WHITE PAPER

It Takes a Village: Engaging Stakeholders in the Emerging Psychedelics Space

Real-world evidence strategies to support psychedelic-assisted therapy development in TRD.

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Introduction

As we approach an inflection point in the use of psychedelic therapies globally, it is increasingly important to stay abreast of both the drivers of momentum and the barriers to acceptance in treatment-resistant depression (TRD). This report is based on a targeted literature review of the most recent information available as of April 2026 and focuses on TRD as a high-burden, high-cost endpoint of major depressive disorder (MDD) for which existing pharmacologic, psychotherapeutic, and neuromodulation strategies deliver only partial and often short-lived benefits for many patients.

Using TRD as a case study, we highlight unmet needs and emerging psychedelic-assisted modalities across four key stakeholder groups (patients, regulators, providers, and payers/health technology assessment [HTA] bodies) and outline how real-world evidence (RWE) can support strategy, access, and implementation.

Throughout, we emphasize how a rigorous evidence strategy can help sponsors anticipate stakeholder expectations, de-risk development and launch, and ultimately improve outcomes for people living with TRD.

Background

MDD affects roughly one in five individuals over the lifespan, and an estimated 20-30% of these patients develop TRD, typically defined as failure to achieve a clinically meaningful response or remission after at least two adequate antidepressant trials. In the United States, TRD affects millions of adults and is associated with markedly higher disability, healthcare utilization, and all-cause and suicide-specific mortality than treatment-responsive MDD, as well as substantial indirect costs from lost productivity and functional impairment.

Despite a wide range of antidepressants and adjunctive options, approximately 30% of patients do not attain remission even after multiple medication switches and combinations. Against this backdrop, each stakeholder group brings distinct priorities and evidence expectations that should shape how psychedelic-assisted therapies for TRD are developed, evaluated, and brought into real-world practice (Table 1).

The SLR Bottleneck

Manual screening of thousands of abstracts creates delays that push back HTA submissions, regulatory filings, and market access timelines by months.

Rising Regulatory Standards

FDA, EMA, Health Canada, CDA-AMC, and NICE all require HTA-grade evidence synthesis with reproducible, PRISMA-compliant methodologies.

Table 1. Summary of stakeholders involved in TRD, their key needs and call-to-action.

Stakeholder	Key needs to address	Call to action
Patients	- Faster and more durable symptom relief after multiple failed treatment steps. - Better functioning, HRQoL, and ability to work. - Reduced stigma, simpler access, and continuity of care.	- Build development plans around patient-centered endpoints (PROs, QoL). - Use evidence generation to document lived experience and access barriers. - Plan early RWE/HEOR programs capturing daily-life benefits.
Regulators	- Strong evidence on safety, abuse potential, and blinding challenges. - Clear data on durability and comparative effectiveness. - Robust governance for monitoring and post-market evidence.	- Align early with evolving agency expectations. - Design studies addressing durability and safety in real-world populations. - Engage regulators early and often on endpoints and study design.
Providers	- Clear positioning within TRD care pathways. - Practical solutions for staffing, training, and workflow. - Confidence in safety protocols and patient management.	- Generate implementation-focused RWE on workflow and adherence. - Benchmark against current supervised and rapid-acting comparators. - Create evidence-based care-pathway guidance.
Payers / HTA	- Evidence that benefits justify high-touch delivery costs. - Clear impact on hospitalizations, disability, and absenteeism. - Decision-grade economic models and RWE.	- Develop payer value stories grounded in economic burden evidence. - Build flexible economic models reflecting realistic care pathways. - Prospectively plan claims/RWD studies to quantify utilization.

Patients: Prioritizing Burden, Barriers, and Lived Experience

MDD Lifetime Prevalence	Develop TRD	Fail to Achieve Remission	Relapse within 6-12 mo.
1 in 5	20-30%	~30%	Many

TRD is associated with profound deficits in health-related quality of life (HRQoL) and functioning, and these deficits worsen with increasing treatment non-response. Prospective cohort studies show that while responders and remitters experience large improvements in mental-health domains and utilities, non-responders or partial responders show smaller gains and remain far below population norms, indicating substantial residual burden even after multiple treatment steps.

Beyond generic HRQoL indices, qualitative and mixed-methods evidence emphasizes the depth and breadth of the humanistic burden in TRD. Patients report a "cyclic" pattern of crisis-driven help-seeking, short consultations, limited treatment options, and self-management of medication, with feelings of being trapped, invalidated, and inadequately supported.

Stigma is a recurrent theme across patient narratives. Public and self-stigma delays help-seeking and contributes to secrecy, social withdrawal, and reluctance to disclose symptoms to clinicians. Structural stigma, including coverage policies and bureaucratic hurdles, further separates people with severe or persistent symptoms from the clinicians and services they need.

Across conventional TRD treatments, onset of benefit is generally measured in weeks rather than days, and many patients relapse within 6-12 months, underscoring the appeal of rapid-acting interventions from a patient-centered perspective.

Call to action for sponsors — anticipate the needs of patients

- Systematically characterize patient-level unmet needs in TRD, including HRQoL, functioning, stigma, and access barriers, using systematic literature reviews to inform value propositions and trial endpoint selection.
- Design development programs that embed meaningful patient-reported outcomes (PROs) and lived-experience insights, ensuring that therapies are evaluated not only on symptom change but on recovery, daily functioning, and acceptability.
- Consider early HEOR and RWE planning focused on patient-relevant benefits (work participation, caregiving, social functioning) to support future payer and policy discussions.

Regulators: Guidance, Governance, and Evidence Expectations

Regulatory bodies play a central role in determining whether and how psychedelic-assisted therapies are integrated into TRD care. Esketamine (SPRAVATO®) illustrates a precedent for supervised, rapid-acting pharmacologic interventions — it is FDA-approved for TRD and governed by a REMS that mandates supervised administration and post-dose monitoring.

By contrast, psychedelics such as psilocybin remain investigational in TRD, and the FDA has issued draft guidance emphasizing unique trial design considerations, including blinding challenges, abuse potential, acute psychological effects, and the need for robust safety monitoring.

The single largest recent catalyst is the April 18, 2026 Executive Order signed by President Trump, aimed at loosening federal restrictions, allocating major funding, and fast-tracking clinical pathways for psilocybin, MDMA, LSD, and ibogaine for mental health applications. The Executive Order allocates USD 50 million in federal funds to match state-level research efforts.

Coupled with FDA momentum (granting Breakthrough Therapy status to psilocybin-assisted therapy for MDD and TRD), there is clear urgency being created by political will, regulatory momentum, funding, and public health pressure.

Key Regulatory Milestones & Context

How the regulatory landscape is shaping psychedelic-assisted TRD development

REMS

Esketamine REMS Precedent

SPRAVATO® (esketamine) is FDA-approved for TRD with a REMS mandating supervised administration and post-dose monitoring — setting a framework for future psychedelic therapies.

EO

April 2026 Executive Order

Trump EO allocates $50M in federal funds to match state research efforts and fast-tracks clinical pathways for psilocybin, MDMA, LSD, and ibogaine.

BTD

FDA Breakthrough Therapy Designation

COMPASS Pathways received Breakthrough Therapy Designation for psilocybin in TRD. Two phase 3 studies met primary endpoints in 2025-2026.

Call to action for sponsors — anticipate the needs of regulators

- Align early with regulatory expectations by using systematic reviews and landscape assessments to synthesize evolving FDA/EMA guidance, precedents (e.g., esketamine REMS), and psychedelic-specific trial design considerations.
- Design programs that explicitly address regulatory concerns about durability, comparative effectiveness, safety in real-world-like populations, and governance of supervised administration.
- Engage regulators "early and often" to pressure-test study designs, endpoint strategies (including PROs), and safety-monitoring frameworks for psychedelic-assisted TRD therapies.

Providers: Clinical Complexity, Workflow, and Real-World Effectiveness

For providers, TRD is characterized by severe, persistent symptomatology, high suicidality, and multimorbidity, with many patients remaining in chronic episodes or recurrent partial remission despite intensive treatment. As the number of failed treatment steps increases, remission becomes less likely and each subsequent line of therapy tends to yield smaller incremental benefits.

Conventional pharmacologic strategies can deliver clinically meaningful symptom reductions but only for a subset of patients. Systematic reviews and network meta-analyses indicate that acute response/remission rates rarely exceed 40-50%, and many patients remain symptomatic with tolerability constraints limiting scalability.

Rapid-acting glutamatergic agents and psychedelic therapies are frequently cited as promising solutions. Ketamine and esketamine consistently produce large, rapid reductions in depressive symptoms. However, durability remains a challenge: without structured maintenance, many patients relapse within weeks to months.

The strongest TRD-specific randomized evidence to date is the COMP360 phase 2b trial (N=233), which showed significantly greater depression severity improvement with 25 mg psilocybin vs. 1 mg at Week 3 (LSMD = -6.6; $p < 0.001$). COMPASS Pathways has also reported two phase 3 studies meeting primary endpoints in 2025-2026.

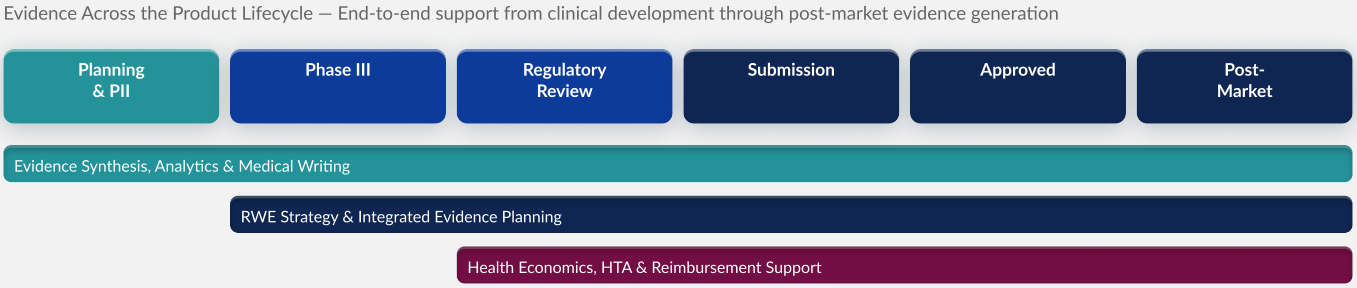


Figure: Evidence Across the Product Lifecycle

Call to action for sponsors — anticipate the needs of providers

- Use evidence generation to characterize clinical burden in TRD and benchmark psychedelic-assisted interventions against ketamine and ECT.
- Generate RWE addressing real-world effectiveness, safety, and implementation (adherence, resource use, staffing, and training).
- Develop evidence-based care-pathway and sequencing narratives for provider adoption and guideline inclusion.

Payers, HTA Bodies, and Market Access: Economic Value and Evidence Standards

US Adults with TRD	Annual Direct Costs	National MDD Burden	TRD Share of MDD Burden
~2.7M	$12–19K	$92.7B	$43.8B

A large body of observational and modeling work shows that TRD imposes substantially higher direct and indirect costs than both non-TRD depression and no depression. Annual direct medical costs for TRD patients in US datasets typically range from approximately USD 12,000-19,000, consistently exceeding those for managed depression and more than doubling costs in non-depressed controls.

TRD is estimated to affect 30.9% of the 8.9 million adults with medication-treated MDD in the US, accounting for an estimated USD 43.8 billion of a USD 92.7 billion national burden of MDD. Hospitalization costs increased disproportionately and often account for one-quarter to over one-half of total direct costs among TRD-likely patients.

Indirect costs related to work loss and disability add substantially to this burden. TRD-likely employees have roughly twice as many days of absenteeism and significantly more work-loss days than employees with non-TRD depression.

RWE capturing sustained clinical outcomes, healthcare utilization, and broader societal outcomes can validate model assumptions and support reimbursement decisions by agencies such as ICER, NICE, and CDA-AMC. A US model-based cost-effectiveness analysis suggests psilocybin-assisted therapy may offer economic value under certain assumptions, but authors note the need to better understand longer-term effectiveness in maintaining remission and reducing relapse.

Call to action for stakeholders — payers and HTAs

- Develop payer value stories for psychedelic-assisted TRD therapies grounded in high-quality evidence syntheses of economic and HRQoL evidence, with transparent handling of heterogeneity and uncertainty.
- Build fit-for-purpose economic models that reflect realistic care pathways, long-term trajectories, and relevant perspectives (health system and societal), and that can be updated as new RWE becomes available.
- Plan prospective RWE programs designed to generate decision-grade data on utilization, costs, utilities, and productivity that meet the expectations of agencies such as ICER, NICE, and CDA-AMC.

Final Call to Sponsors: Building an End-to-End Evidence Strategy for Psychedelic TRD Therapies

Psychedelic-assisted therapies are rapidly moving from promise to practice, entering a phase defined by approval, launch, and delivery in routine care. In TRD, this transition exposes a central challenge: the condition remains difficult to define at scale in both clinical practice and real-world databases. Patient populations show substantial heterogeneity in prior treatment exposure, treatment sequencing, and clinical complexity.

Short-term efficacy — while essential — will not on its own be sufficient to address the questions that determine access and adoption, including durability, long-term safety and monitoring requirements, implementation feasibility, and comparative effectiveness and value in real-world settings.

Conclusion

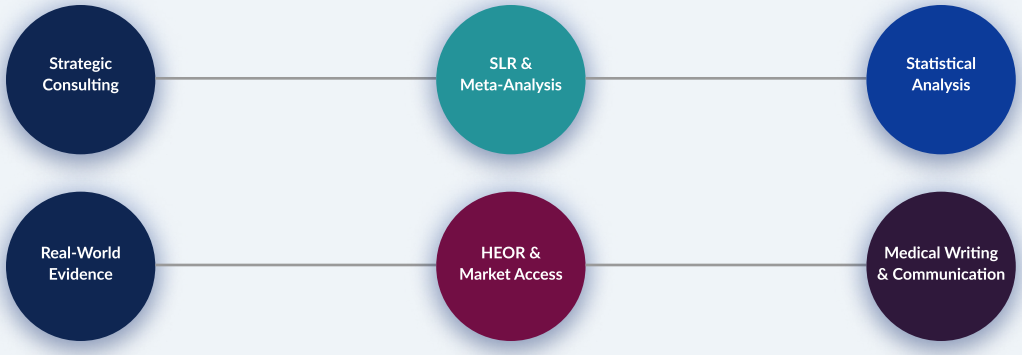
TRD is a prevalent, chronically disabling, and costly endpoint of MDD for which current pharmacologic, psychotherapeutic, and neuromodulation strategies deliver only partial, often short-lasting benefits for patients. Rapid-acting, supervised interventions such as ketamine/esketamine and emerging psychedelic-assisted therapies offer a mechanistically novel way to address some of these unmet needs, with early TRD data showing rapid, clinically meaningful symptom reductions and encouraging signals for longer-term functional gains.

At the same time, durability of effect, comparative effectiveness versus established options, safety and governance in high-risk real-world populations, and equitable, economically sustainable delivery models remain unresolved questions that will determine whether these interventions can move from promising adjuncts to standard components of TRD care.

Robust late-stage trials and coordinated HEOR/RWE programs linking clinical outcomes with healthcare utilization, costs, and productivity are essential to reduce uncertainty for regulators and payers. Comprehensive evidence generation will ensure that any future psychedelic-assisted therapies are implemented in ways that improve the lives of people with TRD and are accessible to those most affected.

Full-Spectrum Capabilities

AI Technology + PhD Expertise + Integrated Strategy



AI Technology + PhD Expertise + Integrated Strategy = The Most Comprehensive Evidence Development Available

References

1. Fekadu A, et al. What happens to patients with treatment-resistant depression? J Affect Disord. 2009.
2. Buchalter ELF, et al. Predicting Remission in Late-Life Major Depression. J Clin Psychiatry. 2019.
3. Rush AJ, et al. Acute and Longer-Term Outcomes in Depressed Outpatients. Am J Psychiatry. 2006.
4. Forthman KL, et al. Treatment resistant depression: Socio-demographic characteristics. J Affect Disord. 2025.
5. Pozuelo Moyano B, et al. Systematic review of clinical effectiveness for treatment resistant late-life depression. 2025.
6. Tatli SZ, Atagun M. Rethinking Treatment-Resistant Depression. Actas espanolas de psiquiatria. 2025.
7. Johnston KM, et al. The burden of treatment-resistant depression. J Affect Disord. 2019.
8. Lex H, et al. Long-term quality of life in TRD after ECT. J Affect Disord. 2021.
9. Talbot A, et al. Experiences of treatment-resistant mental health conditions in primary care. BMC Primary Care. 2022.
10. Scott F, et al. Systematic review of augmentation and combination treatments for early-stage TRD. 2023.
11. SPRAVATO® approved in the U.S. as first and only monotherapy for adults with TRD. 2025.
12. U.S. FDA. Psychedelic Drugs: Considerations for Clinical Investigations. 2023.
13. Executive Order 14401: Accelerating Medical Treatments for Serious Mental Illness. 2026.
14. Compass soars as Trump throws weight behind psychedelic drug development. 2026.
15. Feng Y, et al. Quantitative evaluation of multiple treatment regimens for TRD. 2025.
16. Goodwin GM, et al. Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. NEJM. 2022.
17. Compass Pathways: Q3 2025 Financial Results and Business Highlights. 2025.
18. Compass Pathways Achieves Primary Endpoint in Second Phase 3 Trial for COMP360 Psilocybin. 2026.
19. Goodwin GM, et al. Single-dose psilocybin for TRD: Impact on PROs, anxiety, function, and QoL. J Affect Disord. 2023.
20. Price RB, et al. International pooled patient-level meta-analysis of ketamine infusion for depression. Mol Psychiatry. 2022.
21. Anand A, et al. Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression. NEJM. 2023.
22. Nikolin S, et al. Ketamine for the treatment of major depression: a systematic review. eClinicalMedicine. 2023.
23. COMPASS Pathways receives FDA Breakthrough Therapy designation for psilocybin therapy for TRD. 2018.
24. Hannah LA, et al. Economic evaluation of interventions for treatment-resistant depression. Front Psychiatry. 2023.
25. Zhdanava M, et al. Prevalence and National Burden of TRD and MDD in the United States. J Clin Psychiatry. 2021.
26. Walter E, et al. The cost-of-illness and burden-of-disease of TRD in Austria. J Medical Economics. 2023.
27. Avancena ALV, et al. Psilocybin-assisted therapy for TRD: a model-based cost-effectiveness analysis. 2025.
28. Cepeda MS, et al. Finding TRD in real-world data: data-driven vs. expert-based heuristics. 2018.