IMPACT SUCCESS STORIES

HNN 3.0
HEALTH-NCP-NET

PsyPal is the first EU-funded, multi-site trial of psilocybin-assisted therapy for existential distress and depression in palliative care.

At four clinical sites, 19 organisations from 9 countries generate rigorous evidence and prepare responsible routes to patients with COPD, MS, ALS and atypical Parkinson's disease.



PsyPal

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1. Describe your project through key words/key phrases that identify it.

PsyPal is the first multi-site trial of a psychedelic therapy to be funded by the EU, and we feel this is a big responsibility. In key phrases: psilocybin-assisted therapy, palliative care, existential distress and depression in life-limiting illness, and a double-blind, placebo-controlled trial.
Chronic, deteriorating illness is a major challenge in anyone's life. For some people it brings end-of-life distress, and for some this becomes severe depression that is not easily influenced by regular talk therapy or antidepressants, which also take relatively long to work. These patients have little energy, and some have little time. Our hypothesis is that psilocybin therapy, psilocybin combined with psychotherapy, works relatively rapidly with a large effect and will do better than what we currently have.

2. In terms of impact, what will be the most tangible your project will achieve?

Most studies so far were small and uncontrolled, often in patients who actively sought this treatment or had earlier psychedelic experience. With growing public interest, such positive expectations can inflate results, so the literature probably does not represent the larger group of palliative care patients.
The most tangible outcome will be robust evidence on efficacy. We compare high-dose with low-dose psilocybin; the low dose acts as an active placebo, which helps keep patients, therapists and researchers blind. Two sessions are embedded in 10 contacts with the therapist, and the primary outcome is measured at three months. Low-dose participants are then offered one high-dose session, which also limits disappointment in the control group.
Durability is a key open question for researchers and regulators, so a six-month naturalistic follow-up tests whether the improvement lasts.
The trial follows the design the EMA (European Medicines Agency) now expects for psychedelics - randomised, double-blind and placebo-controlled - so positive results can support a registration file. Our industry partner Avextra, a German producer, will be able to apply for registration partly based on our data.

3. Please describe your project's overall impact, if applicable, at the European level.

PsyPal also looks ahead to implementation. We work with regulators, care providers and the professional organisations that may train future therapists. Our guidance paper, based on 21 stakeholder interviews, sets out 10 recommendations for European coalitions, and we held a joint symposium with the European Psychiatric Association in 2025.
No classical psychedelic is yet authorised in the EU, while the US is in front. Esketamine shows that approval alone does not ensure access, so maybe we can think of other models that are societally and financially more sustainable. The drug is only roughly 3% to 12% of treatment costs; therapist time matters most.
Because PsyPal is publicly funded, our aim is to steer towards registration in a societally acceptable form: a return on investment, but not the highest profit possible.

4. As an applicant, what advice would you have wanted in the Horizon project design process?

My main advice concerns recruitment and partnerships. A trial like this depends on clinical departments that are not into psychedelics at all. In the Netherlands, we actively recruit patients in the pulmonology department, where most of them have not heard about this option. Together with these colleagues we look for patients with, for example, depression and COPD; we inform them, pre-screen and screen them, and those who meet the inclusion criteria and are positive about participating can experience this treatment.

This makes our study less biased, but it means that clinicians such as pulmonologists and neurologists have to be open to the idea that this might help their patients, because they are the ones who inform patients about the trial. You really need to work with a team that is as curious as we are to see how this may help patients.

Applicants should also be realistic about inclusion. We started with COPD in the Netherlands and have now opened sites for all four patient categories, but it has been very difficult to find patients with ALS whose disease progression allows them to follow this treatment and who also meet the inclusion criteria for depression. Inclusion is not as rapid as we had hoped, but we are learning and we are getting better at it. Finally, plan regulatory dialogue from the start: the EMA explicitly encourages early and continuous engagement on trial design.

5. Please highlight aspects of your Horizon project's strengths that you consider important and that may constitute good practice for other applicants.

One key strength is the rigour of the design. We run a double-blind, placebo-controlled trial set up according to all regulatory standards, which addresses the main weakness of the existing evidence and means that positive results can contribute to formal registration.

Another strength is the consortium. We work with a wide range of collaborators in a highly interdisciplinary group of clinicians, researchers, advocates and patient representatives. Patients and their representatives play a very important role, and European organisations such as the European Association for Palliative Care (EAPC), the European Psychiatric Association (EPA) and the European Federation of Neurological Associations (EFNA) are partners.

We also address mechanistic questions. If psychedelics work as we hope, and there is a growing evidence base that they do, it is intriguing to understand how. Is it purely neurobiological, for example by increasing neuroplasticity? Or is it more experiential and existential, with people becoming more open to coping with difficult feelings and experiences? My personal idea is that it has to be a combination of the two. We also ask whether a positive outcome requires an overwhelming, challenging session, or whether a milder one is enough. This matters for the field: some developers are designing compounds without the psychedelic experience, while others argue that the experience is necessary for lasting effects.

Finally, the design is fair to participants and looks beyond the trial. Everyone who takes the trouble to participate can experience a high-dose session, the six-month follow-up shows whether improvements last, and our work with regulators and professional organisations prepares for implementation. For me personally, and for us as a large group of clinicians, researchers, advocates and patient representatives, it is really very inspiring and rewarding to do this trial.

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