Set, Setting and Site Activation: Running Psilocybin Trials in Ontario

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Psychedelic therapy could 'reset' depressed brain



Magic Mushrooms Might Be the New Anti-Depressants

There are 700,000 Canadians living with treatment-resistant depression. Psilocybin could help them get better.

Can Magic Mushrooms Heal Us?

ROM



Psychedelics: Art. Culture. Science.

1 · INTENTION

Why we still need rigorous psilocybin trials

“Low certainty evidence suggests psilocybin combined with psychological support may provide benefit to patients with major depressive disorder, treatment-resistant depression and substance use disorders.”

Rosenblat JD, Husain MI. Psilocybin. JAMA. 2026.

What the next trials must fix

- Functional unblinding: >90% of participants guess their allocation
- Expectancy bias and inadequate control arms
- Small, highly selected, homogeneous samples
- Short follow-up and limited dose–response data
- No assessment of psychotherapy fidelity
- Unresolved mechanism of effect

1 · INTENTION

Where our trip began



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Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression

G.M. Goodwin, S.T. Aaronson, O. Alvarez, P.C. Arden, A. Baker, J.C. Bennett, C. Bird, R.E. Blom, C. Brennan, D. Brusch, L. Burke, K. Campbell-Coker, R. Carhart-Harris, J. Cattell, A. Daniel, C. DeBattista, B.W. Dunlop, K. Eisen, D. Feifel, M.K. Forbes, H.M. Haumann, D.J. Hellerstein, A.I. Hoppe, M.I. Husain, L.A. Jelen, J. Kamphuis, J. Kawasaki, J.R. Kelly, R.E. Key, R. Kishon, S. Knatz Peck, G. Knight, M.H.B. Koolen, M. Lean, R.W. Licht, J.L. Maples-Keller, J. Mars, L. Marwood, M.C. McElhiney, T.L. Miller, A. Mirow, S. Mistry, T. Mletzko-Crowe, L.N. Modlin, R.E. Nielsen, E.M. Nielson, S.R. Offerhaus, V. O'Keane, T. Páleníček, D. Printz, M.C. Rademaker, A. van Reemst, F. Reinholdt, D. Repantis, J. Rucker, S. Rudow, S. Ruffell, A.J. Rush, R.A. Schoevers, M. Seynaeve, S. Shao, J.C. Soares, M. Somers, S.C. Stansfield, D. Sterling, A. Strockis, J. Tsai, L. Visser, M. Wahba, S. Williams, A.H. Young, P. Ywema, S. Zisook, and E. Malievskaia

2018 → 2022

Our first psilocybin trial: CAMH was a site in the phase IIb trial of single-dose psilocybin for TRD, published in the *NEJM*.



Toronto

Toronto's CAMH gets 1st federal grant to study magic mushrooms as treatment for depression

Study to explore if psilocybin can alleviate depression without psychedelic side effects

CBC News · Posted: Jul 27, 2022 6:00 AM ET | Last Updated: July 27

July 2022

The first federal (CIHR) grant to study psilocybin, for PSI-RIS: can psilocybin work without the psychedelic effects?

1 · INTENTION

From one trial site to a portfolio of trials

2018 — First trial: phase IIb site

2022 — First CIHR psilocybin grant

2022 — *NEJM* phase IIb results

2023–25 — Mechanistic trials launched

2026 — **8 trials, 3 sites**

Trial	Design	N	Status
PSI-RIS	3-arm RCT: psilocybin ± risperidone (5-HT2A block)	41	Completed
PSI-1V2	RCT: one vs two 25 mg doses, optional EEG/fMRI	75	Recruitment complete
COMPASS	2-arm RCT: 25 mg vs 1 mg, optional open label	581	Recruitment complete
TRANSCEND	Open label: TRD with chronic neuropathic pain	16	Recruiting
PSI-TNT	Pilot RCT: role of psilocybin monitors	40	Recruiting
PSynVesT PET	Open label: synaptic density, with TMS-EEG	12	Recruiting
AD-PSILO	Adjunctive RCT: 25 mg vs 1 mg; TWH, TGH, CAMH	90	Awaiting regulatory approval
PSIMBA PET	5-HT2A occupancy at 5/10/25 mg in MDD	12	Awaiting regulatory approval

2 · SET

Three layers of approval before the first dose

FEDERAL · HEALTH CANADA

Clinical Trial Application

FDR Part C, Div. 5: protocol, consent, IB, CMC, GMP attestation. 30-day review → No Objection Letter.

Restricted-drug authorization

CDSA Schedule III / FDR Part J. Investigator applies with an institutional letter **after** the NOL; licensed-dealer supply; import permit if made abroad.

PROVINCIAL · ONTARIO

Streamlined ethics

Clinical Trials Ontario: one REB of record for a multi-site trial (e.g., TWH, TGH, CAMH).

INSTITUTIONAL

Research office

Contracts, budget, inter-site agreements, trial registration.

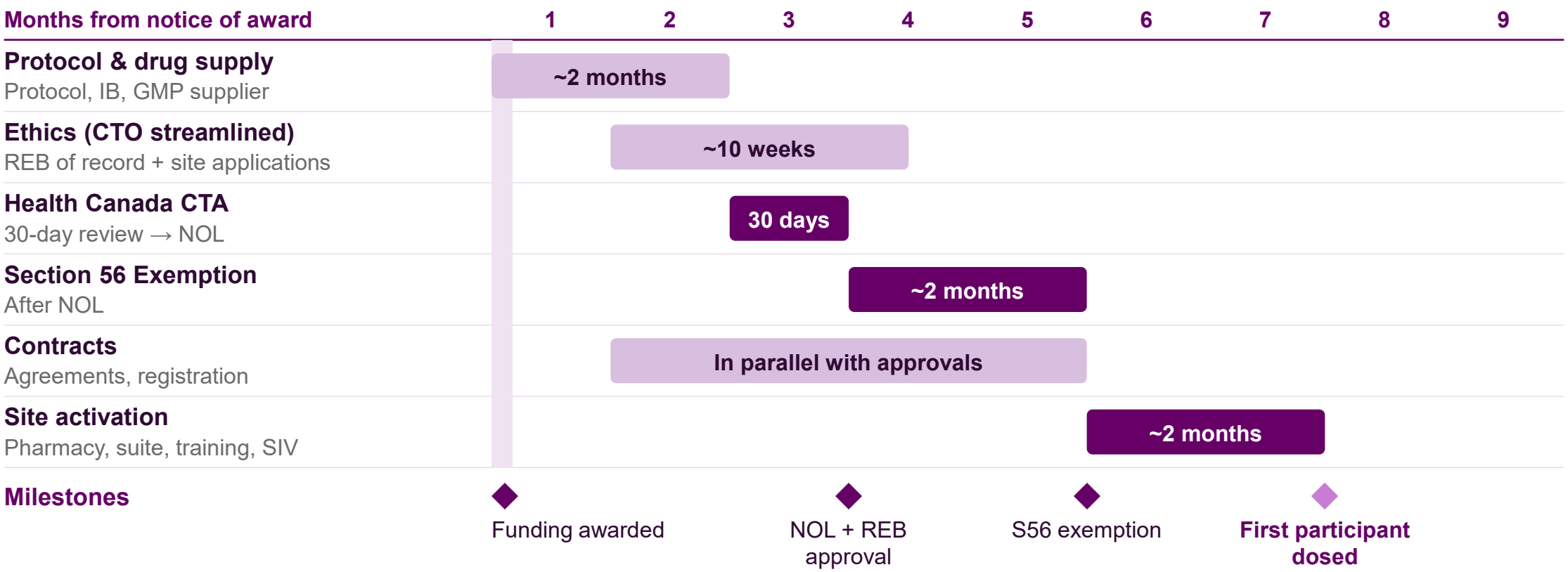
Pharmacy & space

Secure storage, delegated chain of custody, blinded dispensing; a non-clinical room for 6–8 h sessions.

Health Canada. Clarification of requirements for conducting clinical research with psilocybin (Jan 2022). Modernized Clinical Trial Regulations proposed Dec 2025.

2 · SET

From funding to first dose: the timeline



Dark bars = regulatory critical path; light bars run in parallel. Indicative durations; real timelines vary by sponsor, drug source and site.

Every trial design tests an active ingredient

Design choice	Question it answers	Ontario trial · status
Psilocybin 25 mg ± risperidone 1 mg	Are psychedelic effects needed?	PSI-RIS · n = 41, completed
One vs two 25 mg doses	Does a second dose add benefit?	PSI-1V2 · n = 75, enrolled
Role of psilocybin monitors	What does the support contribute?	PSI-TNT · n = 40, recruiting
25 mg vs 1 mg active placebo, on stable antidepressant	Can patients stay on their antidepressant?	AD-PSILO · n = 90, 3 sites, in approval
[18F]SynVesT-2 and [11C]Cimbi-36 PET	Synaptic density; 5-HT2A occupancy	PET pilots · n = 12 each

Site readiness: getting the setting right



Our psilocybin dosing room: clinical support, non-clinical feel

The room

Comfortable and private for 6–8 hour sessions, with curated music and medical support close by.

The team

Two trained monitors per session; manualized therapy (~16 h in PSI-RIS) with fidelity checks.

The drug

Secure pharmacy storage, chain of custody, reconciliation and blinded dispensing.

Safety

Adverse-event monitoring, suicidality, and a plan for difficult experiences.

3 · SETTING

Institutional support: quality and safety by design

High-quality, safe psychedelic trials depend on the institution, not just the investigator.

Health Canada can inspect any site for GCP, GMP and controlled-substance compliance.

Governance

Sponsor oversight, endorsement for S56 exemption, insurance, protected staff time.

Quality assurance

SOPs, GCP training, internal audits and inspection readiness.

Monitoring

Independent monitors verify source data and track protocol deviations.

Safety oversight

DSMB review, medical cover, timely AE/SAE reporting to REB and Health Canada.

Drug accountability

Pharmacy reconciliation and diversion prevention for a restricted drug.

Data integrity

Validated, PHIPA-compliant data capture with audit trails.

4 · THE JOURNEY

The participant’s trip through the trial

Day −7

Screening

MINI, ATHF-SF, HAMD-17 > 14; medical review; taper if required (≥ 4 weeks)

Days 1 & 7

Preparation

Two sessions: what to expect, setting intentions, handling difficult moments

Day 14

Dosing

25 mg vs 1 mg psilocybin; 5–8 hour session with two monitors

Days 15–29

Integration

Three sessions to make meaning of the experience

Weeks 5–25

Outcomes

Primary: MADRS change at Week 5; follow-up to Week 25

Robust medical oversight is critical: Most trials require tapering serotonergic medication (including antidepressants) and our sites provide weekly psychiatric reviews during the medication washout, and regular psychiatric check-ins in the post-dosing phase.

4 · THE JOURNEY

Avoiding a bad trip: lessons from the road

01

Sequence the approvals

S56 exemption application can’t start until the NOL arrives.

02

Lock drug supply early

GMP supplier, Investigator’s Brochure and import permit are the long poles.

03

Run reviews in parallel

Submit to CTO; one REB of record covers all sites.

04

Budget the dosing day

Two monitors for 6–8 hours, plus preparation and integration sessions.

05

Design against unblinding

Use active placebos (e.g., 1 mg) and measure blinding and expectancy.

06

Recruit beyond referrals

Community outreach and diverse research teams to widen who takes part.

5 · INTEGRATION

Take-home messages

1. **Start the regulatory clock on day one.** Plan roughly 6–9 months from award to first dose.
2. **Design for the question.** Control, dose and therapy are the active ingredients you are testing.
3. **Build on institutional support.** Quality assurance, independent monitoring and CTO’s streamlined ethics make safe multi-site trials feasible.

Discussion / Q&A



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