the NHS.

8.6.3 Netherlands

Current Legal Framework

The Netherlands provides three distinct pathways for implementing psychedelic therapies before achieving regulatory approval. Compassionate use creates opportunities for experimental treatments in cases where conventional approaches have failed, though this route is limited to substances already in clinical trials. The doctor's certificate pathway enables individual prescriptions under the Healthcare Inspectorate's (IGZ) oversight but carries significant administrative requirements. Most promising is the naturalist research route, which requires an Opium Act exemption from the Ministry of Health but allows for broader implementation and systematic data collection.

These pathways reflect the Netherlands' historically progressive stance on drug policy while maintaining necessary regulatory controls. The recent MDMA State Committee report confirms these routes as viable options, though each presents distinct challenges in terms of scalability and administrative burden.

Working with Regulators and Payer Groups

Early and sustained engagement with *Zorginstituut Nederland* (ZiN) is essential for successful implementation. ZiN's evaluation framework centres on four fundamental criteria: effectiveness, cost-effectiveness, necessity, and feasibility. Successful integration requires developers to present comprehensive evidence packages addressing each criterion, particularly emphasising long-term healthcare cost implications and societal benefits.

Key Recommendations for the Netherlands

- **Leverage Progressive Drug Policies:** Healthcare policymakers should build upon the Netherlands' liberal stance on drug policy to establish frameworks for integrating psychedelic therapies into healthcare settings.
- **Expand Training Programmes:** Professional medical associations, in consultation with academic institutions, should develop accessible, standardised, and accredited training curricula for therapists, ensuring a scalable workforce to deliver psychedelic therapies.
- **Pilot Real-World Evidence Studies:** Healthcare providers and academic medical centres should utilise the existing network of clinics to conduct pragmatic trials, gathering real-world evidence to inform HTA submissions and reimbursement frameworks.
- **Engage Zorginstituut Nederland (ZiN) Early:** Developers should collaborate with ZiN two years before market entry to align on cost-effectiveness models, budget impact evaluations, and trial designs that meet local requirements.
- **Address Affordability Concerns:** Health insurers and developers should collaborate on pricing and reimbursement strategies, including bundled payments and partial reimbursement models, to reduce patient out-of-pocket costs while demonstrating economic value.
- **Use Legal Pathways:** Healthcare providers and researchers should leverage the three available routes (compassionate use, doctor's certificate, naturalist research) while developers work toward regulatory registration.
- **Public Education and Advocacy:** Professional medical societies and patient advocacy groups should lead campaigns that address stigma, differentiate clinical therapies from unregulated approaches, and promote evidence-based narratives about safety and effectiveness.

Engagement should begin at least two years before intended market entry, allowing time to address regulatory concerns and adapt protocols to meet Dutch healthcare standards. This timeline also enables developers to conduct additional studies if needed to address specific ZiN requirements, particularly around cost-effectiveness in the Dutch context. Developers should specifically align with ZiN on the inclusion of indirect benefits in cost-effectiveness modelling, such as productivity gains and reduced caregiver burden, as the Netherlands uniquely considers these broader societal impacts in their value assessments.

Training and Workforce Development

The current landscape of therapist training in the Netherlands shows promise and limitations. The OPEN Foundation's ADEPT programme represents an important first step in establishing structured training protocols. However, significant questions remain about how much of this training will be recognised by medical authorities once formal implementation begins. The program's current status as 'educational' rather than professionally accredited highlights the need for further development of training standards.

Cost and Coverage Solutions

Implementing sustainable financing models requires careful consideration of the Dutch healthcare system's unique characteristics. Innovation in payment structures is essential, with several potential approaches deserving exploration.

Outcome-based payment agreements could link reimbursement to treatment effectiveness, helping to manage financial risk for insurers. Bundled payment systems might combine therapy and medication costs into single packages, either for a course of psychedelic treatment or for a 6-12 month period of care for a specific condition, simplifying administration and potentially reducing overall costs.

The development of these payment models should account for both direct treatment costs and longer-term healthcare savings. The economic analysis should capture reduced hospitalisations, decreased medication use for chronic conditions, and improved workforce participation among successfully treated patients. Early pilot programs with insurers could help demonstrate the viability of these approaches while generating data to support broader implementation.

Research Implementation

Pragmatic research programs represent the most promising path forward. They offer a balanced approach to treatment delivery and evidence gathering. These programs can operate at a larger scale than compassionate use or individual doctor's certificates while maintaining scientific rigour through structured data collection and analysis.

Implementation should focus on creating a network of research sites to deliver treatments while systematically gathering data on outcomes, safety, and cost-effectiveness. This approach allows for developing best practices specifically suited to the Dutch healthcare context while building the evidence base needed for broader implementation.

Long-term follow-up studies should be integrated into these programs from the start, tracking clinical outcomes and broader measures of social functioning and economic impact. This comprehensive approach to data collection will help address remaining questions about long-term effectiveness and safety while providing valuable insights for future implementation efforts. ■

8.6.4 Czech Republic

Regulatory Framework and Research

The Czech Republic presents unique opportunities for advancing psychedelic therapy implementation, building on its established research infrastructure and progressive drug policies. The country's demonstrated capacity for innovation in medical research, particularly through institutions like the Prague Clinical Research Center, provides a strong foundation for expanding these treatments.

Early engagement with SÚKL (State Institute for Drug Control) and payers will be crucial for establishing apparent approval and reimbursement pathways. The regulatory body has shown flexibility while maintaining rigorous safety standards, creating an environment where innovation can thrive with appropriate oversight. Developers should work closely with SÚKL to clarify requirements for combined drug-therapy treatments, focusing on streamlining approval processes without compromising safety standards.

Key Recommendations for the Czech Republic

- **Engage Regulators for Pathway Clarifications:** Developers should work closely with SÚKL and other regulatory bodies to clarify approval pathways and adapt submission requirements for psychedelic therapies.
- **Leverage Real-World Evidence:** Healthcare providers and academic institutions should implement registry-based and observational studies to provide evidence that supports long-term safety and efficacy.
- **Develop Risk-Sharing Agreements with Payers:** Health insurance funds and developers should collaborate on innovative reimbursement contracts tied to patient outcomes to mitigate concerns about cost and efficacy.
- **Expand Public-Private Partnerships:** The Ministry of Health should encourage and facilitate partnerships between government bodies, research institutions, and private organisations to fund and conduct clinical trials.
- **Enhance Training Infrastructure:** Professional medical associations, in collaboration with academic institutions, should establish certification programs and workforce development initiatives to address therapist shortages and ensure high-quality delivery.
- **Position Czech Republic as a Research Hub:** The Ministry of Health and academic institutions should build on existing expertise and facilities to make the country a centre for psychedelic research and pilot programmes in Europe.
- **Pilot Expanded Access Programs:** SÚKL and healthcare providers should establish early access frameworks for treatment-resistant cases to build acceptance and collect data for broader adoption.
- **Highlight Economic Benefits:** Developers, health insurance funds, and research institutions should conduct economic evaluations to showcase cost savings and to strengthen reimbursement arguments with evidence of reduced hospitalisations and productivity gains.
- **Address Regional Disparities:** The Ministry of Health and regional authorities should develop policies that support equitable access, including funding grants or subsidies for rural and underserved populations.

Evidence Generation and Implementation

Real-world evidence collection represents a critical next step for gaining broader acceptance and reimbursement. Registry-based studies and pilot programs, particularly those focusing on treatment-resistant conditions, can help gather essential data on long-term outcomes and cost-effectiveness. The Prague Clinical Research Center is well-positioned to coordinate these research efforts and establish best practices, drawing on its extensive experience with psychedelic research protocols.

Cost and Coverage

The Czech Institute of Health Information and Statistics highlights growing financial pressures on the healthcare system, driven by rising personnel costs, an increasing prevalence of both chronic and acute illnesses, and the escalating expenses associated with healthcare innovations. These factors are placing significant strain on the sustainability of the healthcare insurance system. As a result, the Czech healthcare system's emphasis on economic justification requires careful attention to cost and coverage strategies.

Successful implementation will depend on developing innovative payment models that demonstrate clear cost savings compared to existing treatments. The economic analysis should include documentation of reduced hospitalisation rates and decreased long-term medication use where relevant. Outcome-based payment models could help address initial concerns about treatment costs whilst providing value for the healthcare system.

Infrastructure Development and Training

Infrastructure development presents both challenges and opportunities. While major cities have some existing infrastructure through ketamine clinics, broader implementation requires significant investment in specialised treatment facilities and training programmes. This expansion should focus on creating regional treatment centres and supporting rural healthcare providers to ensure equitable access to care.

Access beyond Prague and other major cities requires carefully coordinated solutions that address both infrastructure and workforce needs. The path forward likely involves a combination of approaches, including mobile treatment teams, partnerships with regional hospitals, and specialised training programmes for local healthcare providers.

While the Czech Republic has strong medical expertise, dedicated training for psychedelic therapy needs development through partnerships with international organisations and local medical institutions. These programmes should build on existing medical training frameworks while incorporating specific protocols for psychedelic therapy. Remote support services could complement in-person treatment, helping to extend the reach of specialised care teams while maintaining treatment quality, particularly in areas where establishing full-scale treatment centres may not be immediately feasible. ■

8.6.5 Other Emerging Regions

Insights from Global Leaders in Psychedelic Therapy

Several regions outside the EU and UK—Australia, Switzerland, the United States, and Canada—have adopted progressive approaches to psychedelic therapy research, regulation, and implementation. These countries provide valuable lessons on regulatory frameworks, evidence generation, and access models that could inform European strategies for psychedelic therapies.

Australia: Early Adoption Through Medical Rescheduling

Australia became the first country to formally reschedule MDMA and psilocybin for medical use in 2023, allowing authorised psychiatrists to prescribe them for PTSD and TRD, respectively. While this regulatory change created a framework for medical access, implementation has faced significant practical challenges.

The Australian model offers important insights, particularly around training requirements for prescribing clinicians and systems for tracking outcomes. Their psychiatry-led approach to policy reform could serve as an example for European countries looking to use existing mental health networks for psychedelic therapy.

However, Australia's experience also reveals key challenges. Treatment costs remain high due to the extensive protocol and lack of structured reimbursement. So far, only dozens of patients have received treatment under the new system. European healthcare systems, particularly those with universal coverage, can learn from this by planning early for reimbursement and accessibility issues.

Switzerland: Incremental Progress with Compassionate Use

Switzerland has a long history of psychedelic research, with five physicians receiving permission to prescribe LSD and MDMA therapy from 1988 to 1993 and later maintaining partial acceptance of substances like LSD and psilocybin under compassionate-use programs since 2014. This regulatory approach has supported patient-specific exemptions, enabling therapies outside standard approval pathways.

Swiss regulators have prioritised clinical evidence generation through partnerships with academic institutions like the University of Zurich, which has spearheaded trials on psilocybin's efficacy in treating depression and anxiety. These studies provide insights into balancing safety protocols with flexible access mechanisms.

European policymakers can draw inspiration from Switzerland's decentralised pilot programs, which allow evidence collection while gradually expanding access. However, scalability remains a challenge, as compassionate-use models may be difficult to implement on a broader scale, as this framework is on a per-patient basis.

United States: Accelerated Pathways

The United States has led the way in using Breakthrough Therapy designations from the FDA, speeding up the review of psychedelic drugs like MDMA and psilocybin. The Breakthrough Therapy designation has fast-tracked Phase III trials and brought these treatments closer to full approval.

Beyond regulatory advances, several U.S. states now see broader insurance coverage for ketamine. More Medicaid programs and private insurance providers are reimbursing this treatment, which improves patient access and signals the growing acceptance of psychedelic therapies.

European regulators could copy some of these strategies by creating pilot programmes or trying conditional reimbursement pathways, especially in countries such as the Netherlands, where there is already experience with managed entry agreements, and insurers have shown flexibility in reimbursement models. By taking these steps, Europe can enable new treatments to reach patients quickly while still gathering essential evidence for safety and effectiveness.

At the same time, high out-of-pocket expenses and uneven access remain problems in the U.S., reminding Europe to focus on affordability and integration into public healthcare systems.

Canada: Controlled Access with Emphasis on Research

Canada has developed a two-track system for psychedelic therapies, combining clinical trials with compassionate access through Health Canada's Special Access Program (SAP). While this allows treatment for patients with severe, treatment-resistant conditions, initial SAP approvals faced significant delays.

Canada's data collection and trials approach, supported by organisations like MAPS Canada, provides valuable lessons for Europe. However, the country continues to face challenges with regional access differences and cost coverage within its public health system. ■

Ensuring Equitable Access

9

As psychedelic therapies move closer to approval and implementation across Europe, ensuring fair and equal access becomes a critical challenge. Early evidence from clinical trials and existing treatment programmes shows concerning patterns of disparity, with access often limited to those with higher incomes, more flexible schedules, and better connections to healthcare systems. These treatments, whilst promising, risk becoming available only to privileged groups unless we take deliberate steps to address barriers to access.

The current landscape of psychedelic research highlights these challenges. Clinical trials have predominantly included white, middle-class participants, with significant underrepresentation of ethnic minorities, immigrants, and economically disadvantaged groups. In Europe, where healthcare systems vary significantly between countries, additional complexities arise around insurance coverage, treatment availability, and cultural acceptance. The intensive nature of psychedelic therapy, requiring multiple sessions and substantial time commitments, creates further barriers for many potential patients.

This chapter examines the key obstacles to equitable access and proposes practical solutions for overcoming them. We explore financial, cultural, and geographical barriers, alongside ethical considerations in patient selection. Drawing from successful models in other areas of healthcare, we outline strategies for these potentially transformative treatments to reach all who might benefit from them, regardless of their background or circumstances. ■

9.1 Current Disparities in Access

Significant inequalities, visible in both clinical research and early treatment programmes, currently mark the pathway to accessing psychedelic therapy. In Europe, this imbalance is particularly concerning given the continent's increasingly diverse population and the high prevalence of mental health conditions among refugee and immigrant communities.

The barriers to access extend beyond clinical trials into practical implementation challenges. Initial treatment programmes in countries where certain psychedelic therapies are already available through compassionate use or special access schemes have revealed systemic obstacles. Without established insurance coverage pathways, treatment costs can exceed €10.000 per course, creating a significant financial barrier.

9.1.1 Clinical Trial Representation Issues

Recent reviews of psychedelic research—primarily taking place in the U.S.—highlight significant demographic imbalances in trial participation. Since 2017, approximately 85% of participants have been non-Hispanic White, with Black (2.9%), Hispanic/Latino (5.9%), and Asian (3.2%) individuals severely underrepresented (Hughes & Garcia-Romeu, 2024). Notably, the second Phase III trial of MDMA for PTSD achieved better diversity, with 26.9% Hispanic/Latino participants and 33.7% identifying as non-White (Mitchell et al., 2023).

The European context presents unique challenges compared to the U.S. approach. While U.S. diversity discussions often focus on racial categories, European studies must address a complex landscape of immigrant populations, including refugees and various ethnic minorities. The EU Clinical Trial Regulation No. 536/2014 requires sponsors to justify non-representative samples but lacks specific guidance on prioritising sociodemographic characteristics (EU, 2014). This regulatory framework, while well-intentioned, has not yet led to consistent improvements in trial diversity. ■

9.1.2 Socioeconomic Barriers

The financial burden of psychedelic therapy presents a significant access barrier. Treatment costs, including preparation, administration, and integration sessions, often cost thousands of euros. Without established insurance coverage frameworks, these expenses remain prohibitive for many potential patients. The variation in healthcare systems across Europe creates additional complexity, with some countries offering potential coverage pathways while others leave patients entirely responsible for costs.

Time commitment requirements pose another substantial challenge. The intensive nature of psychedelic therapy protocols, requiring multiple sessions over several weeks or months, can be particularly burdensome for individuals with inflexible work schedules, caring responsibilities, or limited resources for travel and accommodation. These practical constraints disproportionately affect lower-income individuals and those without robust support systems (Noorani & Mathukumaraswamy, 2023). ■

9.1.3 Cultural and Linguistic Barriers

Language accessibility remains a crucial challenge in both clinical trials and treatment settings. Despite Europe's multilingual nature, trial materials and therapeutic protocols are often available only in dominant languages, creating immediate barriers for immigrant populations and linguistic minorities. This limitation affects not only patient recruitment but also the quality of therapeutic experiences and integration processes.

Cultural perceptions of mental health treatment and psychedelic substances vary significantly across different communities. Historical stigma, religious beliefs, and traditional healing practices can influence how different groups view these treatments. Moreover, many marginalised communities harbour deep-seated mistrust of medical institutions, stemming from historical abuses and ongoing systemic inequities (Haft et al., 2024).

Building trust requires addressing both historical traumas and current systemic barriers. Success in improving access depends not only on removing practical obstacles but also on creating culturally sensitive treatment environments. The trust-building process includes developing culturally adapted protocols, employing diverse practitioners, and engaging with community leaders to build bridges between traditional healthcare systems and underserved populations. ■

9.2 Ethical Considerations

Patient selection for psychedelic therapy involves complex decisions about safety, fairness, and access. As these treatments progress toward approval, we must carefully balance making them available to those who might benefit while maintaining appropriate safeguards. Balancing access and safety requires examining traditional exclusion criteria and considering whether they remain justified by current evidence.

9.2.1 Patient Selection Criteria

The field has traditionally used strict exclusion criteria, particularly around mental health risks. Most trials and treatment programmes exclude people with personal or family histories of psychosis, as well as those with certain personality disorders or active suicidal thoughts (Johnson et al., 2008). These criteria emerged from early research and clinical caution, aiming to minimise risks to vulnerable individuals.

However, recent evidence suggests some of these exclusions may be overly cautious. Several studies have shown successful outcomes in carefully selected patients who would have been excluded under traditional criteria (Sabé et al., 2024). The research findings have led to calls for more nuanced approaches to patient selection based on individual assessment rather than blanket exclusions. ■

9.2.2 Special Populations

Some groups face particular challenges in accessing psychedelic therapy despite potentially having the most to gain. These groups include people with severe mental health conditions, those with complex trauma histories, and individuals from marginalised communities. Current guidelines often exclude these groups from trials and early treatment programmes, creating an ethical tension between safety and access.

The way forward likely involves developing specialised protocols for different populations. Future protocols might include enhanced safety measures, modified treatment approaches, and additional support systems. Several centres are already pioneering such approaches, demonstrating how clinicians can safely offer psychedelic therapy to a broader range of people. ■

9.2.3 Risk Management Approaches

Managing risks in psychedelic therapy requires comprehensive systems beyond simple inclusion/exclusion criteria. The risk management approach includes thorough pre-screening processes, ongoing monitoring during treatment, and robust integration support. Current best practices emphasise the importance of individualised risk assessment rather than rigid rules.

Building trust requires addressing both historical traumas and current systemic barriers. Success in improving access depends not only on removing practical obstacles but also on creating culturally sensitive treatment environments. The trust-building process includes developing culturally adapted protocols, employing diverse practitioners, and engaging with community leaders to build bridges between traditional healthcare systems and underserved populations. ■

9.3 Practical Solutions and Policy Recommendations

Addressing access barriers requires both immediate practical solutions and longer-term systemic changes. This section examines concrete steps that can be taken to improve access and provides policy recommendations to ensure the sustainable and equitable implementation of psychedelic therapy across Europe.

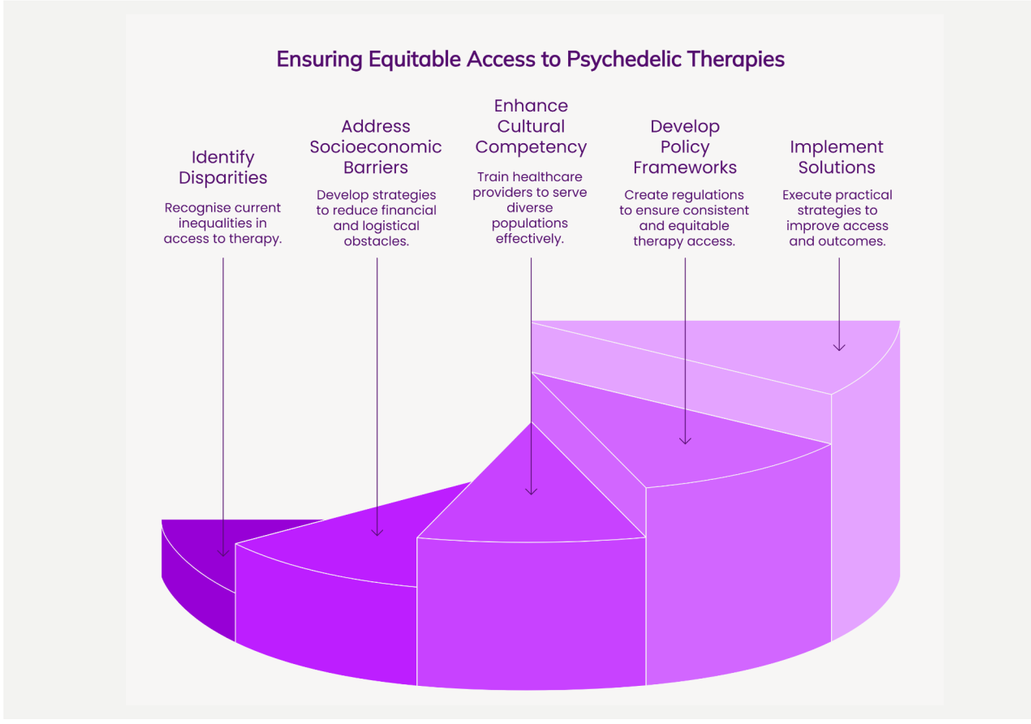
9.3.1 Financial and Geographic Access Solutions

Making psychedelic therapy financially accessible requires multiple approaches. Some European countries are exploring insurance coverage pathways, with early adopters like Switzerland including certain psychedelic treatments under specific insurance schemes. Subsidy programmes and sliding scale payment models offer additional routes to affordability, while some clinics are developing group preparation and integration sessions to reduce costs.

Geographic access presents distinct challenges, particularly in rural areas. Innovative solutions include hub-and-spoke models where urban centres support satellite clinics, and the strategic use of telehealth for preparation and integration sessions. Several countries are developing regional provider networks to ensure more evenly distributed access, though treatment sessions currently require in-person delivery. ■

9.3.2 Cultural Competency and Workforce Development

Building a diverse and culturally competent workforce is essential for expanding access. The workforce development strategy includes developing training programmes that attract practitioners from varied backgrounds and incorporating cultural competency training into standard provider certification. Some training programmes now offer scholarships to practitioners from underrepresented communities and include modules on culturally adapted protocols.



Treatment centres are increasingly adapting their protocols to better serve diverse populations. Cultural adaptation efforts include offering materials in multiple languages, incorporating cultural and spiritual perspectives into integration work, and developing modified approaches for specific cultural contexts. Success in this area requires ongoing collaboration with community leaders and cultural advisors. ■

9.3.3 Policy Frameworks and Implementation

Effective policy frameworks must balance access, safety, and quality standards. Several European countries are developing regulatory approaches, including coverage mandates for certain conditions, diversity requirements for provider certification, and quality standards for treatment centres. These frameworks aim to ensure consistent, high-quality care while promoting equitable access.

Implementation requires robust monitoring and evaluation systems. Early adopters are developing frameworks to track access patterns, treatment outcomes, and patient experiences across different demographic groups. This data supports continuous improvement processes and helps identify areas requiring additional attention or resources. Regularly assessing these metrics enables healthcare systems to adapt and improve their approaches to ensuring equitable access. ■

Access to Psychedelics for Marginalised Populations in Europe

Sergio Perez Rosal [1,2], Monnica T. Williams [3], Sonya Faber [3,4]

[1] Universitätsklinikum Ruppin-Brandenburg, Neuruppin, Germany
[2] Medizinische Hochschule Brandenburg Theodor Fontane, Neuruppin, Germany
[3] University of Ottawa, School of Psychology, Ottawa, Ontario, Canada
[4] School of Public Health and Epidemiology

Introduction: The Need for Equitable Access to PAT

The resurgence of psychedelic therapies has opened new avenues for treating mental health conditions such as PTSD and depression while also making clear the need for culturally informed and equitable approaches (George et al., 2020; Williams, 2020). Equitable access to these treatments remains a challenge, particularly for marginalised populations in Europe.

Critically, therapy for mental disorders relies on fostering a meaningful connection between therapist and patient. In Europe, however, a gap often arises when therapists and patients come from different racial or cultural backgrounds. While “race” does not describe biological differences, it remains an ambiguous and often uncomfortable term in European discourse. Nevertheless, it is used in a deep body of literature (U.S., Canada, UK) capturing "in-group/out-group" dynamics that cannot be described by other terminology. Therefore, racial terminology (e.g., White) is necessary for describing socio-political in-groups that shape the norms and practices of therapy in Europe, independent of biology.

In this context, “racialised” refers to how society assigns individuals or groups to a racial category, often euphemised as “migration history”. Being racialised describes the prejudice or unequal treatment experienced due to race, even though the idea of race itself is not a biological fact but rather a social or historical construct. Calling someone *racialised* highlights how societal biases—not inherent traits—determine differential treatment. This framing allows us to understand how racial differences influence communication, trust, and empathy in therapeutic settings. It highlights why culturally competent therapeutic paradigms are urgently needed for racialised peoples in Europe (Bhui & Morgan, 2018).

The term *racialised peoples* describes those who experience systemic inequities due to being placed into racial categories. In Europe, this often intersects with migration status, ethnicity, and cultural identity. The European Commission (EC) acknowledges that race is a social construct, rejecting biological race while recognising racialised groups as a more accurate way to frame racism as a societal issue (EC, 2023b).

Therapists trained within predominantly Eurocentric frameworks often lack the cultural competence to recognise or respond to the unique social realities of racialised patients. As a result, experiences of systemic racism, microaggressions, and cultural trauma are frequently overlooked, leaving patients feeling invalidated and disconnected (Bhui & Morgan, 2018). This gap in therapist-patient understanding contributes to poorer mental health outcomes and lower engagement in therapy for racialised populations.

Racialised populations in the European Union and the European Economic Area (EU/EEA), including migrants but also, significantly *native* racialised Europeans (i.e. non-White populations), face a higher risk of mental health problems compared to the general population (Apers et al., 2023). Despite this heightened risk, European research on race-related mental health remains alarmingly scarce and underfunded (Cénat, 2020). The first and only systematic review by Apers et al. (2023) identified only 27 relevant studies conducted over 22 years, demonstrating the severe evidence gap. The lack of research reflects an institutional failure to recognise racialised populations as a distinct group with different therapeutic needs within European healthcare systems and research frameworks.

Recent events, such as the racial discrimination faced by refugees fleeing the war in Ukraine, underscore the intersection of racism and war-related trauma. Reports documented that African, Arab, and Indian refugees were pushed to the back of lines at borders, assaulted by guards, and subjected to racial profiling, with some being told that "one foreigner can leave for every hundred Ukrainians" Such incidents illustrate how race-specific systemic inequities intensify mental health burdens, making the need for culturally responsive interventions even more urgent (Cénat et al., 2022).

While awareness of racial trauma in Europe is growing, mental health interventions remain largely inaccessible to racialised groups. Psychedelic therapy, which depends on skilled facilitators and comprehensive therapeutic services, remains out of reach for many. Without systemic efforts to expand access, these treatments risk becoming exclusive to the privileged few, perpetuating inequities already embedded in European healthcare systems (Williams et al., 2023).

Barriers to Access

Barriers to accessing psychedelic therapies are shaped by systemic inequities, restrictive policies, and cultural dynamics that disproportionately affect vulnerable groups. These barriers not only limit the potential impact of psychedelic therapies but also contribute to worsening mental health disparities. For example, the Roma, Europe's largest ethnic minority, experience severe social exclusion, discrimination, and significant barriers to healthcare, including mental health services (Guerro et al., 2024). Despite their heightened risk for mental health issues, research on Roma mental health remains scarce and underfunded.

Financial and Policy Barriers:
In Germany, asylum seekers and refugees face policies that delay access to insurance coverage and further restrict care. For example, we document how refugees often face waiting periods before they can receive insurance coverage for psychotherapy, with additional barriers for non-fluent speakers due to the exclusion of interpreter costs (Hollederer, 2020; Perez-Rosal et al., 2024; Williams et al., 2023). Moreover, some policies deprioritise PTSD as a serious condition, preventing access to life-saving care (Nesterko et al., 2019). Compounding these policy barriers is the lack of investment in culturally adapted interventions. Over the past two decades, fewer than 30 studies have focused on addressing mental health needs for these groups (Apers et al., 2023). The high cost of psychedelic therapy creates a financial burden, placing these treatments out of reach for many low-income individuals (Williams et al., 2020).

Geographic Disparities:
Psychedelic therapies are often concentrated in urban centers, leaving rural and remote areas underserved. Refugees and asylum seekers settled in rural regions face additional hurdles due to the limited availability of specialised healthcare infrastructure (Brücker et al., 2019). These geographic disparities exacerbate mental health inequities, particularly for those who already face socio-economic and linguistic barriers. Research suggests that interventions targeting these broader circumstances, such as improving social relations and addressing socio-economic conditions, can positively impact mental health outcomes (Apers et al., 2023; Williams et al., 2020)

Cultural and Racial Barriers:
Cultural stigma surrounding both mental health and psychedelic therapies disproportionately affects ethnic minorities and refugees, deterring treatment uptake. Experiences of racialisation and discrimination in host countries further compound trauma for many asylum seekers, refugees, second-generation immigrants and non-White native European individuals (Aikins et al., 2021; Apers et al., 2023; Bhui & Morgan, 2018; Nesterko et al., 2019). When therapy fails to acknowledge these lived realities, racialised individuals may experience further alienation and mistrust toward the mental healthcare system.

In one study, retraumatisation occurred in psychedelic therapy settings when therapists failed to address racial trauma, leading to negative therapeutic outcomes for participants of colour (Williams et al., 2023). This underscores the necessity of integrating cultural competency into therapy to ensure that healing environments are inclusive and effective.

Strategies for Improvement

Achieving equitable access to psychedelic therapies in Europe requires systemic and culturally informed strategies. Addressing financial, geographic, and cultural barriers while expanding the competency of the mental health workforce can ensure inclusive care.

Policy Reforms to Address Financial Barriers:
Governments must establish reimbursement models that ensure affordability for marginalised populations. Public insurance should cover not only psychedelic medications but also the intensive psychotherapy necessary for screening, assessment, and treatment (Williams et al., 2020). Financial assistance models, including tiered payment systems and expanded interpreter services, should be introduced to further reduce economic barriers (Apers et al., 2023; Hollederer, 2020).

Expanding Access to Underserved Regions:
Telehealth and mobile therapy units have shown promise in addressing access gaps in other mental health services (i.e depression, psychosis) and could be adapted for psychedelic therapy (Brücker et al., 2019; Păsărelu et al., 2017; Pemovska et al., 2021). Additionally, incentive programs such as subsidised training and loan forgiveness should be implemented to encourage mental health practitioners to work in underserved regions (Apers et al., 2023).

Culturally Competent Care and Community Engagement:
Developing culturally informed therapy programs is essential for building trust and improving access among marginalised populations. Training programs specifically for psychedelic therapy should incorporate modules on racial trauma and cultural competence to equip practitioners with the skills needed to address complex trauma histories, which may include community, cultural, and historical traumas (Perez-Rosal et al., 2023; Williams et al., 2023). One recent initiative, the MDMA-Assisted Therapy Experiential Training for Arab Practitioners, set to take place in Portugal in 2025, aims to equip 18 Arab practitioners with hands-on experiential training. These practitioners, who completed the MAPS/Lykos MDMA-Assisted Therapy educational program in Sarajevo, are part of a pioneering initiative that marks a significant step toward developing culturally attuned psychedelic therapy models (Arab Psychedelic Society, 2024). Similarly, in German-speaking countries, efforts have been made to adapt psychedelic therapy training to local cultural and linguistic contexts. A psychedelic therapy training model tailored for German-speaking health providers and based on the Rochester model (2022) has been published (Perez-Rosal et al., 2024). While each European member state may require a customised approach, participatory methods—such as co-designing interventions with community members—have been shown to enhance trust and improve treatment engagement (Apers et al., 2023; Aikins et al., 2021).

Stigma's role in deterring treatment uptake
Psychedelic therapy remains stigmatised due to legal prohibitions, stereotypes about users, and religious prohibitions. Misinformation associating psychedelics with countercultural movements and substance abuse has contributed to reluctance in seeking treatment, particularly among racialised groups who may already distrust medical institutions due to historical injustices.

Conclusion: Toward Inclusive Psychedelic Therapies

Psychedelic therapies hold enormous promise for addressing some of the most persistent mental health challenges, but equitable access remains a critical goal. Addressing financial, geographic, and cultural barriers through systemic reforms and participatory approaches can ensure these transformative treatments reach those most in need (Apers et al., 2023; Perez-Rosal et al., 2024). By prioritising equity, Europe can set a global standard for accessible and culturally competent psychedelic therapy, ensuring no communities are left behind.

Summary of Potential Reimbursement and Access Pathways

10

As psychedelic therapies move closer to approval in Europe, healthcare systems face a crucial question: How will patients access these treatments? The path from regulatory approval to patient access is complex, particularly for treatments that combine drugs with a psychotherapeutic component. This chapter examines nine different pathways that could make psychedelic therapies available to patients.

The standard route for new medicines may struggle to handle psychedelic therapies. These treatments do not fit neatly into existing systems designed for either drugs or therapy, but not usually both together. Esketamine, which gained regulatory approval in Europe, has faced challenges getting covered by health systems. For future psychedelic treatments, which may have more complex evaluations, these challenges could be more significant.

Alternative pathways may offer solutions. Private insurance and out-of-pocket payment already provide limited access to ketamine therapy in several European countries. Pilot programs and research initiatives are testing new ways to deliver and pay for these treatments. Some countries are exploring innovative frameworks for complex therapies that do not fit standard assessment methods.

This chapter analyses each potential pathway, drawing on real examples from across Europe. We examine how different approaches work, what barriers they face, and which combinations of pathways best support patient access. The goal is not to identify a single perfect solution but to understand how different routes to access could work together as these therapies enter healthcare systems. ■

10.1 Standard National Reimbursement Pathways

Most new medicines in Europe follow a standard pricing, reimbursement, and market access (PRMA) path to get paid for by health systems. After regulatory approval, national bodies assess if the treatment works well enough and offers good value for money. These assessments, called health technology assessments (HTAs), help decide if public healthcare systems or insurance companies should pay for the treatment. While this pathway works well for many medicines, the likelihood of clinically effective psychedelics achieving reimbursement and access in most countries through this pathway may be low due to unique aspects of the evidence and limitations in existing HTA methodologies. The likely result is high variability from country to country in their reimbursement decisions.

Learning from Spravato

The experience with esketamine (Spravato) shows how complex this pathway could be for future psychedelic treatments. Different countries reached very different conclusions about Spravato's value, with Germany, for example, awarding it a considerable clinical benefit with favourable pricing (albeit after a second review). Still, NICE in the UK did not recommend it for use in England & Wales.

The learning here is that developers must approach each national HTA process with a tailored approach with regard to the evidence submitted, the positioning of the therapy in the country's clinical pathway, and a price in line with the payer's value framework. Additionally, relatively limited numbers of patients with TRD have received Spravato treatment even in countries that have approved it for reimbursement, highlighting the challenges around integrating a therapy with novel aspects of administration, a unique patient-specific experience, and a requirement for in-clinic observation.[27]

[27] We discuss Spravato in more detail in Appendix 14.5.

Key Challenges

The current assessment methods weren't designed specifically for treatments like psychedelics. They face several significant hurdles:

Clinical evidence requirements often do not fit psychedelic therapy trials. Standard trials should ideally compare new treatments directly against current treatments, but this is harder with psychedelics, where keeping studies 'blind' is challenging. Also, these treatments may lack the long-term data at launch that assessment bodies want to see.

Some reimbursement evaluation groups will consider trying to assess the efficacy and costs of the drug separately from the therapy sessions that might be part of the care protocol to deliver it. Where this is relevant, this split may be methodologically impossible to do, but if completed, it makes it harder to show the full value of the combined treatment. Such an approach in trying to split out the therapeutic components may also create additional challenges in reimbursement, as only the drug might be reimbursed, with no straightforward reimbursement for any therapist or other HCP time to support the use of the therapy with patients.

Setting up clinics to deliver psychedelic therapy will require some investment in facilities and staff training. Current assessment methods may include these setup costs when deciding if treatments offer good value, which can penalise therapies with novel administration and patient management requirements. These costs are also likely to be difficult to determine accurately before use in real-world practice, creating additional challenges for the standard national reimbursement and HTA evaluation processes.

Lessons from Other Complex Treatments

Health systems have historically struggled to assess innovative treatments that do not fit standard models. Cell and gene therapies have faced similar challenges, leading to delayed access and eventual changes to assessment methods. Even combination drug treatments in cancer care—which may be more methodologically straightforward than psychedelic therapy for an HTA evaluation—have proved difficult to evaluate and agree on fair pricing and reimbursement conditions for each component of care, often limiting access for patients.

Opportunities in Some Markets

Among the countries studied, the Netherlands shows more promise for psychedelic treatments using standard reimbursement pathways. The Netherlands' national HTA evaluation may consider broader societal benefits, not just direct medical costs. Dutch insurers already pay for therapist sessions for many mental health conditions as part of the basic insurance coverage package, and they reimburse these sessions alongside Spravato and ketamine treatments. These characteristics of accepting a broader range of value and having drug and therapist reimbursement channels in place may provide the flexibility needed for different psychedelics treatments to gain access.

Limited Prospects

Given these challenges, psychedelic treatments will likely struggle to gain broad access across Europe through the standard assessment pathways as they stand. Even if psychedelic therapies prove clinically effective in clinical trials, the current HTA and reimbursement processes are not particularly well-suited to evaluate their unique features. Although most stakeholders prefer that psychedelics be assessed fairly and effectively through the standard national reimbursement pathway for drug therapies, healthcare systems may need to use alternative pathways to make these treatments available to patients if assessment methods remain unadapted. ■

Challenges and Opportunities for Standard National Reimbursement Pathways

Country	Primary Evaluation Pathway for Pricing and Reimbursement	Key Challenges	Key Opportunities
Germany	AMNOG & HTA via G-BA	High evidence requirements for comparative effectiveness; Separation of drug vs therapy components; Rigid physician budget caps; Inadequate accounting for infrastructure costs	Strong centralised system; Potential for reassessment (as with Spravato); Private insurance incentives for adoption; Established novel treatment pathway
United Kingdom	NICE HTA (England); SMC (Scotland)	Strict QALY thresholds; Limited consideration of indirect value; Drug/therapy funding separation; Implementation timeframe challenges	Managed access via IMF; Legal funding mandate; Conditional reimbursement options; Centralised implementation structure
The Netherlands	ZiN HTA + Ministry of Health	Multiple insurer negotiations; Need for specialised service codes; Initial access limited to specialised centres	Broader societal benefit assessment; Existing therapy/drug payment mechanisms; Strong pilot programme tradition; Established mental health bundled payments
Czech Republic	SÚKL approval + private insurers	Limited billing mechanisms for combined therapies; Regional variability; Concentrated specialised infrastructure	Precedent for conditional psychiatric treatment approvals; Private insurance flexibility; Risk-sharing openness; Pragmatic evidence approach

10.2 Modified National Reimbursement Pathways

Instead of following the standard national PRMA evaluation approach, health systems could proactively adapt and optimise the evaluation methodology or overall reimbursement process to account for notable differences in the way evidence can be generated for psychedelics and the infrastructure required to implement these therapies. The adaptation process could involve modifying current clinical assessment frameworks to capture better the unique therapeutic contexts and outcomes of psychedelic treatments while leveraging established reimbursement mechanisms to support their integration.

If health authorities and policymakers optimised current pathways to address the unique aspects of these treatments, clinically effective psychedelics would have a much better chance of gaining widespread access. Of all the pathways described in this chapter, the modified national reimbursement pathway is the one that is most likely to lead to broad and equitable access to psychedelics.

Changes to Treatment Assessment

Several key changes to HTA processes could help evaluate psychedelic therapies more fairly:

First, evaluators should assess treatments as complete packages—drug plus any psychotherapeutic component together—rather than any attempts to try to evaluate the drug component alone. The evaluation should reflect how these treatments will work in practice.

Second, the requirement for head-to-head clinical trials against current treatments in order to achieve favourable reimbursement or pricing conditions could be relaxed where developers provide clinical justification. These head-to-head trials are particularly challenging for psychedelic therapies due to difficulties with blinding and where there is a more complex treatment protocol.

Third, assessment bodies need new guidelines for analysing psychedelic therapy studies. These should address specific challenges like blinding issues and potential reporting bias in ways that maintain scientific rigour while acknowledging practical limitations.

Broader Value Consideration

Healthcare assessment bodies could improve their evaluation of psychedelic therapies by taking a broader view of treatment benefits beyond immediate clinical results. This approach could look at longer-term impacts, such as patients' ability to return to work or live independently, alongside broader benefits, including reduced hospital visits and less need for other treatments.

A complete assessment would also consider the broader societal benefits that HTAs often miss in standard evaluations. These include economic factors such as lower disability payments, increased tax revenue when patients return to work, and the positive effects on families and communities when people recover from conditions that previously resisted treatment. By looking at these broader benefits, assessment bodies would better capture the full impact of psychedelic therapies in their evaluations.

Utilisation of Conditional Reimbursement

One approach that could help address the issue of gaps in longer-term clinical and economic outcomes, and also how psychedelic therapies may perform in a real-world health system, is the greater use of conditional reimbursement. Psychedelic therapies that show promise but do not neatly meet, for example, the existing standardised HTA criteria or set value thresholds or have a higher degree of uncertainty, would greatly benefit from an initial controlled period of access.

Health authorities and manufacturers can establish conditional reimbursement with clear criteria for where they might grant it, with clear commitments made by the manufacturer and health service to generate and analyse the specific data required to address the uncertainty. Such conditional ⤴ reimbursement schemes could also include tailored pricing arrangements for individual therapies to ensure appropriate risk sharing between the manufacturer and the payer, or manufacturers could receive payment only when patients achieve outcomes (i.e a pay-for-performance arrangement).

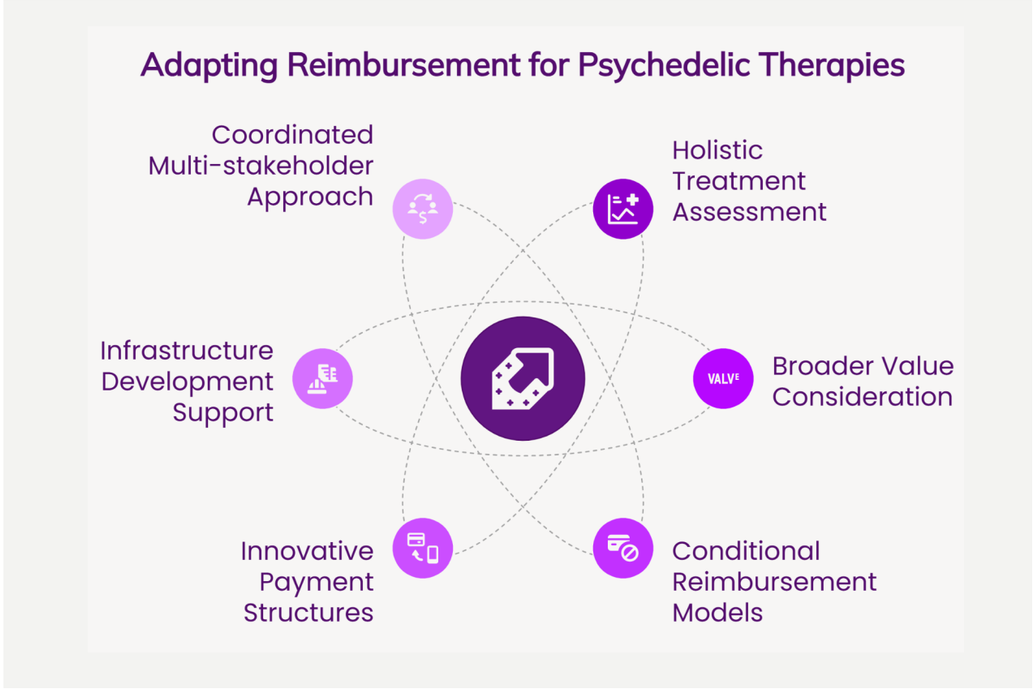
Learning from Other Complex Treatments

Similar changes have already occurred for other innovative treatments. The Innovative Medicines Fund (IMF) in England and Wales has been critical for providing temporary funding for some cell and gene therapies while gathering evidence about their long-term effects. Similarly, multiple European countries have successfully developed specialised assessment methods for Advanced Therapy Medicinal Products (ATMPs), proving that evaluation systems can evolve to meet new therapeutic challenges.

New Payment Models

Beyond changing how healthcare systems assess treatments, they need new ways to manage the costs of psychedelic therapy. The current systems, designed for traditional pharmaceuticals, may struggle with treatments that combine drugs, therapy, and specialised facilities. However, several promising approaches have emerged from different healthcare systems.

- **Fixed-Cost Allocations** The Netherlands offers a particularly useful model, where some care providers receive a set fee to manage a patient for 6-12 months. This approach allows providers to use innovative treatments when appropriate without getting caught up in separate payment streams for drugs, therapy, and facilities. Traditional payment models like diagnostic-related groups (DRGs) or drug-only reimbursement often discourage using treatments with high upfront costs, even if they might save money in the long run. A more flexible, outcomes-focused approach could better support the adoption of psychedelic therapies.



- **Pay-for-Outcomes Arrangements** More sophisticated payment models could link reimbursement directly to patient outcomes rather than just paying for services delivered. Some Dutch insurers offer providers bonus payments when treated patients do not require readmission within six months. This arrangement encourages innovation and nvestment in effective treatments, even with higher initial costs. Similar models could work for psychedelic therapies, with payments tied to achieving remission, maintaining health at specific time points, or reducing overall healthcare usage.

Implementation Challenges

Making these changes work requires careful planning and investment in infrastructure. Clinics need appropriate facilities and trained staff to deliver psychedelic therapy safely. Support for infrastructure development might require direct investment from national healthcare bodies or predictable reimbursement models that help clinics plan investments. Even approved treatments might remain unavailable without proper infrastructure support due to practical barriers.

Coordinated Funding

One of the biggest challenges is that drug costs, therapy sessions, and facility costs often come from separate budgets. This fragmentation makes it harder to implement treatments that do not fit neatly into existing categories. New approaches could include combined funding packages covering all treatment components, clear guidance on acceptable resource use for insurers, and special budgets for multidisciplinary care. Determining a core service specification with health system authorities could provide a reference point to inform new funding arrangements. Healthcare administrators and policymakers would need to implement these changes to ensure that all necessary components of psychedelic therapy can be funded together.

Stakeholder Involvement

Changes to HTA, reimbursement approaches and payment systems need support from multiple groups, including national commissioning bodies, insurance companies, professional medical organisations, healthcare providers, and patient advocacy groups. While these modifications would still operate within existing national reimbursement pathways and healthcare frameworks, they represent significant changes requiring careful implementation. Success likely depends on starting with pilot programmes that follow new therapies from modified HTA evaluations into real-world practice to monitor clinical effectiveness and financial sustainability before broader adoption. ■

10.3 Private Insurance Care Provision

Private insurance represents a potentially significant pathway for accessing psychedelic therapies, particularly in the early stages of their introduction to healthcare systems. While national health services and basic insurance plans may be slow to adopt these novel treatments, enhanced private insurance policies could offer earlier and broader coverage options for suitable patients.

This pathway is especially relevant because private insurers often have more flexibility in their coverage decisions and may be more receptive to innovative treatments that can demonstrate value beyond traditional medical outcomes. Additionally, payments for clinical staff may be higher, which supports the financial viability of therapies requiring more in-clinic time. Although this route will only serve a portion of the population, it could play a crucial role in establishing the real-world use of psychedelic therapies.

The Scale of Private Insurance

The proportion of people with enhanced private healthcare insurance varies significantly between European countries. In the UK, private insurance typically provides access to selected services unavailable through the NHS, particularly in areas like mental health and oncology. In countries with insurer-based systems, enhanced policies often come through workplace employer schemes or individual decisions to take out premium policies.

For some countries, like the Netherlands, supplementary insurance presents a popular add-on to mandated insurance coverage. Eighty percent of the Dutch population chooses this alternative private-like insurance. Across most European countries, enhanced private coverage typically reaches 10-20% of the population, predominantly among higher-earning individuals.

Opportunities for Access

Private insurers may be better positioned than national systems to approve and cover psychedelic treatments. Their decision-making processes tend to be more agile and often take a broader view of treatment value.

Private insurers are particularly attuned to workplace-related benefits, such as helping people return to work and improving productivity. This focus aligns well with the potential benefits of psychedelic therapies in treating conditions that often affect workplace performance, such as depression and PTSD. Over recent years, enhanced mental health therapy provision has become a growing trend in private health insurance plans, reflecting increased demand from employed individuals seeking support for their mental health.

Limited But Important Role

While private insurance will only provide access to a small portion of the population, its role in establishing psychedelic therapies should not be underestimated. In many countries, private insurance coverage may be one of the first pathways through which patients can access these treatments.

Private clinics operating under insurance contracts can build valuable experience and develop clinical expertise. Furthermore, healthcare professionals often work across both private and public systems, allowing for the cross-fertilisation of knowledge and insights.

The influence of private insurance coverage extends beyond its immediate beneficiaries. Healthcare systems may significantly limit access to psychedelics without changes to how they evaluate and fund these therapies. In such scenarios, the experience gained through private insurance coverage, alongside fully out-of-pocket payments, will be crucial in supporting the establishment of private clinics. These clinics can serve as centres of excellence, generating real-world evidence and building the case for broader patient access through public healthcare systems. ■

10.4 Private Out-of-Pocket Payment For Patients

Private out-of-pocket payment represents one of the most straightforward pathways for accessing psychedelic therapy. However, it inherently limits access to those who can afford to pay for treatment themselves. This pathway already exists across Europe for various mental health treatments and may serve as an important early route for psychedelic therapy access, even as broader reimbursement options develop.

Current Private Treatment Landscape

In every European country, private clinics offer services funded directly by patients or their families. Patients seeking psychedelic treatments may find this arrangement particularly relevant, as existing healthcare systems often fall short of providing adequate treatment for PTSD, depression, anxiety, eating disorders, and addictions. Many patients already seek private care for these conditions, accessing treatments that may be difficult to obtain through public healthcare systems. These include repetitive transcranial magnetic stimulation (rTMS) for depression, intensive behavioural therapies for addiction, and specialised trauma treatments like trauma-focused cognitive behavioural therapy (TF-CBT) and eye movement desensitisation and reprocessing (EMDR) for PTSD.

Ketamine as a Case Study

The role of private payment is particularly evident in the current landscape of ketamine therapy. For off-label ketamine treatments, private payment is often the only route to access. Even for approved treatments like esketamine (Spravato), in countries where national health systems have not approved reimbursement, such as England, private clinics provide access to those willing to pay, typically charging between €2,000 and €5,000 for a course of treatment.

Limitations and Barriers

However, this pathway faces significant limitations. Private clinics offering psychedelic therapy are likely to concentrate in larger urban centres, creating geographical barriers for many potential patients. Combined with the substantial costs of treatment and the limited number of clinics, these factors mean that only a small proportion of patients who might benefit from psychedelic therapy will be able to access it through private payment alone.

Hybrid Models and Insurance Integration

Some countries, particularly the Netherlands, have developed an interesting hybrid model where insurers combine coverage for psychotherapy with private payment for the drug component of treatment. In these cases, patients pay out-of-pocket for the psychedelic drug and certain treatment elements, while the psychotherapeutic care is covered or partially covered by insurance. This model currently operates in Dutch clinics offering ketamine and esketamine treatments, providing a potential template for future psychedelic therapy provision.

Lessons from the United States

The experience in the U.S., where out-of-pocket payment for ketamine treatment is common, offers some insights into the limitations of this approach. While private payment has allowed for the establishment of hundreds of ketamine clinics, treatment centres often struggle to attract enough patients who can afford their services. The high cost of out-of-pocket payment suggests that even when treatment facilities are available, the requirement for substantial out-of-pocket payment significantly constrains access to those who might benefit from these therapies. ■

10.5 Innovative Alternative Access Pathways

The innovative alternative access pathway represents the most theoretical of all potential routes to market for psychedelic therapies. Yet, it could prove crucial for addressing these treatments' unique challenges. This pathway would likely emerge as a government or health system-led initiative specifically designed to accommodate therapies that address key unmet needs while falling outside conventional assessment frameworks.

The Need for Alternative Pathways

For psychedelic therapies, standard assessment processes like Germany's AMNOG or England's NICE evaluations may prove particularly challenging. The need for alternative pathways stems not from seeking special dispensation for psychedelics but rather from recognising that conventional HTA expectations might be impractical or inappropriate.

The unique nature of psychedelic therapy trials, which often can not follow standard double-blind protocols, and the need for specialised treatment settings create evidence packages that differ significantly from typical pharmaceutical submissions. Psychedelic therapies might require three or four studies to meet existing evidence standards, while manufacturers typically address standard regulatory and HTA evidence needs with one or two Phase III trials.

Current Country-Specific Initiatives

The UK has made some progress in this direction through its Innovative Licensing and Access Pathway (ILAP), which aims to accelerate the time to market for innovative medicines. The pathway, relaunched in early 2025, provides enhanced regulatory guidance and connects stakeholders across the system to support study design, development, approval processes, and implementation within the national health service.

However, even this pathway ultimately requires a standard NICE (England and Wales) or SMC (Scotland) HTA review, potentially limiting its usefulness for psychedelic therapies. While a separate, standalone process designed explicitly for psychedelics might provide an alternative access route in some countries, developing such frameworks could take a decade or more, as evidenced by the slow adaptation of systems to accommodate Advanced Therapy Medicinal Products (ATMPs).

Moreover, psychedelic therapies face unique challenges compared to other innovative treatments like ATMPs. Psychedelic therapies operate in the mental health space, which traditionally receives less attention and funding than physical health conditions, faces ongoing stigma, and presents more complex challenges in demonstrating and capturing value within existing assessment frameworks.

Learning from Other Innovative Therapies

The introduction of ATMPs, such as cell and gene therapies, has provided valuable lessons. Several manufacturers in Germany and the UK have successfully negotiated innovative payment models with insurers, including pay-for-performance arrangements.

Developers and payers have successfully used this approach for treatments like Luxturna, Kymriah, and Yescarta, demonstrating how novel therapies can achieve reimbursement through creative solutions that address payer and provider needs. Healthcare systems could adopt similar models for psychedelic therapies, allowing them to measure treatment outcomes and link them to payment structures. However, payers may view these agreements differently for psychedelic therapies since these treatments cost less than recent cell and gene therapy launches and target much larger patient populations.

European Collaborative Initiatives

Across Europe, several collaborative initiatives could support alternative access pathways. The WHO/Europe Access to Novel Medicines Platform, launched following the Oslo Medicines Initiative (2020-2022), represents a significant development in this →

space. This platform brings together public and private sectors to address challenges around access to innovative treatments, particularly focusing on affordability and health system sustainability. Given the expected high costs of psychedelic therapies, this type of collaborative framework could prove valuable in developing viable access solutions.

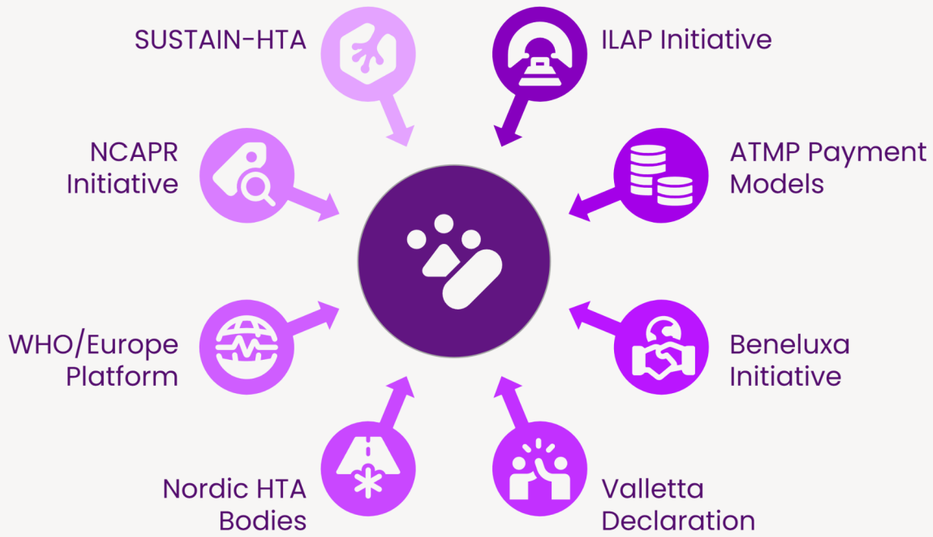
The National Competent Authorities on Pricing and Reimbursement (NCAPR) explores dynamic pricing frameworks that could suit psychedelic therapies, particularly by tying payments to long-term performance data. With funding from EU4Health and backing from the European Commission (EC), NCAPR focuses on efficiency, affordability, transparency, and innovative payment methods. These priorities align well with the challenges presented by psychedelic therapies.

Regional collaborations are also delivering some outcomes. The Beneluxa Initiative, while primarily focused on ATMPs, demonstrates how countries can work together to agree on access for innovative treatments. Belgium and the Netherlands have been particularly active in this space. Similarly, the Joint Nordic HTA Bodies and Nordic Pharmaceutical Forum show how regional cooperation can facilitate access to innovative therapies. The Valletta Declaration Group, while maintaining a lower profile, serves as a platform for information exchange and is expected to increase its activity in the coming years. These collaboratives may benefit from the introduction of EU HTA between 2025 and 2030, as the Joint Clinical Assessment (JCA) will provide a common clinical evaluation available at the same time as an EMA approval, which they can use to prioritise therapies or engagement with manufacturers.

Future Prospects and Challenges

While the development of alternative access pathways, specifically for psychedelics, remains

Potential Initiatives to Facilitate Access to Innovative Medicines



theoretical, several factors could accelerate their emergence. The SUSTAIN-HTA initiative, supporting the HTA Coordination Group and its Subgroup on Methodology, aims to align HTA methodologies across Europe. It has also stated an interest in exploring broader concepts of value and new pricing models to make evaluations more accurate and relevant. Initiatives such as this could create opportunities for more flexible approaches to evaluating psychedelic therapies. However, it may take the failure of one or more psychedelic therapies to achieve positive HTA outcomes before countries seriously consider developing alternative pathways.

The emergence of early examples, such as the Netherlands' hybrid model, where insurance covers psychotherapy while patients pay for the drug component, suggests that innovative solutions are possible. As psychedelics move closer to market, there is hope that individual countries or the European Commission will proactively discuss innovative alternative access pathways rather than waiting for conventional approaches to fail.

Implementation Considerations

Any alternative pathway must balance several key elements: rigorous evidence requirements, practical feasibility for providers, and financial sustainability for healthcare systems. Healthcare systems could adopt a more balanced approach by supporting the use of psychedelic products in real-world practice while simultaneously gathering additional evidence rather than demanding comprehensive study data packages before granting any access.

must address treatment setting requirements, therapist training and certification, outcome monitoring, and payment structures. Dynamic pricing frameworks, as explored by NCAPR, could be particularly relevant, allowing for initial uncertainty about long-term outcomes while ensuring value for healthcare systems. Such frameworks could incorporate real-world evidence collection, allowing pricing and access decisions to evolve as more data about treatment effectiveness in clinical practice becomes available. ■

10.6 Charity or Philanthropy-Based Care Services

The charitable and philanthropic pathway represents a unique aspect of psychedelic medicine, characterised by significant involvement from non-commercial stakeholders in development and potential service provision. This pathway could play a crucial role in establishing initial treatment services and funding access for specific patient groups, particularly in underserved areas of mental health and addiction services.

Non-Commercial Development Landscape

The psychedelic sector stands out for its unusually high proportion of non-commercial stakeholders involved in therapy development. Notable not-for-profit organisations such as MAPS and the Usona Institute have initiated clinical trials with psychedelics. Beckley Foundation and Heffter Research Institute have been instrumental in funding early clinical trials during the "psychedelic renaissance". More recent additions like Norrsken Mind continue this tradition of philanthropic involvement in psychedelic research and development.

Public and Philanthropic Research Funding

Public and philanthropic funding has supported psychedelic research globally, with significant commitments from both national and international bodies. The scale of this funding has been substantial, particularly in recent years. In the United States, the National Institute on Drug Abuse (NIDA) has made major investments, including nearly $4 million to Johns Hopkins University for psilocybin research in tobacco addiction, up to $14 million to Gilgamesh, and $15 million to New York University (NYU) researchers through the Defense Advanced Research Projects Agency (DARPA). Additional U.S. funding has come through the Department of Veterans Affairs (VA) and the National Institutes of Health (NIH) for various psychedelic studies.

In Europe, several major government-backed initiatives are underway. The German government has funded the EPIsoDE study investigating psilocybin for major depressive disorder. At the same time, the European Union has allocated over €6.5 million to the PsyPal project—coordinated by the University Medical Centre Groningen—which explores psilocybin therapy for psychological distress in palliative care patients. The Medical Research Council (MRC) and National Institute for Health Research (NIHR) partnership, along with developer Awakn, has funded a £2.4 million ketamine research trial in alcohol dependency, alongside funding for psilocybin research in opioid addiction and gambling. Additional European support has come from bodies such as Poland's Medical Research Agency.

While these funding amounts are significant and demonstrate growing institutional support for psychedelic research, they represent only a fraction of the total investment needed to bring psychedelic therapies through clinical trials and to market. The complete development pathway, including multiple Phase III trials and the necessary infrastructure for delivery, requires investment levels that typically exceed the resources available through public and philanthropic sources alone.

Role in Service Provision

While non-commercial entities may face challenges in managing full regulatory review and commercialisation processes, they could be vital in supporting access post-approval. Charities and non-profits become particularly important when they already support patient care in areas such as addiction services and mental healthcare.

Addiction Services Model

Addiction services provide an instructive example of potential charitable involvement. In the UK, while national smoking cessation programmes are centrally funded, drug and alcohol addiction services often operate through localised funding. They may also involve third-party providers with limited resources. The decentralised funding structure and resource limitations create opportunities for non-commercial entities to support service provision in multiple ways.

Organisations can potentially directly fund treatment services, enabling immediate access for patients who might otherwise face lengthy waiting times or financial barriers. They might also support the development of necessary infrastructure, including dedicated treatment rooms and monitoring equipment. Additionally, these entities could fund comprehensive staff training programmes to ensure the proper delivery of psychedelic therapies.

Innovative Partnership Models

Novel collaborations between commercial and non-commercial entities are emerging. An instructive example is the evolution of Awakn Life Sciences' ketamine-based alcohol dependency treatment programme, which combines public research funding (through NIHR) with innovative service delivery partnerships. Their collaboration with a mental healthcare charity and private investment company demonstrates how different stakeholders might work together to provide treatment access while sharing risks and potential returns.

Future Potential

While Europe lacks an equivalent to the powerful advocacy and funding role of the U.S. Veterans Affairs, mental health charities at national and European levels could significantly influence service provision. Even temporary charitable support during initial post-approval periods could generate valuable evidence and momentum for broader service provision across healthcare systems.

This pathway could prove particularly valuable in reaching traditionally underserved populations who might not engage with conventional healthcare services but who potentially have the most to gain from psychedelic therapies. By supporting initial access and generating real-world evidence, charitable pathways could help build the case for broader healthcare system adoption of psychedelic therapies.

However, while these funding amounts are substantial, they fall significantly short of the total investment needed to bring psychedelic therapies through clinical trials and to market. The complete development pathway, including multiple Phase III trials and the necessary infrastructure for delivery, requires investment levels that typically exceed the resources available through charitable and philanthropic sources alone. ■

10.7 Pre-Marketing Authorisation Access

Recent developments in Switzerland and Australia demonstrate emerging governmental approaches to psychedelic therapy access through special provisions.

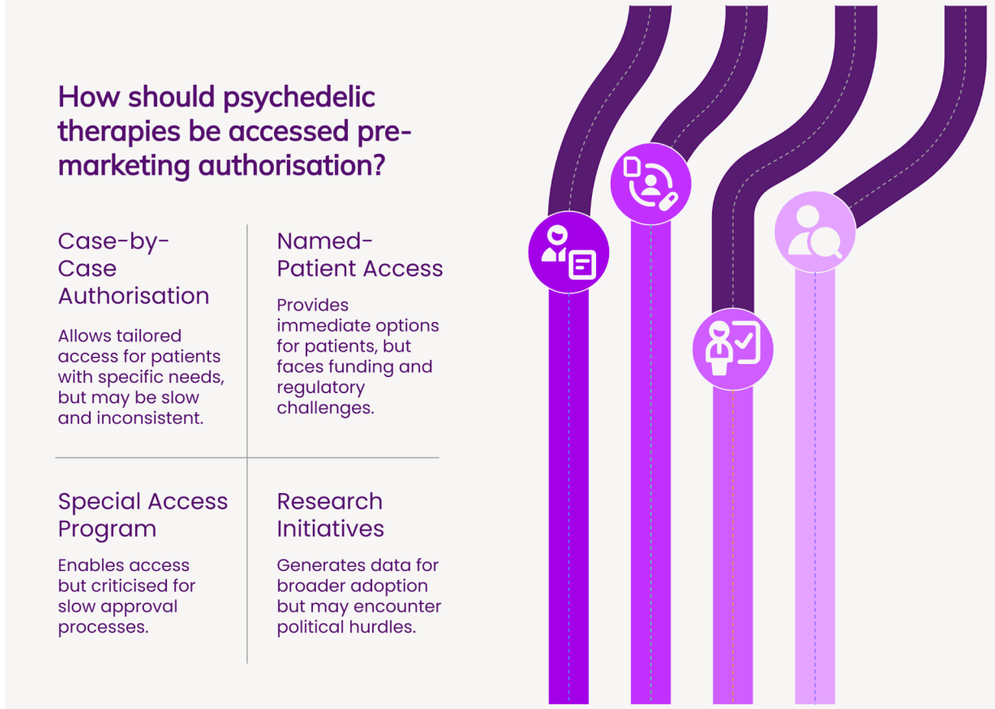
Switzerland has established a framework where psychiatrists can apply for authorisation to administer specific psychedelics, evaluating applications on a case-by-case basis. Australia made headlines when its Therapeutic Goods Administration (TGA) authorised specially licensed psychiatrists to prescribe MDMA for treatment-resistant PTSD and psilocybin for TRD, marking a significant shift in the regulatory approach. End-of-life care presents another compelling case for compassionate use access, alongside treatment-resistant conditions, given the urgent nature of patient needs and potential therapeutic benefits.

Named-Patient Access Routes

Several European countries maintain provisions for named-patient access to unapproved treatments, particularly for severe conditions or mental health emergencies. This mechanism operates outside standard health technology assessment channels, allowing clinicians to source treatments for individual patients through controlled importation pathways. These provisions are particularly relevant for patients who have exhausted conventional treatment options or face life-threatening conditions. Two key challenges in pre-authorisation access are securing funding for treatment and overcoming barriers related to Schedule 1 controlled drug status, which can significantly restrict handling and administration.

Canadian Model: Progress and Challenges

Canada's Special Access Program (SAP) represents the potential and limitations of compassionate use frameworks. The programme's implementation has drawn criticism, even though it theoretically enables eligible patients to access psilocybin and MDMA. Stakeholders note that approval processes often move slowly and inconsistently, highlighting the challenges of balancing urgent patient needs with regulatory oversight.



Dutch Initiative and Future Prospects

The Netherlands is exploring an innovative approach through its proposed MDMA research initiative. A state commission has recommended conducting a large-scale naturalistic study of MDMA therapy for PTSD. While this approach could theoretically offer a blueprint for other European countries, combining practical access with structured data collection, its implementation faces significant political hurdles. Despite the commission's evidence-based recommendations, the current political climate and ongoing debates around drug policy make swift adoption unlikely.

Operational Challenges and Considerations

While compassionate use pathways circumvent some traditional licensing requirements, they present their own challenges. Regulators must maintain robust safety monitoring while facilitating timely access. Resource requirements for outcome monitoring and data collection can be substantial, particularly in real-world settings outside controlled trials. Healthcare providers need specific training and infrastructure to deliver these treatments safely.

Strategic Importance

These pathways serve multiple strategic functions in advancing psychedelic therapy access. They provide immediate options for patients who cannot wait for full approval processes, generate real-world evidence to support broader adoption, and offer alternative treatments not yet integrated into standard reimbursement systems. While these programs may not match the scale of formal approval pathways, they represent a crucial option for urgent cases. They could catalyse broader acceptance of psychedelic therapies within healthcare systems.

Future Implications

Compassionate use and early access programs could evolve into springboards for broader medicinal legalisation under defined conditions. They create a precedent for controlled medical use while generating valuable safety and efficacy data. Although these pathways alone cannot meet the entire demand for psychedelic therapies, healthcare systems can incorporate them as an important component of a comprehensive access strategy, particularly during the transition period before establishing formal approval and reimbursement systems. ■

10.8 Continuation of Unregulated and Underground Therapeutic Use

The underground use of psychedelics for therapeutic purposes has existed for decades, operating outside formal healthcare systems and legal frameworks. While strictly illegal in most countries, enforcement varies significantly across Europe. Some regions, like the Netherlands, maintain unique positions with unregulated substances, such as psilocybin-containing truffles, being used in unregulated therapy.[28] Similar patterns of limited enforcement exist in Portugal, Spain, and the UK, where underground therapeutic networks continue to operate.

Drivers of Continued Underground Use

Several factors contribute to the persistence of underground therapeutic use. Limited access to approved treatments, long waiting lists, and lack of reimbursement for legal psychedelic therapies create barriers that drive people toward unofficial alternatives.

A growing concern is the increasing public awareness of psychedelics' therapeutic potential through media coverage and research publications. The combination of widespread publicity and limited legal access creates a particularly dangerous situation where vulnerable individuals, desperate for mental health treatment and aware of these potential benefits, may feel compelled to seek help through whatever means available. Without accessible, regulated options and insurance coverage, more people will likely turn to underground networks or unregulated above-ground providers, potentially exposing themselves to significant risks.

Even when legal options become available, approved indications often restrict access to specific patient groups, leaving others to seek alternative routes. Additionally, some communities maintain a deep-seated distrust of mainstream healthcare systems or prefer traditional healing approaches, making underground networks their preferred choice regardless of legal status.

This situation presents a critical challenge for policymakers, healthcare payers, and governments. The gap between the growing awareness of therapeutic potential and limited legitimate access creates a public health risk that cannot be addressed through prohibition alone. A comprehensive approach to regulation and access is needed to protect vulnerable individuals seeking treatment.

Safety and Quality Concerns

The unregulated nature of underground therapy presents significant risks. Practitioners' qualifications and experience vary widely without oversight, ranging from well-trained professionals operating outside the law to inexperienced practitioners. The absence of medical screening, proper containment, and emergency support systems creates serious safety concerns.

When adverse events occur, they often go unreported, limiting our understanding of risks while potentially damaging public perception of all psychedelic therapy, including legal programmes.

Data and Evidence Implications

Underground use creates a significant blind spot in our understanding of psychedelic therapy's real-world impacts. Without systematic data collection or adverse event reporting, valuable information about benefits and risks remains hidden. This gap affects research, policy development, and safety monitoring, making developing evidence-based standards for legal therapeutic use harder.

[28] While described as 'therapy', these services operate outside medical and therapeutic regulatory frameworks. Practitioners cannot legally claim therapeutic benefits or treatment outcomes, and their activities may constitute unlicensed practice of medicine or psychology in many jurisdictions. These services might more accurately be characterised as psychedelic facilitation or coaching, though such terms also raise legal and ethical considerations. The lack of clinical oversight, standardised protocols, or quality controls distinguishes these services from regulated medical or psychological treatments.

Economic and Access Considerations

Even if future legal psychedelic therapies become available, two key factors will likely sustain underground markets. First, without comprehensive insurance coverage, the high costs of approved treatments will drive many people toward more affordable underground alternatives. Second, regulatory restrictions limiting approved uses to specific conditions will leave many potential patients without legitimate access options, particularly those with conditions that fall outside approved indications.

While underground services may offer broader accessibility and lower costs, this comes with significant risks due to a lack of quality control, standardisation, and safety protocols. This parallel system could also complicate efforts to establish legitimate markets and develop sustainable reimbursement pathways, as it may undermine pricing structures and create conflicting treatment standards.

Future Outlook

Even as legal access to psychedelic therapy expands, underground use is likely to continue and potentially increase. Some patient populations may remain excluded from approved programmes, while others may prefer alternative approaches outside mainstream healthcare. This reality suggests a need for comprehensive policy approaches that address both legal access and harm reduction strategies for those who continue to seek underground treatment.

The challenge for policymakers and healthcare systems lies in acknowledging this parallel system while working to expand safe, legal access. The experiences of countries like the Netherlands, with its quasi-legal psychedelic markets, may offer insights into managing the interface between underground and regulated therapeutic use. However, the primary goal should remain to establish robust, accessible, and regulated therapeutic pathways that reduce the need for underground alternatives.

Ironically, when regulators and payers restrict access to psychedelic therapies due to evidence gaps or uncertainties, patients may ultimately seek treatment through underground channels where risks are higher and oversight is minimal–effectively undermining the very protections these restrictions aim to provide. ■

10.9 Cross-Border Healthcare and Medical Tourism

Even before the formal approval of psychedelic therapies, patients have been travelling within Europe to access treatments in countries with more permissive frameworks. The Netherlands, Spain, and Portugal have become informal hubs for those seeking psychedelic treatment, though these services often operate in legal grey areas. Some clinics openly advertise to international patients, while others maintain more discrete operations.

Future Framework Under EU Directives

The EU Cross-Border Healthcare Directive could provide a formal pathway for accessing psychedelic therapies once they receive approval in some Member States. This directive allows EU citizens to seek medical treatment in other EU countries and claim reimbursement up to the cost level of equivalent treatment in their home country. As different EU countries adopt varying approaches to psychedelic therapy approval and reimbursement, this mechanism could become increasingly relevant.

Practical Considerations

While cross-border healthcare offers a potential solution for patients in countries with restricted access, several practical challenges exist. Treatment protocols for psychedelic therapy often require multiple sessions and extended stays, making international travel logistically complex and expensive. Distance complicates integration sessions and follow-up care, and language barriers could affect the therapeutic process. Additionally, home country healthcare systems might resist reimbursing treatments not yet approved in their jurisdiction.

Strategic Implications

Cross-border access could create pressure for the harmonisation of psychedelic therapy regulations across Europe. Countries that become early adopters might influence broader acceptance by demonstrating safe and effective delivery models. However, this pathway will likely remain a niche option, primarily serving patients with sufficient resources and mobility to access care abroad. Developing cross-border treatment networks could nonetheless contribute valuable data on different regulatory and delivery approaches. ■

11 Critical Observations From Collaborators

The integration of psychedelic therapies into European healthcare systems represents a complex challenge that extends beyond the scope of traditional pharmaceutical market access. While previous chapters have examined specific aspects of regulatory pathways, reimbursement mechanisms, and implementation approaches, this chapter offers broader perspectives from key stakeholders in the field.

Our contributors bring diverse expertise spanning commercial strategy, healthcare systems, policy development, and market analysis. Martin Gisby of Magnetar Access, offers insights on commercial strategy and reimbursement pathways; Floris Wolswijk, founder of Blossom, examines the future of psychedelic reimbursement in The Netherlands; Josh Hardman of Psychedelic Alpha, provides analysis of market access challenges and opportunities; Tadeusz Hawrot from PAREA, explores lessons from HIV/AIDS activism for mental health advocacy; and Viktor Chvátal and Sumudu Gouri Boyina from PsychedelicsEUROPE, review country-specific perspectives with a focus on the Czech Republic.

These essays deliberately look beyond immediate regulatory and reimbursement hurdles to examine longer-term questions of sustainability, scalability, and systemic impact. They highlight both opportunities and potential pitfalls, offering insights that may help stakeholders avoid common misconceptions and better prepare for the complexities ahead. While the contributors' views may appear cautionary, they reflect a shared commitment to ensuring that psychedelic therapies can be implemented in ways that are both practically feasible and genuinely beneficial to European healthcare systems and their patients.

Through these diverse perspectives, we aim to contribute to a more nuanced understanding of what the successful integration of psychedelic therapies might look like and what it will take to achieve it. ■

11.1 Reducing the Risks for Commercialisation of Psychedelics

Martin Gisby

One of the key drivers of psychedelics research and clinical development is the for-profit commercialisation model of medicine, which is similar to most other areas of medicine. There are, however, many other entities in the psychedelics research landscape, including non-profits, charities and philanthropic funds, and academic researchers. While there is plenty of passionate debate on the merits of commercialising psychedelics and what economic & clinical model is morally appropriate, the commercial medicines route is the most likely route to secure broad and legal access to psychedelics for patients suffering from certain conditions.

A key question is which groups are going to have the resources and capability to prepare requests for marketing authorisations, maintain those licenses across Europe, and provide the support to clinicians and health systems to use these therapies safely. The resources required to do so are significant, meaning that even non-profit driven approaches require a clear commercial model, which will need to be underpinned by securing pricing, reimbursement and market access across countries. With this in mind, the following sections seek to highlight key considerations and opportunity/risk trade-offs that developers will need to make to balance the therapeutic potential of psychedelic treatments against hard economic truths.

Which Patient Population?

The population of interest for treatment with a therapy—the target patient population—is a central pillar of both the clinical and commercial strategy. With potential benefits across different conditions and potentially broad applicability, the desire to choose a broad patient group and address the needs of a greater number of patients is obvious. Developers and researchers must be cognisant that—in Europe at least—medicines with indications covering broad mental health conditions have struggled to commercialise successfully over the last decade.

When established treatments consist primarily of inexpensive generic medicines, new therapies face downward pricing pressure, either directly through payer price referencing and negotiations, or indirectly through the way this influences health economic outcomes like cost-effectiveness. Larger populations also predictably cause greater concern to payers over the additional budget impact. Therefore, therapy indications encompassing broad patient groups, such as Major Depressive Disorder (MDD) and Generalised Anxiety Disorder (GAD), will be very difficult to commercialise in Europe through national health systems.

A more risk-managed approach for developers in Europe is to focus on smaller populations with the greatest clinical need and demonstrate a significant clinical benefit. This increases the likelihood of positive HTAs and more favourable pricing and reimbursement decisions. It may seem unethical not to pursue broader patient populations if the therapeutic potential is there, but a poor commercialisation strategy in Europe may lead to insufficient revenue to cover ongoing commercialisation costs, or potentially to no market access at all.

It is also worth considering that even if pricing and reimbursement hurdles were not present, for many years after psychedelics receive a marketing approval, there is unlikely to be enough infrastructure to support use across large populations, and clinician advocacy for using these therapies widely will not be immediate.

In summary, careful selection of the target population is key for Europe, and making these decisions early and in the context of a future commercial framework is likely to be in the best interests of future patient access to these therapies.

Beware the Common Pitfalls of Drug Commercialisation in Europe

Although discussed in the report, it is important to call out some key considerations for developers. It is important not to assume that where good clinical outcomes are achievable, reimbursement and market access are assured. There is a long list of drugs and innovative therapies with excellent efficacy that have failed to achieve market access in Europe, including those with far less complex evidence packages and administration requirements than psychedelics have.

It is common not to be able to meet the value criteria of all country payers, through, for example, variations in expectations around study comparators, study endpoints, and what value is accepted. Early clinical development decisions tend to set the path to success or failure. Focusing initially on a smaller set of countries where the product is aiming to be commercialised helps prioritise the study, evidence and health economic needs. Developers frequently focus on PRMA processes in Germany, France, Italy, Spain and the UK to feed this into development decisions from Phase II clinical study design and onwards.

A critical approach in today's drug market is to be flexible in considering how to enter into European markets, with tailoring of target patient groups, careful positioning in the local clinical pathway, and adaptive pricing helping navigate country-specific hurdles. Maintaining a rigid view and demanding absolute consistency across countries—even if coming from an ethical perspective on patient equity—risks leading to no access situations as payers do not need to or wish to consider alignment with other country systems or value frameworks.

Unique Psychedelics Commercialisation Issues - Entering Into New Territory

There are some 'new-to-everyone' aspects of psychedelics that present as uncertainties and potential risks that have not all been covered in this report and that developers should keep in mind:

- Multiple groups are completing clinical studies with the same active ingredient, e.g. psilocybin, LSD, MDMA. It is normal for only one developer to have the full intellectual property rights to commercialise a drug, but not so for psychedelics. This raises questions on what impacts this might have on critical commercial processes such as; intellectual property rights, regulatory exclusivity, pricing pathways and price referencing, and the potential for drug substitution.
- There has been a pivot to optimise psychedelic clinical studies to improve acceptability by regulatory bodies, including improving blinding, reducing psychotherapeutic components of care, and focussing on endpoints favoured by regulators. In this pivot, there is a risk that the already significant gap between what regulators wish to see and what payers expect to see will be even more pronounced for psychedelics. Developers must make any such decisions with both the regulator and payer in mind, and find the appropriate balance of opportunity and risk for the specific therapy and the specific indication - regulatory approval without reimbursement is a scenario all stakeholders wish to avoid.
- Scheduling of drugs is country-specific, as are re-scheduling processes. There is a need to understand how these processes will work, the time involved, and the potential scenarios that may play out. These need to be accommodated in market access planning and timelines, as well as working through any specific hurdles to implementation that remain after re-scheduling.

In addition to the above, the potential complexity of psychedelics therapy, i.e. an acutely psychoactive drug, plus therapeutic components, plus in-clinic treatment over hours—as well discussed within the report—are also new territory for developers, clinicians and health systems. This differentiated approach from traditional drug treatment, along with uncertainties such as those listed above, is a key reason why large pharma have shown limited interest in taking first-generation psychedelics assets into their drug pipelines and leading this commercialisation.

When More than One Market Access Pathway May Be the Optimal Approach

Commercialisation of therapies through the national HTA and reimbursement pathways is the most common route to market, and this should remain a goal across psychedelics stakeholders as it holds the potential for the greatest access and greatest equity for patients. This route is, however, likely to require some modification to adequately evaluate psychedelics and support optimal implementation. It would seem prudent for more than one reason for developers to look at additional market access pathways, such as those outlined in Chapter 10, including private insurer pathways, patient out-of-pocket, and charity or philanthropy-based care services.

If the national reimbursement route fails to deliver market access, these more restricted pathways may be the primary access route for patients. However, it is worth acknowledging that even in a situation where the national reimbursement pathway endorses reimbursement and access, the local implementation may be slow and restricted to certain sites of care. These additional routes of access, driven by private and charitable providers, are often more agile and quick to embrace new treatment approaches, and could play a key role in the early adoption of therapies, generating early insights into real-world practice, and thereby accelerating wider use in the clinical community. In particular, charity or philanthropic-based services often reach segments of society that are less likely to engage or be within the core health service provision. Developers should embrace partnerships that allow for these additional routes to be planned and implemented as a complementary approach to the national reimbursement system.

How Can All This Possibly Be Considered and Planned For?

With the number and variation in healthcare systems and reimbursement processes across Europe being so great, and with so many novel aspects of psychedelic therapy to consider, it is a potentially overwhelming situations for developers, especially if teams are small groups that lack prior experience of commercialising therapies, or the focus is on North America, with Europe further down the priorities list.

The key is to prioritise the patient group, the countries of primary interest, and the most relevant potential market access pathways, then map out when certain decisions need to be made. These decisions can be evaluated in turn to ensure the market access strategy and the commercial model are valid and steadily refined as the therapy moves through clinical development and closer to the market. A plethora of experienced consultants and advisors can be tapped into along the way, but a priority should be to identify the key stakeholders in the health system and engage with them as early as possible.

Many of the challenges to psychedelics market access do not have clear solutions and joint-working will be key, which means engagement at the earliest opportunity, a level of transparency on gaps in knowledge from all sides, and a flexible and agile approach to progressing common solutions. The alternative is to wait and have these gaps exposed very publicly at the point of market entry, but without the time or level of common stakeholder alignment in place to implement proper solutions. The latter scenario will leave many stakeholders unsatisfied and ultimately the patients with unmet needs who these promising treatment options may benefit will be penalised. ■

11.2 The Future of Psychedelic Reimbursement in The Netherlands

Floris Wolswijk

Even in a Best-Case Scenario, Capacity is a Major Bottleneck

Reimbursing psychedelic therapy is an important step, but it will not be enough. Even if approval, pricing, and integration go smoothly, there is a bigger issue: A lack of therapists to meet demand.

Unlike antidepressants, which a healthcare provider can prescribe in minutes, psychedelic therapy is resource-intensive. Based on discussions with trial therapists and psychedelic facilitators, most can manage one session per week. This limitation is due to the intensive nature of the therapy–sessions demand significant emotional processing and recovery time, precluding the possibility of multiple sessions per week. That is, at most, 50 patients per year per therapist, or 25 if two sessions are needed.

The Netherlands has 15,000 psychologists and 3,500 psychiatrists, treating around 1.5 million patients annually—an average of 80 per professional. Even if 1,000 therapists were trained in psychedelic therapy, they could only treat 50,000 people annually. While that may sound like a lot, it falls far short of demand. In the Netherlands, approximately 350,000 people suffer from treatment-resistant mental health conditions, including depression, PTSD, anxiety disorders, and alcohol addiction, who do not respond to standard care.

While psychedelic therapy will join the existing treatment landscape, its resource-intensive nature presents unique implementation challenges. Drug developers are actively exploring less therapist-dependent models, where nurses or other healthcare professionals could supervise sessions with reduced psychological support. While this might help address the capacity bottleneck, it represents a significant departure from the intensive therapeutic approach used in clinical trials. Understanding these evolving treatment models and their implications will be crucial as these therapies enter clinical practice.

The One-and-Done Myth vs. The Reality of Re-Treatment Needs

Advocates often frame psychedelic therapy as a one-off treatment—take a dose, process the experience, and move on. Such framing makes it sound simple, more like surgery than long-term psychiatric care.

However, mental health rarely works in such a binary manner. While psychedelic therapy for PTSD may approach a one-off model—where effective trauma processing might obviate further treatment—depression, anxiety, and addiction are different. They are not necessarily tied to discrete past events but to ongoing struggles shaped by stress and life circumstances.

A single psychedelic session may trigger significant change, yet for many, the benefits diminish over time, necessitating re-treatment. If, for example, half of the treated patients require another session within a year or two, the demand for treatment resources will double over time. This pattern of retreatment only exacerbates an already limited supply of trained professionals.

Health insurers and policymakers tend to focus on the cost per treatment. However, if psychedelic therapy necessitates repeat sessions without demonstrable improvements in long-term outcomes, in that case, the health system will incur higher cumulative costs without a corresponding reduction in the burden of other treatments. In other words, without a clear plan that shows improved outcomes, psychedelic therapy may simply shift costs without alleviating the overall strain on mental health services.

The Growing Pressure on an Already Overloaded System

Psychedelic therapy is entering a mental healthcare system already at its limit. The Netherlands has long faced waiting lists, staff shortages, and rising costs—problems that have only worsened.

Demand for mental health services has surged, partly due to the lasting effects of COVID-19. More people than ever need treatment for depression, anxiety, and trauma. Simultaneously, burnout drives many professionals out of the field, further restricting access to care.

Psychiatric treatments, including interventions such as rTMS and esketamine, are becoming more expensive. They require specialist staff and dedicated facilities. Although effective, these treatments are challenging to scale. Psychedelic therapy faces the same hurdle—it is not a pill but a time-intensive treatment requiring highly trained professionals.

The strain on healthcare providers' time raises a key question: Where does the time come from? No extra therapists are waiting to deliver psychedelic therapy. Every session takes hours a healthcare provider could have spent on another patient. Without more resources, other treatments will suffer.

Then, there is the issue of funding. Will psychedelic therapy fit within existing mental health budgets, or will it require additional funds? If these treatments do not yield better outcomes than existing ones, we risk incurring extra costs without reducing the overall care burden. Reimbursement models must account for this possibility.

Treatment Innovation vs. Systemic Constraints

Psychedelic therapy is not the first mental health treatment to show promise—yet promise doesn't always translate to access. Regulators approved esketamine for depression, yet many patients still cannot obtain it due to its high cost, need for supervision, and clinical delivery requirements. Similarly, neuromodulation techniques such as rTMS offer strong results for treatment-resistant depression, but the expensive equipment and shortage of trained professionals limit its scalability.

Even traditional psychotherapy struggles with access. Therapy works, but the supply of therapists is grossly inadequate, with long waiting lists and a growing gap between demand and availability. Psychedelic therapy is no exception. It is not solely a matter of treatment efficacy—the fundamental question is whether the healthcare system can deliver it at scale.

If psychedelic therapy remains a niche treatment available only in specialist clinics, it will benefit some patients without easing the broader systemic burden. Moreover, expanding too quickly without a concurrent workforce expansion will strain resources and create new bottlenecks. A key consideration is whether psychedelics can reduce long-term care requirements for patients with chronic conditions, thereby positively impacting overall system capacity over time. However, achieving such outcomes will demand not only significant therapeutic breakthroughs but also large-scale treatment programmes and robust outcome data.

Are 2nd- and 3rd-Generation Psychedelics Part of the Answer?

If psychedelic therapy is going to reach more people, a fundamental change is necessary. The current model is slow, expensive, and overly dependent on a limited number of trained therapists. Even with full reimbursement, demand will far exceed supply.

This challenge has spurred discussion about next-generation psychedelic treatments. Instead of integrating MDMA and psilocybin into an already overburdened system, researchers are exploring ways to render treatment faster, more scalable, and easier to access. One approach involves modifying existing psychedelics. Several companies are developing shorter-acting versions of MDMA and psilocybin; if a session were reduced from eight hours to three, therapists could potentially treat more patients. These second-generation psychedelics do not alter the core treatment model but could make it more practical and affordable.

A more radical alternative is the development of 'psychoplastogens' that do not require therapist supervision. These third-generation psychedelics aim to retain therapeutic benefits without the accompanying hallucinogenic effects, allowing for at-home administration much like conventional antidepressants. Even if this class is not as efficacious as first- or second-generation psychedelics, the ⤴

model of introducing drugs with incremental benefits over existing treatments—ones that healthcare providers can easily prescribe to thousands of patients—is a tried and tested approach that healthcare systems can successfully implement. While not intended to replace therapist-led treatment entirely, these innovations offer an alternative that might relieve some of the strain on an already stretched system.

Psychedelic therapy has the potential to help those who have exhausted other treatment options. However, securing reimbursement is only the first step. Without a strategic plan to address capacity constraints, workforce shortages, and long-term treatment needs, we risk creating a system that simply shifts costs rather than reducing the overall burden on mental health services. ■

11.3 Beyond Guinea Pigs: Ensuring Access to Psychedelic Therapies for Europeans

Josh Hardman

With several pivotal programs currently underway in the United States, we could see the first psychedelic therapies approved by a regulator within the next few years. But, the timeline for approval and market access in Europe remains uncertain, with the U.S. being the primary focus for psychedelic drug developers.

While any approval, anywhere in the world, will rightly be viewed as a momentous milestone for the field, it will only be the starting line for making these therapies available to those who might benefit most; especially in Europe, where this report focuses.

That is why psychedelic drug developers, policymakers, payors, regulators, healthcare practitioners and systems, patient advocacy groups, and other stakeholders must begin the work of scoping out these unique medicines' integration into the complex systems of Europe today.

Perhaps most foundationally, psychedelic drug development programs must produce data that allows health technology assessment (HTA) bodies to compare these relatively expensive and complex interventions to the standard of care. Such programs should give HTAs confidence in modelling costs and benefits over the medium term by providing reliable inputs to such models, including elements such as data on durability. While European HTAs have similarities to one another, drug developers might be wise to design programs and data packets with specific markets and assessors in mind.

They needn't go it alone, however, with evidence suggesting that early engagement with HTAs can lead to faster review and market access timelines. Both Maignen and Kusel (2020) and Wang et al. (2024) show that sponsors that used the UK's NICE scientific advice pathway shaved months off their eventual appraisal processes.

Some issues are outside of the control of drug developers, however. Those include a general lack of funding for behavioural and mental healthcare interventions versus other fields of medicine like oncology in many of the EU Member States and the UK; HTA models that often valorise costs and benefits narrowly at the healthcare level, as opposed to recognising those realised at the societal level; and, in many cases, underfunded healthcare systems that have stretched budgets and resourcing shortfalls. Take the UK, for example, where I live: There is not exactly a surplus of specialised treatment environments or trained professionals. That raises all sorts of questions around service readiness or the likelihood of equitable access to psychedelic therapies, if approved—the high upfront costs and logistical burdens of psychedelic therapies would need to be rationalised against the operational realities of our National Health Service.

While drug developers must be attentive to developing interventions that can ultimately plug into existing healthcare systems and produce relevant data to support their reimbursement, there is room for innovation and implementation-readiness activity to be carried out by other stakeholders. For example, government-funded studies could support the exploration of alternative delivery paradigms for psychedelic therapies to increase scalability and reduce resource intensity. Those might include things like group or simultaneous dosing and/or preparation/integration sessions.

Governments and other non-industry research priorities might be carried out in the post-approval context, too. Those could include pharmacoeconomic or head-to-head studies that seek to ascertain the value of one therapy over another. In the U.S., for example, the Patient-Centered Outcomes Research Institute (PCORI) is funding a comparative effectiveness study of esketamine (Spravato) vs. IV racemic ketamine in treatment-resistant depression. Such studies might be of particular relevance to European countries that have taxpayer-funded healthcare systems, as it is in the interest of the public purse to determine the relative value of interventions.

While it might be some time before we see generic psychedelics come to market in Europe, owing to patents and other exclusivity periods, these studies could at least put any approved therapies head-to-head with existing treatment options.

While "multi-stakeholder approach" often strikes me as an empty term, here is a case where it is surely appropriate! As such, I am pleased to have made a small contribution to this report, which aims to provide various stakeholders with insights into the state of play of psychedelics and reimbursement pathways in Europe, but also what we hope is actionable advice, especially that contained in Chapter 8.

To be sure, none of this is straightforward. Perhaps that is why many psychedelic drug developers are looking to side-step the complicating factors of long-duration dosing sessions and accompanying psychotherapy by moving toward shorter-duration psychedelic-based medicines that are administered in increasingly hands-off protocols. In other cases, drug developers are aiming to engineer out the trip entirely, though this report does not look substantially at this development.

But, even shorter-acting psychedelics delivered within a very slim psychological support protocol might face challenges in Europe. Look at Spravato, for example. Despite the backing of a company worth $375+ billion, the product's availability and reimbursement across the bloc and in the UK remains uneven, as is explored in Section 2.2.2. And yet, Spravato is still a blockbuster drug thanks to strong sales in the U.S., which remains the key market of focus for most developers of new drugs.

The challenge is real, then, but nowhere near that which Europe and its citizens face when it comes to mental and behavioural health. And as I said in Brussels in late 2023, I fear that if we do not focus on ensuring access to innovative mental health treatments in Europe during their development, we risk Europeans becoming guinea pigs (Greenacre, 2023). What I meant is that we could see a scenario where Europeans serve as test subjects in the early- and mid-stage clinical trials of such interventions as they have done in the psychedelics realm—but do not realise the benefits of such research through access to innovative therapies after they are approved in jurisdictions like the U.S.

But through a proactive approach, the genuine engagement of appropriate stakeholders, and perhaps the leveraging of innovative risk-sharing programs and Member States, psychedelic therapies just might 'work' for Europeans. ■

11.4 From Crisis to Change: What Mental Health Advocacy Can Learn From the HIV Movement

Tadeusz Hawrot

Mental health is critically important to everyone, everywhere. Yet, it stands out as an area with some of the most glaring unmet needs. Psychedelic therapies have the potential to address critical gaps in treatment for various mental health conditions in Europe. However, before reaching patients, they must first gain approval from the European Medicines Agency (EMA), followed by integration into national healthcare systems for accessibility and reimbursement.

Europe has been a fertile ground for psychedelic research, with numerous early and mid-stage clinical trials underway. The contributions of European scientists, research institutions, and study participants have driven this progress. Despite these advancements, the continent faces a significant bottleneck: a lack of late-stage clinical programmes necessary to secure regulatory approval. Based on current timelines, it appears unlikely that any psychedelic therapy will receive EMA approval before the end of the decade. Even after approval, national reimbursement systems will likely require additional years to make these treatments accessible to patients.

One key factor identified in this report that could accelerate this process is clinical advocacy. The presence of researchers, clinical groups, and patient organisations actively advocating can positively influence access timelines.

The history of the HIV treatment movement offers valuable lessons in this regard.

Activists built the success of HIV/AIDS advocacy on strategies that can inform psychedelic therapy and mental health advocacy. A key element was activists' deep engagement with science. Activist groups didn't just advocate—they educated themselves to challenge regulators, pharmaceutical companies, and research institutions. Their expertise in clinical trial design, drug approval, and policy allowed them to influence decision-making.

Another defining strategy was combining public pressure with institutional engagement. Protests and civil disobedience brought attention to the crisis, while trained representatives worked inside regulatory and funding agencies to shape policy. This "inside-outside" approach ensured that those most affected had a voice in decision-making.

HIV/AIDS activists also mobilised affected communities, turning fear and grief into an organised movement. Those directly impacted took action, refusing to wait for change. Psychedelic and mental health advocacy must do the same, catering for patients, families, and professionals who understand the urgency of better treatment options. Their voices highlight the consequences of regulatory delays and the need for access.

Transparency was another cornerstone of HIV/AIDS activism. Activists pushed for openness in drug pricing, clinical trial data, and regulatory processes, ensuring treatments were not just developed but also made accessible. Psychedelic and mental health advocates must demand similar accountability to prevent therapies from being limited to expensive private clinics, ensuring broader public access.

Perhaps one of the most significant achievements of HIV/AIDS activism was its success in shifting public perception. In the early years of the epidemic, the public heavily stigmatised HIV, associating it with marginalised communities and moral judgment rather than treating it as a public health crisis. Activists worked relentlessly to change this narrative, framing HIV treatment as a human rights issue and pushing for broad-based political and financial commitments. Psychedelic therapies face a different but related challenge—decades of prohibition, underfunding, and misinformation have shaped public attitudes, making regulatory progress slower and more fraught with controversy. Advocacy efforts must work to change this narrative, establishing them as legitimate medical interventions for urgent mental health needs.

Finally, securing sustained political and financial support was crucial to the HIV/AIDS response, leading to major funding initiatives and policy shifts. Psychedelic and mental health advocates must do the same, ensuring research, clinical trials, and reimbursement pathways receive necessary investment. Engaging with regulators and integrating these treatments into broader health strategies at the national and EU levels will be essential for long-term impact.

For those interested in the impact of activism on healthcare, How to Survive a Plague chronicles how ACT UP and TAG activists, many with no prior expertise, became key players in HIV/AIDS policy, forcing action from governments and pharma. The film captures their protests, negotiations, and lasting impact—offering lessons still relevant for psychedelic and mental health advocacy (*surviveaplague.com*).

Recognising the impact that coordinated advocacy can have, organisations like PAREA strive to mobilise a broad coalition of stakeholders—including people with lived experience, scientists, clinicians, and civil society groups—to advance policy discussions and regulatory progress. By fostering dialogue between those developing psychedelic therapies and those in charge of approving and funding them, we aim to ensure that promising treatments do not remain locked behind bureaucratic or financial barriers.

The lessons from HIV/AIDS activism demonstrate that meaningful change requires a combination of expertise, organisation, public pressure, and persistence. By adopting these strategies, psychedelic and mental health advocates can accelerate the process of making these treatments widely available, ensuring that scientific progress translates into real-world impact for people living with mental health conditions. ■

11.5 Advancing Psychedelic Therapy Reimbursement in the Czech Republic

Viktor Chvátal and Sumudu Gouri Boyina

To successfully advance the reimbursement of psychedelic therapies, advocacy must operate at both the EU and national levels. Based on the Treaty on the Functioning of the European Union (TFEU), public health falls within the responsibility of the EU Member States. The divergence of the national healthcare systems further strengthens this reality. Nevertheless, in the last few years, we have seen a growing interest in the EU institutions in health and mental health. Additionally, the current pressure of the new EU establishment on "competitiveness" and "resilience" creates a general discursive framework towards which the emerging sector of psychedelic therapies should be able to articulate its positions and advocacy narratives.

In multi-level, mutually interconnected governance, the EU needs active Member States and their best practices to catalyse discussion in Brussels. For example, a domestic cost-effectiveness study would advance psychedelic therapies at the Member State level while providing partial answers to current major European challenges.

The Czech Republic, during its Presidency of the Council of the EU in 2022, put mental health back on the top of Europe's agenda through the organisation of an international governmental conference titled "Resilient Mental Health in the European Union". With the participation of PsychedelicsEUROPE, part of the conference focused on psychedelic therapies. Overall, the advanced psychedelic ecosystem in the Czech Republic allows the country to aspire to a position as a regional role model when it comes to psychedelic therapies.

Moreover, the Czech Republic offers an example of the long-term tradition of evidence-informed policymaking regarding illicit substances. For example, the progressive Act on Psychomodulatory Substances came into force on January 1, 2025. ⤴

Regarding emerging novel mental health treatments, the Czech Republic was among the first EU countries to provide ketamine therapy (PSYON clinic), which is now partially reimbursed by major public health insurance funds.

To this date, neither the EU nor Member State level discussion has sufficiently grasped the topic of advancing the regulatory framework, reimbursement schemes, or budgets. While Brussels waits to see if the new Commission will devote the same attention to mental health as the last one (a situation mainly triggered by the impact of COVID-19 and the war in Ukraine), political lobbying at the national level is often fragmented and lacks both well-defined objectives and project management.

Currently, the emerging sector of psychedelic therapies in the Czech Republic (as in other EU Member States) lacks a cost-effectiveness study that would foster structured dialogue with regulators and payers. Indeed, engaging key stakeholders in budgetary discussions would showcase the sector's maturity vis a vis state authorities that are used to this kind of exchange with representatives of traditional therapies.

Simultaneously, the growing pool of treatment providers in the Czech Republic is neither collectively organised in advocacy terms nor clearly defined in terms of their vested regulatory interests. The state is rather ubiquitous in the primarily public Czech healthcare system, further increasing the need for a comprehensive public affairs strategy that would potentially speed up the integration of psychedelic therapies into a national healthcare system.

From the broader perspective of Central and Eastern Europe (CEE), the Russia-induced war in Ukraine represents another part of a contextual mosaic of psychedelic therapies. Thanks to migration and geographical proximity, post-traumatic stress disorder (PTSD) has become an important topic not only for Ukraine but also in particular for all EU countries. In this regard, PsychedelicsEUROPE co-organised a governmental event in May 2024 to provide a platform for both Czech and Ukrainian stakeholders to discuss the potential of psychedelic therapies in PTSD treatment. The follow-up event planned for mid-June 2025 aims to introduce fresh data to decision-makers, regulators and payers to further elaborate on both cost-effectivity and the PTSD angle of psychedelic therapy.

A joint memorandum of experts will be adopted at this event and will be formally handed over to the new Czech government following the general parliamentary elections in Autumn 2025. This aims to secure continuity in a constructive regulatory exchange between experts and advocates for psychedelic therapies and state authorities on topics of critical importance, including reimbursement schemes. Amongst other things, it should be a joint interest of engaged stakeholders in the Czech Republic to motivate the state apparatus to emulate the Dutch model and establish a State Committee that would investigate the use of specific substances within the framework of psychedelic therapies. ■

Glossary of Terms and Concepts

12

This glossary provides definitions of technical terms used throughout the report for clarity and accessibility. The reimbursement of psychedelic therapies involves complex terminology from multiple fields, including pharmaceuticals, mental healthcare, regulatory policy, and health economics. Whether you are a healthcare professional, policymaker, researcher, or patient advocate, understanding these terms is essential for engaging with the material effectively.

The terms defined here range from specific aspects of psychedelic treatments (such as 'set and setting' or 'integration therapy') to complex reimbursement concepts (like 'health technology assessment' and 'quality-adjusted life year'). Each definition aims to be comprehensive yet accessible, avoiding unnecessary jargon while preserving accuracy.

12.1 Purpose of the Glossary

This glossary also serves as a quick reference guide. Terms are organised by category—psychedelic therapy terms, clinical trial terminology, reimbursement and health economics vocabulary, and regulatory language—allowing readers to quickly locate definitions as they encounter unfamiliar terms in the main text.

We recommend reviewing relevant glossary sections before reading the corresponding chapters for readers new to psychedelic medicine or healthcare reimbursement. This will help establish a foundation for understanding the more detailed discussions that follow. ■

12.2 Psychedelic Therapy Terms

Psychedelic Compounds

Psychedelics encompass a broad class of psychoactive compounds that can induce significant alterations in perception, mood, and consciousness. These substances are typically categorised into several groups:

Classical Psychedelics refers to compounds that primarily act on serotonin 5-HT2A receptors. This group includes naturally occurring substances like psilocybin and mescaline, as well as semi-synthetic compounds like LSD. These substances typically produce profound changes in consciousness, including alterations in perception, emotion, and cognition.

Psilocybin (4-phosphoryloxy-N,N-dimethyl-tryptamine, 4-PO-DMT) is a naturally occurring compound found in over 200 species of "magic" mushrooms. When ingested, it is converted to psilocin in the body, which produces psychedelic effects lasting 4-6 hours. This psychedelic is currently being investigated for (treatment-resistant) depression, end-of-life anxiety, and addiction disorders.

LSD (Lysergic Acid Diethylamide, acid, lucy) is a semi-synthetic compound first synthesised from ergot alkaloids in 1938. It produces powerful psychedelic effects lasting 8-12 hours. LSD is being studied for anxiety disorders, depression, and addiction.

MDMA (3,4-Methylenedioxymethamphetamine, midomafetamine, molly, XTC) is a synthetic compound that produces distinctive empathogenic effects, enhancing feelings of empathy and emotional openness. Unlike classical psychedelics, MDMA primarily affects the release and reuptake of serotonin, dopamine, and norepinephrine. It is being mainly studied for PTSD treatment.

Ketamine (Ketalar, Vitamin K), while not a classical psychedelic, is a dissociative anaesthetic that can produce profound alterations in consciousness. Its rapid antidepressant effects have led to the development of an esketamine nasal spray for (treatment-resistant) depression (**Spravato**).

DMT (N,N-Dimethyltryptamine) is a powerful, short-acting psychedelic found naturally in many plants and animals, including humans. When combined with monoamine oxidase inhibitors (MAOIs) in **ayahuasca**, its effects become orally active and longer-lasting.

5-MeO-DMT is a potent psychedelic compound found in various plant species and the Sonoran Desert toad. It produces intense but brief psychedelic experiences and is being investigated for depression and anxiety disorders.

Psychoplastogens represent a newer category of compounds designed to produce therapeutic effects similar to psychedelics but without acute hallucinogenic effects. These compounds aim to promote neural plasticity while minimising perceptual alterations.

Treatment Components

Psychedelic therapy describes the structured use of psychedelic compounds within a broader therapeutic framework. The term encompasses the full spectrum of approaches—from pharmaceutical models prioritising the psychedelic compound to integrative therapeutic models where the drug serves as a catalyst within a comprehensive psychological treatment programme.

Psychedelic-Assisted Therapy (PAT), or psychedelic-assisted psychotherapy, emphasises the adjunctive role of the psychedelic compound within a therapeutic framework. It follows a three-phase model: preparation sessions, supervised dosing sessions, and integration therapy. This approach emphasises the central role of therapeutic processing and the therapeutic alliance in facilitating psychological change alongside the pharmacological effects of the psychedelic compound.

MDMA-Assisted Therapy (MDMA-AT, MAT) represents a specific form of PAT using MDMA. It typically involves 2-3 monthly eight-hour dosing →

sessions, with multiple preparation and integration sessions. The therapy leverages MDMA's empathogenic effects to enhance therapeutic processing, particularly for trauma-related conditions like PTSD.

Therapeutic Approaches vary across the spectrum of psychedelic treatments. More intensive therapeutic models place the therapeutic relationship and psychological processing at the centre of treatment, viewing the drug as a catalyst for deeper psychological work. In contrast, minimal 'psychological support' models emphasise a more limited role for the therapist, focusing primarily on ensuring safety and comfort during drug administration while attributing therapeutic benefits primarily to the pharmacological effects of the compound itself.

Preparation involves structured sessions before psychedelic administration to establish therapeutic rapport, set intentions, address concerns, and prepare the patient psychologically for the experience. This phase typically includes medical screening, psychological assessment, discussion of personal history and treatment goals, and education about the psychedelic experience.

Set and Setting refers to two critical factors in psychedelic therapy. 'Set' encompasses the patient's mindset, intentions, and psychological preparation for the experience. 'Setting' describes the physical and social environment where the treatment occurs, including the therapy room, music, and the presence of trained therapists.

Integration refers to the process of making meaning from and incorporating insights gained during psychedelic sessions into daily life. This crucial phase involves therapeutic support to help patients process their experiences and translate them into lasting behavioural and psychological changes.

Therapeutic Alliance describes the relationship between the patient and therapy team in psychedelic therapy. This bond is important given the vulnerable nature of psychedelic experiences and their potential to address deep-seated psychological material.

12.3 Clinical Trial and Research Terms

Randomised Controlled Trial (RCT) represents the gold standard in clinical research, where participants are randomly assigned to either receive the investigational treatment or serve in a control group. Randomisation helps ensure that group differences occur by chance, reducing potential bias. In psychedelic research, RCTs typically compare the investigational compound plus therapy to either a placebo or an active comparator plus similar therapeutic support.

Blinding refers to procedures where participants, researchers, or both (double-blinding) are unaware of the treatment assignment. While crucial for minimising bias, blinding presents unique challenges in psychedelic trials due to the noticeable subjective effects of these compounds. Functional unblinding occurs when participants or researchers can guess their treatment assignment based on drug effects. While this challenge exists with many psychoactive medications, it is particularly pronounced with psychedelics.

Active Placebo describes a control substance that produces some noticeable effects but lacks the primary therapeutic action of the investigational treatment. In psychedelic trials, low doses of the study drug or other mild psychoactive compounds may serve as active placebos to improve blinding.

Comparator Arm refers to the group receiving either placebo or standard treatment against which the investigational therapy is compared. For psychedelic trials, comparators might include existing treatments (like SSRIs for depression), placebo with similar psychological support, or lower doses of the psychedelic compound.

Open-Label Trial describes a study where participants and researchers know which treatment is being administered. While more susceptible to bias than blinded trials, open-label studies can provide valuable information about real-world treatment effectiveness and safety.

Treatment-Resistant criteria define the population that has not responded adequately to previous therapeutic interventions. These criteria often specify the number, duration, and types of previous treatments that must have failed before a patient is considered treatment-resistant.

Primary Endpoint represents the main outcome measure used to evaluate a treatment's efficacy. In psychedelic trials, this often involves validated rating scales for specific conditions, such as the MADRS for depression or CAPS-5 for PTSD.

Secondary Endpoints include additional outcome measures that help evaluate other aspects of treatment effectiveness. These might consist of quality-of-life measures, functional improvements, or changes in other symptom domains.

Adverse Events (AEs) are unfavourable and unintended medical occurrences during a clinical trial, whether or not considered related to the study treatment. In psychedelic trials, a careful distinction is made between the expected effects of the compound and genuine adverse events.

Independent Raters are clinical assessors who evaluate patient outcomes without knowledge of treatment assignment and are separate from the therapy team. Their use helps reduce potential bias in outcome assessment.

Dose-Finding Studies are early-phase trials designed to determine optimal dosing regimens. For psychedelics, these studies must balance therapeutic effectiveness with psychological and physiological safety.

Long-Term Follow-Up (LTFU) describes the continued monitoring of participants after the primary treatment period to assess the durability of therapeutic effects and identify any delayed adverse events. This is particularly important for psychedelic therapies, which may produce lasting changes from limited dosing sessions.

Intent-to-Treat Analysis includes all randomised participants in the analysis, regardless of whether they completed the study protocol. This conservative approach helps maintain the benefits of randomisation and provides a more realistic estimate of treatment effects.

Statistical Significance indicates that observed differences between treatment groups are unlikely to have occurred by chance, typically defined by a p-value less than 0.05. However, statistical significance must be considered alongside clinical significance - the practical importance of the observed effect.

Clinical Significance refers to the practical importance of observed treatment effects, considering factors like magnitude of benefit, individual variation, and real-world implications.

Protocol refers to the detailed clinical trial plan, specifying all procedures, inclusion/exclusion criteria, outcome measures, and statistical analyses. For psychedelic trials, protocols must carefully detail safety procedures, therapist qualifications, and setting requirements.

Phase I trials focus primarily on safety and pharmacological properties, typically conducted in healthy volunteers. For psychedelics, these studies help establish basic safety parameters and explore psychological effects in a controlled setting.

Phase II trials evaluate preliminary efficacy and continue safety assessment in small patient populations. These studies often help determine optimal dosing and treatment protocols for larger trials.

Phase III trials are more extensive, definitive studies designed to confirm efficacy and safety in larger patient populations. These trials typically form the basis for regulatory approval and must closely mirror intended clinical use.

Efficacy refers to a treatment's ability to produce desired effects under controlled trial conditions. While **Effectiveness** describes real-world performance under typical clinical conditions.

Sample Size and **Power Calculations** determine the number of participants needed to detect clinically meaningful treatment effects with statistical confidence. Underpowered studies may fail to detect real treatment benefits.

Inclusion/Exclusion Criteria define which participants can enter a trial. For psychedelic studies, these typically include careful psychiatric screening and contraindication assessment.

Dropout Rate refers to the percentage of participants who discontinue participation before study completion. Understanding reasons for dropout is crucial for assessing treatment acceptability and feasibility.

Safety Monitoring involves systematically assessing and recording adverse events, vital signs, and other safety parameters. In psychedelic trials, this includes both physiological and psychological monitoring during dosing sessions.

Durability of Response describes how long treatment benefits persist after the intervention. This is particularly relevant for psychedelic therapies, which aim to produce lasting changes from limited treatment sessions.

Subgroup Analysis examines treatment effects in specific participant populations, helping identify who might benefit most from the intervention or require modified approaches.

12.4 Reimbursement and Health Economics Terms

Health Technology Assessment (HTA) represents a systematic evaluation process that examines the clinical, economic, social, and ethical implications of introducing a new healthcare intervention. For psychedelic therapies, HTAs must consider unique factors such as the combined drug-therapy model, specialised delivery requirements, and potential societal impacts.

Cost-Effectiveness Analysis (CEA) compares different interventions' relative costs and outcomes to determine value for money. The **Incremental Cost-Effectiveness Ratio** (ICER) calculates additional cost per unit of benefit gained compared to existing treatments. **Quality-Adjusted Life Year** (QALY) combines length of life with quality of life, where 1 represents a year in perfect health. **Cost-Utility Analysis** (CUA) represents a specific type of CEA using QALYs as the outcome measure.

Budget Impact Analysis assesses the financial implications of adopting a new treatment within a healthcare system's budget constraints. For psychedelic therapies, this includes considering both drug costs and associated delivery infrastructure.

Value-Based Pricing determines price points based on demonstrated benefits to patients and healthcare systems. For psychedelic therapies, this considers factors such as durability of treatment effect, reduction in other healthcare utilisation, improved workforce productivity, and reduced caregiver burden.

Managed Entry Agreements (MEA) facilitate access to new treatments while managing uncertainty about their real-world performance. **Coverage with Evidence Development** allows temporary coverage while collecting additional effectiveness data. **Risk-sharing Agreements** distribute financial risks between manufacturers and payers. **Performance-based Agreements** link payment to achieved outcomes.

Direct Medical Costs represent immediate healthcare expenses, including drug acquisition costs, therapy and supervision time, facility and infrastructure requirements, and monitoring and follow-up care.

Indirect Costs encompass broader economic impacts such as lost productivity, caregiver time, transportation costs, and social service utilisation.

Health Economic Modeling uses mathematical simulations to project long-term costs and benefits, which is particularly important for treatments with high upfront costs but potential long-term savings.

Willingness to Pay (WTP) threshold represents the maximum amount a healthcare system is prepared to pay for one additional QALY. This varies by country and context.

Market Access refers to the process of healthcare innovations becoming available to patients through regulatory approval, pricing negotiations, reimbursement decisions, and healthcare system integration.

Real-World Evidence (RWE, Phase IV studies) describes data on treatment effectiveness, safety, and costs collected outside clinical trials, which is crucial for validating reimbursement decisions.

Payment Models describe how healthcare services are reimbursed. These include **fee-for-service** payments for each care component, **bundled** payments covering all aspects of a treatment episode, and **value-based** payments linked to outcomes.

Healthcare Resource Utilisation tracks the use of healthcare services. This is important for understanding the current costs of illness and potential cost offsets from new treatments.

Payer Mix describes the different types of organisations, including public insurance, private insurance, and self-pay, that might fund treatment, affecting overall reimbursement strategy.

Coverage Determination describes the process by which payers decide whether and how to reimburse a new treatment. In the UK, this occurs primarily through NICE evaluations, while in Germany, the G-BA (*Gemeinsamer Bundesausschuss*) makes these decisions following benefit assessment by IQWiG.

Statutory Health Insurance (SHI) systems in Germany and the Czech Republic operate through multiple non-profit insurance funds. These funds must provide a standardised basic benefits package but may compete on supplementary services and efficiency.

National Health Service (NHS) systems, as seen in the UK, provide universal coverage through tax funding. Decisions about new treatments are typically made centrally through bodies like NICE, though implementation may vary across regional NHS trusts.

Hybrid Systems, such as in the Netherlands, combine SHI and private insurance elements. The Dutch system requires all residents to purchase private insurance, but insurers must offer a government-defined basic package (*basisverzekering*) at regulated prices.

Reference Pricing, critical in Germany and the Czech Republic, sets reimbursement levels based on prices in other countries or for similar treatments. Germany uses internal reference pricing (comparing similar drugs) and external reference pricing (comparing prices across countries).

Prior Authorisation requires healthcare providers to obtain approval from insurers before delivering certain treatments. This process (*Voranfrage*) is common in Germany for novel or expensive therapies.

Formulary Placement determines the tier or category of coverage for a treatment, affecting patient cost-sharing. The Netherlands uses a preference policy (*preferentiebeleid*) where insurers may designate preferred products within a therapeutic class.

Sickness Funds (*Krankenkassen* in Germany, *zdravotní pojišťovny* in Czech Republic) are the public insurance organisations that manage healthcare coverage. These funds negotiate with providers and manufacturers while operating under national regulatory frameworks.

Regional Variation in coverage exists within each system. In the UK, this can lead to "postcode lotteries" where access varies by region. In Germany, individual sickness funds may have different treatment policies that are not governed by national decisions.

Drug Budgets (*Arzneimittelbudget* in Germany) set spending limits for physicians or practices, influencing prescribing patterns. The Czech Republic uses similar budgetary controls to manage pharmaceutical spending.

Additional Payment Systems (*Zusatzentgelt* in Germany) allow for separate reimbursement of certain treatments outside standard payment schemes, which is particularly relevant for innovative therapies with unique delivery requirements.

Risk Structure Compensation (*Risikostrukturausgleich* in Germany, *risicoverevening* in the Netherlands) redistributes funds between insurers based on their member risk profiles, ensuring fair competition while maintaining access for high-risk patients.

Supplementary Insurance (*Zusatzversicherung* in Germany, *aanvullende verzekering* in the Netherlands) provides coverage beyond basic packages. This might become relevant for psychedelic therapies not initially included in basic coverage.

12.5 Regulatory and Legal Terms

Innovation Funds (*Innovationsfonds* in Germany) support the evaluation and implementation of new healthcare delivery models. This becomes potentially relevant to novel treatment paradigms like psychedelic therapies.

The **European Medicines Agency** (EMA) serves as the centralised regulatory authority for the European Union, evaluating marketing authorisation applications and providing scientific opinions on medicines. For psychedelic therapies, the EMA offers procedures like **PRIME** (PRIority MEdicines) designation for promising treatments addressing unmet medical needs.

National Regulatory Bodies maintain specific roles within their jurisdictions. **The German** Federal Joint Committee (**G-BA**) makes binding drug benefits and reimbursement decisions. **In England** and Wales, the National Institute for Health and Care Excellence (**NICE**) provides evidence-based guidance on effective treatments and care, assessing clinical and cost-effectiveness of health technologies and making recommendations on their use within the NHS. **In Scotland**, the Scottish Medicines Consortium (**SMC**) advises NHS Scotland on the clinical and cost-effectiveness of newly licensed medicines, while Healthcare Improvement Scotland (**HIS**) provides evidence-based advice and develops clinical guidelines. **The Netherlands'** Zorginstituut Nederland (**ZiN**) advises on healthcare package inclusion and quality standards. **The Czech** State Institute for Drug Control (**SÚKL**) oversees drug registration and pricing.

Drug Scheduling varies by jurisdiction but generally categorises substances based on medical use and abuse potential. In the EU, most classical psychedelics fall under **Schedule I** of the UN Convention on Psychotropic Substances. Australia recently rescheduled MDMA and psilocybin to Schedule 8 (controlled drugs) when used in approved medical contexts, representing a significant regulatory shift.

Marketing Authorisation represents the approval to market a medicine through either the EMA's centralised procedure or national authorities. This requires comprehensive evidence of quality, safety, and efficacy.

Good Manufacturing Practice (GMP) encompasses requirements ensuring consistent production and quality control standards. For psychedelic compounds, GMP certification presents unique challenges due to complex synthesis and stability requirements.

Pharmacovigilance describes the ongoing monitoring of drug safety after market authorisation. This includes adverse event reporting systems and risk management plans, which are particularly important for novel therapeutic paradigms.

Expanded Access Programs (Managed Access Programs) allow pre-approval access to investigational treatments for patients with serious conditions. Various terms describe these programs: **Compassionate Use** (EU/US), **Early Access Programs** (UK), **Expanded Access** (US), **Special Access Programme** (CA), **Special Access Scheme** (AU), or **Named Patient Programs**.

Right to Try laws, while primarily US-focused, influence global discussions about access to investigational treatments for severe conditions, potentially affecting psychedelic therapy access pathways.

Risk Management Plans outline strategies to identify, characterise, and minimise drug-related risks. For psychedelic therapies, these typically include specific protocols for patient screening, therapy delivery, and aftercare.

Standard Operating Procedures (SOPs) detail specific processes ensuring regulatory compliance and consistent quality. These become particularly important for psychedelic therapy centres regarding drug handling, therapy delivery, and emergency procedures.

Qualified Person (QP) designates individuals legally responsible for certifying batch release in the EU, ensuring compliance with marketing authorisation and GMP requirements.

Post-Marketing Requirements include studies and surveillance activities required after approval to gather additional safety and effectiveness data under real-world conditions.

License Holder Obligations encompass responsibilities regarding safety monitoring, periodic reporting, and maintaining product information currency. These obligations extend to both the pharmaceutical entity and licensed therapy providers.

Regulatory Inspections verify compliance with various requirements, from manufacturing facilities to therapy delivery sites. These may include announced and unannounced visits to ensure ongoing compliance.

Certificate of Suitability (CEP) demonstrates that a substance's quality meets European Pharmacopoeia standards, important for active pharmaceutical ingredients in approved medicines.

Drug Diversion Prevention describes measures preventing controlled substances from entering illegal channels, particularly relevant for Schedule I/II substances used in clinical settings.

12.6 Stakeholder Terms

Therapy Provider Licensing establishes requirements for practitioners authorised to deliver psychedelic therapy, including specific training and certification requirements that vary by jurisdiction.

Payers encompass organisations responsible for healthcare financing. **Public payers** include national health services and statutory health insurance funds, while **private payers** include commercial insurance companies and self-insured employers. Each operates under different regulatory frameworks and decision-making processes.

Healthcare Professionals involved in psychedelic therapy delivery form a multidisciplinary network. **Psychiatrists** provide medical oversight and prescribing authority. **Psychotherapists** deliver preparatory and integration sessions. **Facilitators**, who can be psychotherapists, nurses or other healthcare workers specially trained in psychedelic therapy protocols, guide patients through medicine sessions. **Integration Specialists** help patients process and incorporate insights from their experiences.

Medical Advisory Boards provide expert guidance on clinical protocols, safety measures, and quality standards. These boards typically include experienced clinicians, researchers, and sometimes patient representatives.

Treatment Centres serve as specialised facilities equipped for psychedelic therapy delivery. These may operate as independent clinics, within hospital systems, or as part of research institutions.

Patient Advocacy Groups represent patients' interests in policy discussions and support access to treatment. These organisations often engage in education, advocacy, and support services while helping shape treatment protocols and access pathways.

Professional Associations represent practitioners involved in psychedelic therapy, establishing practice standards and providing continuing education. These may focus on specific modalities or serve broader psychiatric/psychological communities.

Research Institutions conduct clinical trials and other studies that advance the field. These include academic medical centres, independent research organisations, and industry-sponsored research sites.

Regulatory Affairs Specialists navigate complex approval and compliance requirements, liaising between therapy providers and regulatory authorities.

Quality Assurance Teams ensure adherence to safety protocols and treatment standards, which is particularly important in specialised therapy settings.

Ethics Committees review and monitor research protocols and treatment programs, ensuring patient safety and ethical practice standards.

Training Providers develop and deliver specialised education programs for healthcare professionals entering the field. These organisations often collaborate with research institutions and experienced practitioners.

Policy Makers shape the regulatory and legal framework for psychedelic therapy, including legislators, regulatory officials, and health policy experts.

12.7 Abbreviations and Acronyms

Outcome Assessors evaluate treatment effectiveness and safety, often including clinician-rated and patient-reported measures.

Support Staff includes various roles essential to treatment delivery, from administrative personnel to medical assistants and facility managers.

ADME: Absorption, Distribution, Metabolism, Excretion

AMNOG: Arzneimittelmarktneuordnungsgesetz (German Pharmaceutical Market Reorganization Act)

AWMSG: All Wales Medicines Strategy Group

AUD: Alcohol Use Disorder

BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices, Germany)

BIA: Budget Impact Analysis

CAPS: Clinician-Administered PTSD Scale

CBG-MEB: College ter Beoordeling van Geneesmiddelen–Medicines Evaluation Board (Netherlands)

CBT: Cognitive-Behavioral Therapy

CEA: Cost-Effectiveness Analysis

CPAG: Clinical Priorities Advisory Group (UK)

CRO: Contract Research Organization

CUA: Cost-Utility Analysis

DARWIN EU: Data Analysis and Real World Interrogation Network (EMA initiative)

EBM: Einheitlicher Bewertungsmaßstab (Uniform Value Scale, Germany)

EC: European Commission

EFPIA: European Federation of Pharmaceutical Industries and Associations

EMA: European Medicines Agency

EPIsoDE: Efficacy and Safety of Psilocybin in Treatment-Resistant Depression

EU: European Union

FAERS: FDA Adverse Event Reporting System

FDA: U.S. Food and Drug Administration

GAD: Generalized Anxiety Disorder

G-BA: Gemeinsamer Bundesausschuss (Federal Joint Committee, Germany)

GLP: Good Laboratory Practice

GKV: Gesetzliche Krankenversicherung (Statutory Health Insurance, Germany)

GOÄ: Gebührenordnung für Ärzte (Physician Fee Schedule, Germany)

GVS: Geneesmiddelenvergoedingssysteem (Medicine Reimbursement System, Netherlands)

HAM-D: Hamilton Depression Rating Scale

HTA: Health Technology Assessment

HST: Highly Specialised Technologies (NICE pathway)

ICER: Incremental Cost-Effectiveness Ratio

ICSs: Integrated Care Systems (UK)

ILAP: Innovative Licensing and Access Pathway (UK)

IMPD: Investigational Medicinal Product Dossier

IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Germany)

IRP: International Reference Pricing

JCA: Joint Clinical Assessment (EU)

MAAs: Managed Access Agreements

MADRS: Montgomery–Åsberg Depression Rating Scale

MAIC: Matching-Adjusted Indirect Comparison

MAPS: Multidisciplinary Association for Psychedelic Studies

MAA: Marketing Authorisation Application

MDD: Major Depressive Disorder

MEAs: Managed Entry Agreements

MHRA: Medicines and Healthcare products Regulatory Agency (UK)

NCE: New Chemical Entity

NHS: National Health Service (UK)

NICE: National Institute for Health and Care Excellence (UK)

NIDA: National Institute on Drug Abuse (US)

NLM: National Library of Medicine (US)

NMA: Network Meta-Analysis

OCD: Obsessive-Compulsive Disorder

NVvP: Nederlandse Vereniging voor Psychiatrie (Dutch Psychiatric Association)

PAREA: Psychedelic Access and Research European Alliance

PAT: Psychedelic-Assisted Therapy

PD: Pharmacodynamics

PK: Pharmacokinetics

PRIME: Priority Medicines (EMA scheme)

PROs: Patient-Reported Outcomes

PsyPAN: Psychedelic Participant Advocacy Network

PTSD: Post-Traumatic Stress Disorder

QALY: Quality-Adjusted Life Year

QIDS-SR: Quick Inventory of Depressive Symptomatology

RCT: Randomized Controlled Trial

REA: Relative Effectiveness Assessment

RWE: Real-World Evidence

SHI: Statutory Health Insurance

SMC: Scottish Medicines Consortium

SNRI: Serotonin-Norepinephrine Reuptake Inhibitor

SSRI: Selective Serotonin Reuptake Inhibitor

STA: Single Technology Appraisal (NICE)

SÚKL: Státní ústav pro kontrolu léčiv (State Institute for Drug Control, Czech Republic)

TGA: Therapeutic Goods Administration (Australia)

TRD: Treatment-Resistant Depression

UN: United Nations

VZP: Všeobecná zdravotní pojišťovna (General Health Insurance Company, Czech Republic)

ZiN: Zorginstituut Nederland (Netherlands Healthcare Institute)

References

13

This chapter contains the complete list of sources cited throughout our report. You'll find academic publications, clinical trial results, regulatory documents, and industry reports that informed our analysis and recommendations.

For additional insights, we've drawn extensively from conversations with experts across the field - these stakeholder interviews are documented in Appendix 14.2. Together, these references provide the evidence base for our findings and establish the foundation for advancing patient access to psychedelic therapies in European healthcare systems. ■

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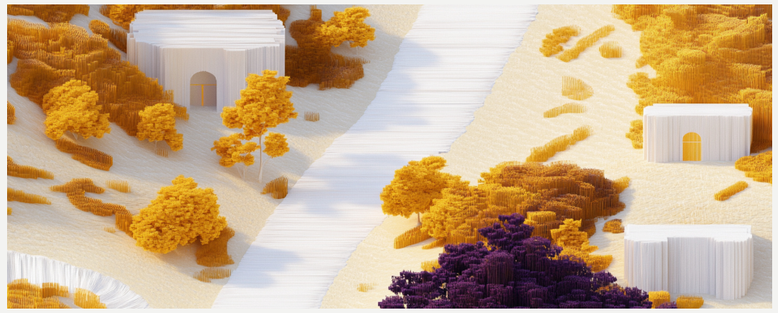
14 Appendices



The appendices provide supplementary information and detailed analyses that support the main report but would have disrupted its flow if included in the core text. Here, readers will find our comprehensive research methodology, including data collection procedures and analytical frameworks that guided our investigation.

We've documented our stakeholder consultation process, featuring insights from key opinion leaders, clinicians, patients, regulators, and industry representatives whose perspectives have been invaluable in shaping our understanding of the European landscape for psychedelic therapies.

These appendices also contain detailed information on relevant stakeholders across Europe, supplementary data tables, and an in-depth case study of Spravato's reimbursement journey, which offers important precedents for novel psychiatric treatments. Additional sections explore regulatory frameworks in detail, provide context on developments in the United States market, and highlight initiatives like Norrsken Mind that are addressing critical gaps in mental healthcare innovation.

Together, these materials provide a robust foundation for those seeking to understand the full complexity of bringing psychedelic therapies into mainstream European healthcare systems. ■

Please find all the appendices on our companion website.

Click the text of the appendices to visit the site.

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Get in Touch

Thank you for reading our report on paving the way for psychedelic therapy reimbursement in Europe. The path ahead is complex—but together, we can transform promising clinical evidence into real-world patient access.

If you're a drug developer, payer, policymaker, provider or investor ready to accelerate reimbursement strategy, we're here to help. Get in touch to discuss tailored market-access guidance, pragmatic policy insights, and hands-on support to navigate regulatory hurdles, shape HTA submissions, and design innovative payment models that work within European health systems.

Contact the Authors
Martin Gisby, Director, Magnetar Access
martingisby@magnetaraccess.com | linkedin.com/in/martingisby/

Floris Wolswijk, Founder, Blossom
floris@blossomact.com | linkedin.com/in/floriswolswijk/

Whether you're planning a Phase III trial, seeking payer engagement, or building delivery infrastructure, let's connect to turn reimbursement challenges into clear, actionable pathways. We look forward to collaborating on the next steps to make psychedelic therapies accessible and sustainable for patients across Europe. ■