Changing Minds: Bioethical Dimensions of Psychedelic-assisted Psychotherapy

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Abstract

As psychedelic-assisted psychotherapy (P-AT) approaches licensing and mainstream implementation, its ethical aspects remain largely at a preliminary stage of understanding. This thesis examines three previously underexplored challenges that emerged from interviews with former clinical trial participants and their families: a substantial need to reconsider the appropriate post-trial obligations of P-AT research teams; the influence of patients' broader social-ecological environments on outcomes following treatment; and inadequacies in how adverse events are conceptualised and recorded in P-AT trials.

Drawing on semi-structured interviews with ten trial participants, the research initially aimed to develop a grounded theory of 'non-clinical changes' following P-AT. While participants' accounts included such changes, interviews revealed more immediately pressing ethical concerns that demanded attention. This discovery prompted a methodological evolution toward case-based ethical analysis, an approach better suited to examining emerging ethical challenges in novel therapeutic contexts. Through detailed examination of three cases, the thesis: (i) identifies distinctive features of P-AT that generate particularly strong obligations for post-trial support; (ii) demonstrates how patients' *matrices*—the environments they come from and return to—can critically shape therapeutic trajectories; and (iii) demonstrates how current frameworks for adverse event reporting, inherited from conventional drug trials, fail to capture negative and consequential outcomes that matter deeply to patients.

The analyses advance understanding of P-AT through three contributions: a framework for meeting the extended post-trial obligations in P-AT that simultaneously advances our broader understanding of the modality; a renewed understanding of 'the matrix', a concept developed during early psychedelic research in light of developments in our understanding of neuroscience and the development and maintenance of psychopathology; and paths forward for reconceptualising adverse events in P-AT that move beyond pharmacological definitions to encompass the full range of outcomes that are salient to patients.

While these cases cannot establish universal claims about P-AT practice, they identify important considerations that warrant attention as the field develops, demonstrating the value of empirical bioethics in surfacing ethical challenges before they become entrenched in clinical practice. The findings point to specific ways that P-AT research and practice could evolve to meet those challenges. Specific recommendations include enhanced post-trial support structures, systematic assessment of social-environmental factors, and more comprehensive adverse event monitoring frameworks.

Preface

A single line was enough to commit me to studying the ethical dimensions of psychedelic-assisted therapy (P-AT). In the summer of 2018, while working at psychedelic science NGO the Beckley Foundation, I came across Tehseen Noorani's qualitative study *Psychedelic therapy for smoking cessation.*

> "Quitting smoking was often reported as one of the least important effects of the study for participants in retrospect."

Plenty of medical interventions have beneficial off-target effects, of course. But this line, integrated with everything I knew at the time about psychedelics, was enough to convince me that P-AT was not going to slot neatly into our ways of doing, and thinking about, medicine. We can probably make it fit well enough, at least in the medium term, through careful work and necessary compromises. In 2018, I had recently 'drunk the kool-aid', started my first job in the field, and was blinded enough by fervour that I felt that we had enough evidence, that we knew well enough that these substances were safe and effective, and making them available as rapidly as possible was an urgent priority.

Six years later, I, and to a greater-or-lesser extent the rest of the field, has come down from the high and the hype, and I wish that we had six more years to figure out how P-AT is actually going to work in practice, at every level. The small details instead of the grand visions. Not the dramatic and compelling breakthroughs, but the quiet and grounded tending. Jack Kornfield uses the phrase 'after the ecstasy, the laundry' to describe the nature of the spiritual task at hand after the crescendo, the innervating but fleeting glory of a spiritual awakening experience. The spiritual task after the crescendo *is* the material, comparatively mundane task that you know is yours to do, met with respectful attention and appreciation. Well, that's the idea.

In some respects, this thesis is my laundry, respectfully attending to the material, the practical matters to help P-AT function in practice in a way that can serve people. People like my participants, who I met during their own laundry - living their lives as best as they saw fit in the months and years after their own dramatic, intense experiences of P-AT.

For this thesis I interviewed ten former participants of P-AT, amounting to ten of what Mike Parker has called 'encounters with experience'. Jon Ives describes this as philosophers "getting their hands dirty, getting out of their Platonic ivory tower, and acknowledging that ethics is about people, not just good arguments." Over the course of the DPhil I have also written some psychedelic ethics 'from the armchair', but there's no doubt that the ethical deliberations herein were made more applicable, more useful, more real, by seeking to respectfully attend to and understand the experiences of these trial participants. The move to a case study-based approach was one I made nervily, but in providing detailed case descriptions of the full experiences three participants went through, I can, to some degree, share

these encounters with experience with the reader. I hope that thereby you can be, as I was, connected with the ground of proper ethical deliberation.

The thesis proceeds as follows. Chapter 1 provides the traditional background context to the subject matter at hand - a brief history of psychedelics in the West (a history which even at its most detailed would be brief in comparison to those of some Indigenous communities with traditions of psychedelic use), as well as an orientation to what psychedelics *are*, what psychedelic-assisted therapy *is*, and the best available (naturalistic) accounts about how they manifest their particular subjective and therapeutic effects.

Chapter 2 provides an overview of key ethical considerations in P-AT, exploring issues around patient vulnerability, therapeutic relationships, and the challenges of navigating uncertainty in informed consent and outcomes. The third chapter explains and justifies the methodology that I adopted for the empirical component of this research, tracking its evolution from a Constructivist Grounded Theory study of *non-clinical changes following P-AT*, to case-based ethical analysis of experiences following P-AT.

Chapter four is the empirical heart of the study, presenting three detailed case studies drawn from my interview with trial participants. The encounters with experience ground the ethical analyses in the chapters that follow.

The fifth chapter argues for the adoption of a particularly expansive (if potentially expensive) programme of post-trial access and care in clinical psychedelic trials, making a case it is not just an appropriate ethical response to some of the distinctive features of P-AT, but could serve to develop the infrastructure that a future psychedelic healthcare system will depend on. In chapter six I show how various aspects of my participants' experiences are best understood by a regrettably neglected concept from the first wave of psychedelic research: the *matrix*, the home and social environment that patients come from and return to after their trial. The final analytic chapter analyses how current approaches to adverse event reporting in P-AT, which are driven by the need to meet the expectations of health licensing agencies, miss some of the most important sequelae of psychedelic treatments.

If you listen closely while you read you will hear two themes playing throughout the thesis. The first is the title music, *changing minds*. It speaks not only to the empirical reality of how minds change, in their various ways, expressed through the ethical considerations outlined in Chapter 2 and illustrated through the close-up encounters with my participants who shared their stories of how they, and their lives changed after treatment. It also speaks to an aim of the thesis, i.e., changing minds of actors in the field. We have only been researching psychedelics again for 20 years, and there are enough of those who already think that we have got the programme basically right.

The second thread is *integration*, principally a term of art among psychedelic practitioners for the process through which people keep the ecstasy close at heart while they do their laundry; or more

plainly, how they stay connected to their acute psychedelic experiences, and behaviourally and intrapsychically incorporate its insights with their day to day life in a harmonious way. But the material of my analysis chapters also point to integrations. In chapters 5 and 6, I call for the integration of P-AT healthcare with the wider infrastructure of social support. In chapter 6 I show that, even if it falls outside of our thinking, patients are already *integrated* with the matrix of those closest to them. The matrix is both a source and site of change, with people dynamically influencing, and being influenced by their matrix at all times. This consideration may fall out of focus, but in the context of administering a pro-plasticity agent like psilocybin to a vulnerable patient, we cannot afford to overlook those relationships of influence.

The chapters that follow aim to be both rigorous and practical – grounded in real patient experiences while engaging with fundamental questions about how best to advance P-AT. By examining how theoretical frameworks align with lived experiences, this work seeks to support the development of practices that better serve patients while maintaining high ethical standards. The goal throughout is to help psychedelic therapy fulfil its therapeutic promise while properly attending to the complex realities of changing minds.

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1. Introduction

1.1. Overview

1.1.1. Psychedelics and P-AT

The subject -and subtitle- of this thesis is *the bioethical dimensions of psychedelic-assisted psychotherapy* (P-AT). Before examining the *bioethical dimensions*, however, I will provide a provisional account of what *I* understand by the subtitle's other key terms: *psychedelic*, and *psychedelic-assisted psychotherapy*. Both terms resist simple definition, and their boundaries are the subject of much contention, as might be expected, given that the phenomena have received a tranche of scholarly attention, especially in the last decade, from fields as diverse as anthropology, sociology, pharmacology, neuroscience (from the molecular to the cognitive), psychiatry, psychology, history, philosophy, public health, law and policy studies, chemistry, environmental studies and bioethics.

In this thesis I concern myself with P-AT involving the so-called 'classic' psychedelics[1]: the semi-synthetic lysergic acid dimethylamine (LSD), and the naturally occurring psilocybin, mescaline, and dimethyltryptamine (DMT). As an initial orientation, it suffices to describe such psychedelics as a class of psychoactive substances that reliably induce pronounced alterations in perception, mood and cognition. Whilst this is a serviceable *description* of psychedelics, it falls short as a *definition*, since there are many psychoactive substances – among them alcohol, amphetamines and heroin- that induce pronounced alterations in perception, mood and cognition that are *not* psychedelic.

While the distinctive subjective characteristics of psychedelics are outlined below (§1.3.1.), for now some attention to etymology can enrich this understanding somewhat. The term 'psychedelic', coined by psychiatrist Humphrey Osmond in a 1956 letter to the author Aldous Huxley, aims to evoke what he characterised as the 'mind (*psukhḗ*) manifesting (*dēlóō*)' features of these substances: their ability to bring forth experiences that seem to reveal aspects of the mind and consciousness that are typically inaccessible to, or hidden from, direct awareness and introspection[2].

Psychedelic-assisted therapy, in turn, refers to an emerging treatment modality in psychiatry that defies easy categorisation. P-AT combines the administration of a psychedelic drug with structured psychological support. Unlike conventional psychiatric psychopharmacological approaches, which

[1] See § 1.2.5. below on the contested ground of the term 'psychedelic', and the significance of *classic* psychedelics.
[2] Cf. Stanislav Grof's characterisation of LSD, following the observation of more than 1,000 clinical administrations, as "a non-specific amplifier of the unconscious…a catalyst or amplifier of mental processes. If properly used it could become something like the microscope or telescope of psychiatry." (Grof, 1980, p.299)

depend on repeated (typically daily) doses and are assumed to exert their therapeutic effects largely independent of extrapharmacological factors, in P-AT psychedelics are administered only a small number of times (~1-3), and always within a carefully curated context. Similarly, while conventional psychotherapy typically involves regular hour-long sessions over weeks and months, with change occurring incrementally through sustained therapeutic dialogue, P-AT centres on extended sessions of 6-8 hours duration, which involve minimal dialogue with therapists[3], who instead encourage the patient to attend to the experience that arises during drug effects. These drug-assisted sessions are bracketed by sober 'preparation' and 'integration' sessions, which will be further described in due course.

Psychedelics also make for unusual entrants into our pharmacopeia because their patterns of use extend far beyond the clinical context. Considering Indigenous sacramental use (Jay, 2019; Luna, 2011; Myerhoff, 1975), the growth of 'psychedelic tourism' (Ovies & Bautista, 2021; Winkelman, 2005), recent state-level legislative changes in the US permitting 'supported adult use' (Marks, 2023), and extralegal use including for recreational, spiritual, or personal development purposes, the vast majority of psychedelic use always has been, and likely always will be, undertaken in non-clinical contexts. While developing a sufficiently comprehensive 'psychedelic bioethics' requires close attention to these varied uses (Jacobs, Earp, et al., 2024; Jacobs et al., 2023), the current thesis focuses on the bioethics of psychedelics specifically within P-AT. Nonetheless, it is instructive to consider the wide *range* of purposes for which people use psychedelics. These drugs are not addictive or dependence-forming (Kelmendi et al., 2022; D. E. Nichols, 2016), and yet the effects of these drugs, both in acute and longer-term time ranges, are valued beyond mere hedonic pleasure.

Within the medical context of P-AT, in which research is principally oriented towards psychedelics' efficacy at reducing psychopathological symptom scores and their safety, the other changes that are desired ends of non-clinical users are liable to be labelled and collated as 'off-target effects'. Whether by virtue of the radical shifts in consciousness during acute drug effects, the shifts in neural functional connectivity thought to underlie these shifts, or the enduring psychological and neurological changes that can last much longer than the drug's presence in the body, psychedelics are valued by users pursuing varied non-clinical outcomes. These effects, which include shifts to personality, beliefs, worldview,

[3] Most P-AT trials require therapists to be licensed mental health professionals (psychologists, psychiatrists, licensed psychotherapists, nurses with psychotherapy training). Some trial sponsors accept the second therapist to be in training, provided they are working under appropriate supervision. Practitioners also require specialised training and clinical supervision in psychedelic therapy work, with many (but not all) sponsors requiring or encouraging experiential familiarity with non-ordinary states of consciousness. As with many dimensions of P-AT, we have yet to establish how variations in therapist training and experience influence treatment outcomes or adverse event rates—a critical knowledge gap given ongoing debates about appropriate qualifications for those administering these treatments.

relationships and life-priorities, appear to impact clinical trial participants too (Belser et al., 2017; Malone et al., 2018; Noorani et al., 2018; Timmermann et al., 2021), and therefore constitute an important part of the P-AT patient experience. As I discuss in Chapter 2, these broader impacts raise significant ethical considerations regarding informed consent, outcome measurement, and the conceptualisation of therapeutic benefit.

1.1.2. This thesis

The current thesis seeks to characterise the patient experience following P-AT, employing social science research methods —here, semi-structured interviews— in service of bioethical reasoning. This focus on patient experience not only aligns with the NHS's commitment in its constitution to 'put patients first' (National Health Service, 2023), but also fulfils a central function of bioethics: 'horizon-scanning' to identify ethical challenges that may emerge with new medical technologies[4]. With P-AT likely to be licensed for clinical use within the next few years, speaking with current trial participants —among the first to receive P-AT within medical contexts for several decades— provides an important opportunity to understand how patients experience and make sense of their treatment journeys. Through this understanding, the thesis aims to identify features of the patient experience that might lead us to rethink how P-AT is currently delivered, particularly regarding harms, support needs, and emerging challenges.

This aim to focus on potential improvements to P-AT, rather than mere description of trial participants' experiences, shapes both the methodology and presentation of the thesis. As described more fully in § 3.4 , while the research began with an intention to develop a Grounded Theory of how 'non-clinical changes' are understood by trial participants, as interviews progressed they revealed ethical challenges that were both more salient to participants and largely unexamined in the literature. This discovery prompted a methodological evolution towards case-based ethical analysis, which would support a more in-depth analysis of a variety of emerging concerns. The three participant case descriptions in Chapter 5, and the ethical analyses that follow in the next three chapters, highlight dimensions of P-AT that warrant careful consideration as the field moves towards clinical intervention: First, I outline a case for expanded post-trial access and care in P-AT trials, on the basis of distinctive, atypical features of the treatment that is being offered. Second, I highlight the crucial role of P-AT patients' social and relational contexts (what early psychedelic researcher Betty Eisner termed 'the matrix') in shaping outcomes. Finally, I show that the 'invisibility' of some of my participants' most challenging post-P-AT experiences within standard trial adverse event frameworks grounds the need to rethink those

[4] *Per* an editorial within the journal *Bioethics*, 'ethicists have an important job in identifying potential problems before they will actually emerge in reality' (Sutrop, 2004: vi).

frameworks. While each analysis draws on participant experiences to identify specific ways that current practice could better serve future patients, they seek neither to make definitive causal claims, nor to foreclose alternative interpretations. Rather, I hope that the contribution of this thesis will be to open up new possibilities for ethical engagement with P-AT, offering my analysis as one piece of the larger puzzle the field must address as it moves towards licensing and wider implementation.

To better situate the ethical challenges of P-AT established in Chapter 2, and the empirical/analytic component of the second half of the thesis, this introductory chapter provides essential historical and scientific context in three parts: first, I provide a brief history of Western medical engagement with psychedelics, beginning in the 20th Century. It must be noted that various Indigenous cultures, principally in meso- and South America, have much longer ritual histories of engaging with psychedelics, and have developed sophisticated knowledge systems surrounding their use (Carod-Artal, 2015; Jay, 2019; Ruffell et al., 2023). However, such use typically occurs within distinct ontological and epistemological frameworks that conceptualise healing, illness, and psychedelics in fundamentally different ways. Although these traditions merit scholarly attention, doing justice to these frameworks would require extensive anthropological and cross-cultural analysis that goes beyond the scope of the current thesis, focusing as it does on contemporary clinical practice. By providing some genealogy of contemporary Western medical-scientific practice, I seek to underline how many of the contemporary challenges facing P-AT are developments, if not outright repetitions, of the challenges faced by early researchers.

Second, I outline contemporary clinical approaches to P-AT, including current best practices surrounding its implementation, including preparation, drug administration, and integration support. The model of P-AT that is described here represents the experience of my interviewees in psychedelic clinical trials, and provides context for understanding their experiences. Finally, I provide an overview of current scientific understanding of how classic psychedelics affect the brain and the mind. This includes their acute effects on consciousness and cognition, their enhancement of neuroplasticity, and emerging theories about their mechanisms of therapeutic action. Together, these introductions establish the historical, clinical, and scientific context needed to appreciate the chapters that follow.

1.2. Historical Context

1.2.1. The discovery of LSD

Despite early research into mescaline (Bresler, 1905; Prentiss & Morgan, 1895) and forerunners in drug-assisted therapy like 'narcosynthesis' (see §1.2.2), psychedelic science traditionally dates its conception to 'Bicycle Day': April 19th, 1943. On this day, Swiss chemist Albert Hofmann first intentionally dosed himself with lysergic acid diethylamide (LSD), a compound he had developed five years prior while researching medical applications of ergot of rye, a fungus that grows on grain producing plants, and is historically responsible for outbreaks of Saint Anthony's Fire, a condition marked by hallucinations.

Hofmann's first accidental exposure to LSD three days prior interrupted his afternoon's work with "a not unpleasant intoxicated-like condition, characterised by an extremely stimulated imagination… a dreamlike state… [and] an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colours" (Hofmann, 2013; p.12). Suspecting that this accidental contact with LSD had caused these unusual effects, days later he intentionally swallowed 250 μg of the compound, incorrectly estimating that this would be the smallest quantity that would produce some effect. In reality, this is around twice a standard recreational dose. The sudden and intense alterations to perception that followed were distressing, as "familiar objects and pieces of furniture assumed grotesque, threatening forms" (p.13). Owing to wartime restrictions on automobile use, he elected to go home with his assistant by bicycle, where, at the height of his anxiety he felt intense fear and despair, certain that he was going mad or dying. When a doctor arrived to confirm that Hofmann had no abnormal symptoms beyond dilated pupils, and that no further medication was indicated, the "horror softened, and gave way to a feeling of good fortune and gratitude," (p.13) allowing him to thoroughly enjoy the remaining hours of the experience:

> Little by little I could begin to enjoy the unprecedented colors and plays of shapes that persisted behind my closed eyes. Kaleidoscopic, fantastic images surged in on me, alternating, variegated, opening and then closing themselves in circles and spirals, exploding in colored fountains, rearranging and hybridizing themselves in constant flux. (pp.13-14)

Hofmann woke up refreshed and 'in excellent physical and mental condition,' and reported his results to senior colleagues at Sandoz. They agreed LSD warranted further investigation and, following animal toxicity studies, forwarded the drug to Zurich psychiatrist Werner Stoll for limited experimentation. Stoll reported extreme emotional and perceptual changes from even small doses and suggested

psychiatric applications. Following publication of his research (Stoll, 1947), Sandoz named the compound *Delysid*, providing samples to requesting clinicians with two suggested indications:

> a) Analytical psychotherapy, to elicit release of repressed material and provide mental relaxation, particularly in anxiety states and obsessional neuroses.
>
> b) Experimental studies on the nature of psychoses: By taking Delysid himself, the psychiatrist is able to gain an insight into the world of ideas and sensations of mental patients. Delysid can also be used to induce model psychoses of short duration in normal subjects, thus facilitating studies on the pathogenesis of mental disease (Hofmann, 2013; p.26)

1.2.2. The state of Psychiatry in the mid-20th Century

Psychiatry at the time of LSD's arrival might be characterised as split between two paradigms - biological and psychodynamic psychiatry. Biological psychiatry understood mental disorders primarily in terms of nervous system dysfunction, best treated by therapies that directly influenced the body, including electroconvulsive therapy (ECT), psychosurgery, and hypoglycaemic comas (Doroshow, 2007; Mashour et al., 2005; Suleman, 2020). In comparison, psychodynamic psychiatry conceived of mental disorders as consequences of environmental stressors, and patients' internal challenges and responses in adapting to them. The means by which patients sought to handle and accommodate environmental stressors were assumed to be unconscious in nature, meaning they could only be uncovered, explored and corrected by extensive talk therapy.

However, this apparent dichotomy masks a more complex reality of significant theoretical and practical integration between approaches. The first iteration of the American Psychiatric Association's nosological manual, the Diagnostic and Statistical Manual: Mental Disorders (DSM-I), couched its accounts in psychodynamic terms, and even research into biological therapies leant on psychodynamic explanations to account for treatment success (see Raz, 2008; Sadowsky, 2006). Similarly, while psychodynamic psychiatry emphasised environmental stressors and unconscious adaptations, practitioners readily incorporated biological interventions when they could facilitate the therapeutic process.

Various forerunners to P-AT, i.e., drug-assisted therapies, were developed in the 1930s and 40s. Practitioners discovered that careful dosing of the barbiturate sodium amytal could temporarily restore mental function to otherwise unreachable patients, creating windows for productive psychotherapy (Bleckwenn, 1930; Lindemann, 1932). This process of drug-assisted therapy was developed and

systematised as 'narcosynthesis' during World War II, using the barbiturate sodium pentothal to treat ‘war neuroses’ (Grinker & Spiegel, 1944). By inducing a semi-conscious, dreamlike state in the patient using the drug, the therapist would encourage veteran patients to discuss the traumatic experiences in war that led to their distress. These experiences, often the subject of total amnesia, could be vividly recalled, or acted out, in a process of ‘abreaction’ during therapy. The sedative effects muted distressing responses to memories, allowing their discussion in subsequent psychodynamic therapy (Grinker & Spiegel, 1945)[5]. Likewise, the stimulant Methedrine (methamphetamine) was advertised in the early 1950s with the tag-line ‘Release the Story for Analysis’, suggesting administration could generate abreaction, ‘spontaneous, free flow of speech’, and the uncovering of ‘previously withheld information’ (Rasmussen, 2008). In contrast to the contemporaneous proposal that a stimulant could facilitate therapy, the manufacturers of the tranquiliser mephenesin, and researchers using the drug, reported that it, too, could support talk therapy, specifically because of its relaxing properties (Tobbell, 2008).

1.2.3. The development of psychedelic therapy

Against this backdrop of blended biological-psychodynamic treatments, and drug-assisted therapies, the ground looked fertile for LSD to be successful. Indeed, the earliest English-language reports of LSD supported the therapy adjunct indication suggested by Sandoz. Busch and Johnson gave small doses (30 - 40 μg) of LSD to eight patients already undertaking psychotherapy, and reported that the drug could 'profoundly influence[...] the course of their progress', with two patients completely discontinuing treatment. The researchers concluded that LSD 'disturbed the barrier of repression and permitted a re-examination of significant experiences of the past, which sometimes were re-lived with frightening realism' (Busch & Johnson, 1950, p.241), and could thereby "serve as new tools for shortening psychotherapy". These findings sparked particular interest within Psychiatry, with over 100 articles investigating LSD published in medical journals by 1951 (Dyck, 2005, p.383).

Early clinical research with psychedelics followed the narcosynthesis framework: small doses of LSD administered weekly as an adjunct to the clinician's preferred therapy style. These long-term, small-dosage treatments became dominant in European LSD-therapy through the 1950s and 1960s, but the lack of a shared theoretical framework prevented its coalescence into a standard paradigm, complicating efficacy assessments. Practitioners of this *psycholytic* ('mind-loosening') therapy witnessed diverse

[5] A striking historical parallel is worth noting here: just as narcosynthesis was developed to treat ‘war neuroses’ - typically understood as an early formulation of what is now called ‘Post-Traumatic Stress Disorder’ (PTSD); MDMA-assisted therapy is currently close to clinical approval specifically for the treatment of PTSD. Both approaches share core therapeutic elements: decreasing the felt sense of threat during the recollection of traumatic memories, followed by integration of that experience in subsequent psychotherapy.

patient reactions. The foremost British practitioner concluded that "every physician probably has to administer LSD in his own way" (Sandison, 1960, p.84). Mortimer Hartman, a California-based psychiatrist in private practice observed that "[i]n our group, for instance, which consists of two Freudians and two Jungians, the latter will get the transcendental experience in the patient much faster than the former. The two Freudians, on the other hand, will evoke the patient's childhood memories more quickly than the two Jungians in the group. These results are due to the different orientations and different kinds of suggestions on the part of the therapists" (quoted in Sandison, 1960, p.132).

Hartman's observation here hints at something crucial about the effects of psychedelics: even when doses are equivalent, two LSD experiences can be markedly different, depending on contextual factors. This flexibility of the drug experience is more apparent at higher dosages. As such, in North America, where large doses rapidly became the norm, and multiple researchers independently noticed the influence of contextual factors, a complementary stream of LSD-therapy developed, focusing extra attention on the manipulation of these factors.

Charles Savage laid the foundations for this distinctly psychedelic mode of therapy in 1949 at the US Naval Medical Research Institute. Moving beyond the narcosynthesis model, he investigated whether LSD-induced euphoria itself could be therapeutic. While he was ultimately dissatisfied with the outcomes of his early research, he began to develop an understanding of the determinants of the subjective experience of LSD. At the 1955 American Psychiatric Association annual meeting he disseminated his findings; the first recorded mention of the LSD experience being driven not only by the dose, but also by extrapharmacological features, the 'mental *set*' of the individual involved, including the patient's personality structure, motivations for and beliefs and expectations about taking the drug, and the 'experimental *setting*,' including the physical environment in which the drug experience took place, but also the other people present, and the nature of the relational dynamics between the patient and those present (Savage, 1956). Savage's contention was that, by tending to these extrapharmacological factors, the experience could be directed, minimising risk of poor reactions and, potentially, supporting benefit. Of particular importance were relational factors: the paper was titled 'LSD Psychosis as a Transaction Between the Psychiatrist and Patient,' and included a clear exhortation: 'I want to stress that *the person with an acute LSD psychosis needs someone with him at all times*.' (p. 38, emphasis original).

While Savage's early insights about set and setting laid the groundwork for understanding how to reliably induce beneficial psychedelic experiences, research into LSD-therapy for alcoholism

undertaken in Saskatchewan, Canada marked a decisive shift away from the narcosynthesis model to a theoretical model that proposed that the nature and content of the psychedelic experience *itself* might be therapeutic. A small (n=24) group of patients with severe, treatment-resistant alcoholism and comorbid psychiatric diagnoses were given 200-400 μg of LSD (or 0.5 mg mescaline) after 2-4 weeks of preparatory psychotherapy. Material that emerged during drug effects was discussed in psychotherapy in the following days, before patients were discharged and encouraged to join Alcoholics Anonymous. At the long-term follow-up, between two months and three years after the drug session, half were *much improved* - "completely abstinent since treatment, or drinking only very small quantities", or *improved* - "definite reduction in alcohol intake" (C. M. Smith, 1958).

The most striking finding from these treatments was that many who improved underwent "exciting and pleasant [experiences which] yielded insight into their drinking problems," or experiences of "a spiritual or religious type" (Hoffer & Osmond, 1968, p.57). As such, the researchers suggested that the drug caused 'an upsurge of previously repressed material', or, in some cases, 'the effects resembled the state of religious conversion' (Smith, 1959, p. 293). One patient's reaction was reported as:

> he had a momentary oneness with God. Had a vision while lying [down] with eyes closed of a spiral staircase with himself talking to another person. This appeared to have great meaning to him. ... He seems to have gained some insight and understanding of himself. (Saskatchewan Archives Board, in Dyck, 2006, p.321)

The Saskatchewan researchers went on to modify set and setting with the intention of fostering these experiences, redesigning treatment rooms with visual and auditory elements to create a relaxing atmosphere more conducive to facilitating these mystical or 'peak' experiences than standard clinical environments (Hoffer, 1967). Unlike the reserved, analytical stance of Jungian and Freudian therapists, psychedelic therapists acted as supportive, encouraging guides.

This treatment paradigm, which came to be known as *psychedelic therapy*, attributed beneficial outcomes to 'peak' experiences that catalysed shifts in attitudes and values, leading to behavioural changes like reduced drinking in alcoholics. These shifts reflected "a higher valuation of [a]esthetic, creative... and perhaps even religious interests" (Terrill, 1962, p.428), differing markedly from traditional psychotherapeutic change. The practice expanded rapidly, aided by Sandoz's liberal LSD distribution policy. By the mid-1960s, approximately 1,000 clinical publications had examined psychedelics in some 40,000 patients with various conditions, including alcoholism, depression, anxiety, and, regrettably, homosexuality (Grinspoon & Bakalar, 1979, p.192; Sandison & Whitelaw,

1957). Yet within a decade, research had effectively ceased without any recognised therapeutic indications, despite promising results.

1.2.4. Failure to launch

While psychedelic research developed through the 1950s and early 1960s, interweaving scientific, cultural, and political developments interacted to make the once fertile ground less hospitable for LSD-assisted therapies. Against the backdrop of these developments, it will be seen that, even if, *per* Hoffer and Osmond, the mystical experience is why psychedelic therapy showed such promise, it also goes some way to explaining why it failed to become an established treatment.

1.2.4.1. Scientific challenges

One important scientific challenge for this research was stemmed from evolving standards of scientific practice that had been developing for decades. These resulted in the introduction of the randomised controlled trial (RCT), the formalised coalescence of a number of standardisation and control practices to reduce conscious and unconscious bias distorting trial results (Armitage, 2003; Doll, 1998; Hill, 1951, 1952). Despite the self-evident general value of RCTs for developing scientific understanding[6], this methodological shift posed both pragmatic and conceptual problems for psychedelic therapy, in effect 'stacking the deck' against it.

The RCT's requirement for both patient and physician to be blinded to the treatment condition was then, and remains now, extremely challenging with psychedelic therapy. The particularly conspicuous subjective effects of LSD - and the verbal and behavioural responses that these effects engender- mean that there is typically little doubt when a patient is given the active drug rather than an inert placebo. This poses a significant methodological challenge, as the breaking of the blind may undermine the integrity of the placebo control. For medications with detectable side-effects – such as sedation and dry mouth in the case of some antihypertensives – researchers can employ an *active placebo* that mimics these effects without affecting the treatment target (in this case, blood pressure). This approach helps mask treatment allocation by creating equivalent subjective effects for all participants. While the use of active placebos might theoretically solve psychedelics' blinding problem, this solution creates something of a paradox[7]: the better an active placebo mimics the subjective effects of an investigational

[6] Nonetheless, philosophical challenges surrounding RCTs as the current 'gold standard' for medical evidence remain actively debated: their privileged status in evidence hierarchies may be overstated, particularly when evaluating complex interventions (Cartwright & Hardie, 2012); and the relationship between randomisation and causation is more nuanced than commonly assumed (Worrall, 2002).

[7] The 'double-blind double bind', if I may…

drug, the better it masks treatment allocation. But given that psychedelic therapy was proposed to be effective *because of* its subjective effects, a placebo that mimicked the very subjective effects hypothesised to be therapeutic would curtail the ability to detect treatment effects, since it would essentially be replicating the proposed mechanism of therapeutic action itself.

More broadly, the RCT methodology embodied assumptions about medical intervention that were at odds with psychedelic therapy's hybrid nature. RCTs are designed to abstract away the influence of extra-pharmacological, and principally psychological factors, on treatment outcomes in a trial. One assumption implicit in this design is that a drug's efficacy depends primarily on its biological activity. Not only did this assumption appear to hold true in the treatment of somatic disease - sulpha and penicillin were effective regardless of the 'set' and 'setting' in which they were administered - but importantly, it also appeared to hold true for the new pharmacotherapies developed for Psychiatry. The antipsychotics and anxiolytics that appeared in the 1950s appeared to be successful "regardless of the treatment environment or the interpersonal skills of the physician" (Oram, 2018, p.100). However, psychedelic therapy explicitly aimed to harness the very extrapharmacological factors that RCTs were designed to control away. This created a particularly challenging situation: the elements considered essential to the treatment had to be minimised to meet prevailing standards for demonstrating efficacy.

1.2.4.2. The cultural challenge

The cultural context proved equally challenging. As authors like Aldous Huxley popularised LSD and an unregulated market emerged, with private practitioners charging up to $600 per session and sometimes diverting the drug for non-medical use, the boundaries between clinical and non-clinical use began to blur. This boundary-blurring was exemplified by Harvard researchers Timothy Leary and Richard Alpert, whose controversial methods included administering psilocybin while themselves under its influence. Their vision for psychedelics extended far beyond therapeutic applications: they advocated for psychedelics as tools for cognitive enhancement, creativity, and what Abraham Maslow termed 'self-actualization' (Maslow, 1965) - the realisation of human potential through alignment with authentic values and goals. After their dismissal from Harvard in 1963, Leary's transformation into a countercultural icon and his establishment of the League for Spiritual Discovery - which declared the still legal LSD a religious sacrament - further eroded the drug's medical legitimacy. Alongside this, Alpert's journey to become the influential spiritual teacher Ram Dass - which he credits LSD for beginning (Ram Dass, 1978) - gave psychedelic sceptics additional reason to doubt the findings from researchers struck by what was described as 'excessive enthusiasm' about LSD (Cole & Katz, 1964; Koning et al., 2024).

Self-experimentation with LSD by researchers —one of the uses of LSD initially recommended by its manufacturers— contributed to significant mistrust among the broader medical community. Editorials in leading medical journals opined that it was "impossible to find an investigator willing to work with LSD-25 who was not himself an addict" (Grinker, 1964, p.78), that "every effort should be made by the medical professional to block the use of the psychotomimetics except under experimentally controlled conditions" (ibid.), and that LSD research should be undertaken "only in controlled settings by scientists capable of impartial, critical judgement" (New England Journal of Medicine, 1965, p.280). Psychedelics are known to induce experiences that are often among the most personally meaningful or spiritually significant of a user's life (Griffiths et al., 2006, 2011; Søgaard Juul et al., 2023; Sweeney et al., 2022), and so it is understandable that familiarity with the unusual states induced by LSD was seen by the medical community not as a clinical virtue, but rather a methodological liability that jeopardised researchers' objectivity (Giffort, 2020, p.54)

The indiscreet use of psychedelics outside clinical contexts further diminished societal support for the research. LSD became increasingly associated with counterculture and opposition to established values (Baumeister & Placidi, 1983). Growing public perception of LSD as a social threat (Cornwell & Linders, 2002) led to the 1965 Drug Abuse Control Amendments in the US, which, *inter alia*, labelled LSD as a drug of abuse, and prohibited its manufacture or use outside of legitimate clinical trials. Yet, contrary to the popular perception that the government sought to bring an end to LSD research with the 1965 amendments, this is not so. The amendments themselves explicitly left significant space for clinical research to continue, requiring only that more stringent levels of record-keeping were met to insure against the diversion of the drug.

1.2.4.3. The political challenge

Perhaps the most significant obstacle to licensing LSD came from the 1961-1962 Kefauver-Harris Drug Amendments (1962). Several earlier attempts to strengthen pharmaceutical regulation in the US (Temin, 1980, Ch. 5) gained traction only after the 1961 thalidomide scandal, when a morning sickness drug licensed in Europe caused thousands of birth defects (Tobbell, 2008, p.125). Although ostensibly a response to a *safety* concern surrounding drugs, notably these amendments also extended the remit of the Food and Drug Administration (FDA) to include assessment of *efficacy*, a jurisdiction it had tried and failed to claim in the decades prior. The 1962 Amendment required a new drug's efficacy to be demonstrated through 'adequate and well-controlled investigations' (Title 1, Part A, Sec. 102(c)), and established the FDA as the gatekeeping authority for the interpretation of 'adequate and well-controlled investigations'. Notably, the legislation did not include any formal specification of what such

investigations should consist of, and no official guidelines were provided by the FDA, although in less official communications FDA officials indicated a strong preference for RCTs (Oram, 2018, p.81), the challenges of which we have reviewed.

This preference created significant challenges for psychedelic research. By 1970, numerous trials had explored LSD's potential for treating alcoholism, but studies incorporating FDA-favoured methodological controls consistently failed to find a specific treatment effect. Among these studies, Hollister et al. (1969) and Johnson (1969) administered LSD with 'little or no specific psychotherapy' or with 'no therapist present,' an approach derided by psychedelic therapists as 'psychedelic chemotherapy' (Kurland et al., 1971, p.84). Taking standardisation to its logical extreme, Smart et al. (1966) administered 800 μg of LSD to patients before leaving them, strapped to a gurney, in a dark, quiet room. These studies did not return positive results relative to placebo. Notably, modern psychedelic researchers maintain that 'neglect of context could render a psychedelic experience not only clinically ineffective but also potentially harmful' (R. L. Carhart-Harris et al., 2018).

One large RCT of LSD for alcoholism, using 50 μg LSD as an active placebo to appease the FDA, failed to find a significant treatment effect at the 12-month follow-up (Pahnke, 1970). Although the study reported substantial (54%) levels of 'rehabilitated' drinking behaviours amongst the treatment group, who received therapy with 450 μg of LSD, the active placebo group also improved, leading Charles Savage - one of the study authors - to opine retrospectively that what they had conducted was "not a controlled study but a dose response curve study" (quoted in Oram, 2018, p.151). The challenge proved intractable: adequately demonstrating efficacy to the FDA required controlling away the very extrapharmacological factors that researchers believed made the treatment work.

Despite significant discussion among LSD researchers about the appropriate means of providing acceptable elements of control to their studies (Abramson, 1960, 1967), and some FDA signals of flexibility, calls for methodological nuance gained little traction. Some lamented that the FDA's requirements had "hung a millstone around our necks which is steadily becoming more burdensome" (Hoffer & Osmond, 1967).

The coup de grâce came when Sandoz, facing mounting regulatory hurdles and reputational concerns, discontinued LSD manufacture and withdrew sponsorship from all LSD research (Oram, 2018, p.74). As Sandoz was the only eligible LSD research sponsor in the United States, its sponsorship withdrawal automatically rescinded all LSD researchers' authorisation to conduct research. With overlapping

hurdles exponentially increasing the difficulty of performing research with LSD and other psychedelics, research ultimately trickled to a stop. The field would lie dormant for three decades[8].

The barriers that stalled psychedelic research in the 1970s proved particularly resilient. However, by the 1990s, several developments began to erode these obstacles. Advances in neuroscience provided new methods for understanding psychedelic mechanisms of action (F. Vollenweider, 1998), helping to legitimate their scientific study. Early clinical research, including Rick Strassman's physiological studies of DMT (Strassman, 1994, 1995) demonstrated the safety and feasibility of conducting human trials within modern regulatory frameworks. Simultaneously, the formation of organisations like the Multidisciplinary Association for Psychedelic Science (MAPS, founded 1986) and the Heffter Research Institute (founded 1993) established infrastructure to support regulated clinical trials. Early, small-scale studies with psilocybin[9] began to yield positive, peer-reviewed findings (Grob et al., 2011; Moreno et al., 2006), and momentum rapidly picked up again.

1.2.5. The 'Psychedelic Renaissance' and the definitional question

At the time of writing, psychedelics have returned to clinical research with a vengeance. Several leading research universities have launched dedicated psychedelic science centres, and major medical journals publish psychedelic research with some frequency. Now (Dec 24), some 22 commercial clinical trials of classic psychedelics are in phases II or III, targeting depressive disorders, alcohol use disorder, adjustment disorder, obsessive compulsive disorder (OCD), generalised anxiety disorder, post-traumatic stress disorder (PTSD), anorexia nervosa and binge eating disorder, and bipolar disorder. Other registered trials include caregiver and clinician burnout, palliative care, bereavement, methamphetamine use disorder, opioid dependence, demoralisation within hospice care, cancer pain, cancer-related anxiety, cocaine use disorder, and nicotine dependence (Haichin, 2024).

[8] This characterisation requires some qualification. While *formal* clinical research ceased, psychedelic therapy continued through underground networks, with the use of illicitly obtained LSD (Smith & Appelbaum, 2022). Underground therapists experimented with other drugs, including MDMA before (and after) its prohibition, as well as developing non-drug methods to emulate the psychedelic state (Grof, 1988). This period saw the development of therapeutic practices that departed significantly from conventional clinical approaches, including the controversial use of 'therapeutic touch' and other somatic modalities, which raises serious concerns about boundary violations and patient therapy (Kruger et al., 2025, explored in Ch. 2). As with attempts to meaningfully engage with Indigenous practices with psychedelics, there remains a serious challenge for academic psychedelic researchers seeking to honour the accumulated clinical understanding of underground therapists. While both groups doubtless hold wisdom that is not fully appreciated by academic researchers, such wisdom emerges from epistemological frameworks and modes of validation that differ fundamentally from academic research.

[9] Chosen for the first modern studies partly because of a shorter time of acute drug effects, but also because it carried less cultural and political stigma than LSD.

While mid-20th century scholarly interest in psychedelics focused principally on LSD, as well as, to some extent, the naturally occurring DMT, mescaline, and psilocybin, in more recent use, the term *psychedelic* is seen applied not just to these aforementioned 'classic psychedelics', but also a range of other substances: 3,4-Methylenedioxymethamphetamine (MDMA), ketamine, salvia, scopolamine, ibogaine and, in some cases, cannabis (see Mayet, 2020; Nichols et al., 2023; O'Donnell et al., 2024). This expanded set of 'psychedelics' is extremely heterogeneous, with significant variation across dimensions such as chemical structure, pharmacological mechanism of action, history and patterns of usage, and acute subjective effects (see Table 1 below). It remains to be seen whether a principled framework can delineate the necessary and sufficient conditions to unify so diverse a collection of substances under the label 'psychedelic', or whether the term will continue to function as a loose, heuristic category reflecting partially overlapping, but often distinct properties.

Moreover, determining the boundaries of what qualifies as a 'psychedelic' is not necessarily an objective, disinterested affair: claiming the title for a drug can hold benefits. For instance, ketamine, unlike other psychedelics, is a licensed medicine, principally used as an anaesthetic, but increasingly prescribed off-label in the treatment of a number of psychiatric conditions. Referring to such a treatment as a 'psychedelic medicine' serves two purposes for a clinical provider. It downplays the negative connotations of ketamine, which for many may be associated primarily with veterinary medicine ('it's a horse tranquilliser'), while also allowing a prospective treatment to trade on the media hype associated with 'psychedelics'.

Ultimately, whether it 'makes sense' to count a given substance as a psychedelic depends on what context, and to what end, we are discussing the use of psychedelics[10]. As the focus of this thesis is on bioethical dimensions of *psychedelic-assisted psychotherapy*, it is not concerned with those psychedelics that have no recent history of being explored as medicines for the treatment of psychopathology. Furthermore, the thesis does not encompass *all* psychedelics involved in psychedelic-assisted psychotherapy. Psilocybin, MDMA, and ketamine have all recently been used in practices described as *psychedelic-assisted psychotherapy*, but their acute subjective effects, mechanisms of action, and risk profiles are sufficiently distinct for these to be properly considered as distinct modalities.

[10] For example, during the drafting of the Hopkins-Oxford Psychedelic Ethics Consensus Statement (Jacobs et al., 2024a), it became apparent that the topic of discussion (e.g., mitigating a risk profile; ensuring reciprocity with Indigenous communities; appropriate models of regulation) partially determined which substances were more relevant.

	Psilocybin	Ketamine	MDMA
Acute subjective effects	Visual distortions, altered perception of time and space; enhanced connection with emotions and introspective thought; feelings of unity, transcendence	Detachment from reality, "out-of-body" experiences; calming or dreamlike states; reduction in pain sensation	Heightened feelings of empathy, love, and social connectedness; increased energy and euphoria; heightened response to music and touch
Mechanisms of action	Serotonin receptor agonism (principally 5-HT_{2A}); broad changes in global functional connectivity; increased neuroplasticity	NMDA receptor antagonism; glutamatergic cascade leads to disruptions in thalamo-cortical loops altering sensory and cognitive integration.	Monoamine (serotonin, dopamine, noradrenaline) release and reuptake inhibition; release of vasopressin and oxytocin; reduced amygdala activity
Risk profile	Low physiological toxicity Psychological risks: Anxiety, paranoia, psychotic-like episodes Negligible addiction risk	Moderate toxicity: can cause cardiovascular strain and bladder issues with chronic use Psychological risks: dissociative episodes and potential dependency Moderate addiction risk	Moderate toxicity: hyperthermia, dehydration, cardiovascular stress Psychological risks: Low-moderate addiction risk
Duration of effects	4-6 hours	45 minutes to 2 hours	3-6 hours

Table 1.1.: An illustrative overview of distinctions between psilocybin, ketamine, and MDMA with regards to their clinical use

Among modern clinical trials, psilocybin, a compound found in more than 100 species of 'magic' mushrooms, emerges as the most widely used psychedelic. As such, I consider psilocybin-assisted therapy as the prototypical P-AT, and focus the empirical component of this thesis on those who have participated in a clinical trial involving psilocybin. The bioethically interesting features of psilocybin-assisted therapy largely stem from effects which are more similar than they are different to those of other classic psychedelics. Therefore, unless otherwise specified, many arguments and conclusions presented herein may apply equally to psychotherapy assisted by any of these classic psychedelics. With this in mind, in the next section I shall outline the key characteristics of this range of substances.

1.3. Classic Psychedelics - An Overview of the Scientific Foundations of P-AT

1.3.1. Subjective effects

For readers lacking experiential acquaintance with psychoactive drugs, it is instructive to highlight prominent effects commonly experienced following classic psychedelic administration: visual hallucinations (Kometer et al., 2013), intensified emotions (Carbonaro et al., 2020), subjective time distortion (Wackermann et al., 2008; Wittmann et al., 2007) and synaesthesia (Luke & Terhune, 2013). Another key effect that has drawn bioethical attention (Gearin & Devenot, 2021; W. R. Smith & Sisti, 2021) is *ego-dissolution* — a profound alteration in self-experience characterised by a reduction or loss of the ordinary sense of self as a bounded, separate entity (Lebedev et al., 2015; Nour et al., 2016). This phenomenon can range from mild experiences of reduced self-focus to complete dissolution of perceived boundaries between self and world, accompanied either by pleasant feelings of unity with one's surroundings (Kałużna et al., 2022; Millière et al., 2018), or by dread and anxiety akin to depersonalisation (Studerus et al., 2010).

Metrics for assessing the acute effects of psychedelics abound (Hovmand et al., 2023), and validated instruments can, despite some similarities, reliably discriminate between psilocybin, ketamine, and MDMA (e.g., the OAV[11] scale, Fig 1.1).

[11] **O**zeanische Selbstentgrenzung ('Oceanic Boundlessness'), **A**ngstvolle Ich-Auflösung (Dread of Ego Dissolution), and **V**isionäre Umstrukturierung (Visionary Restructuralisation); (Bodmer et al., 1994).

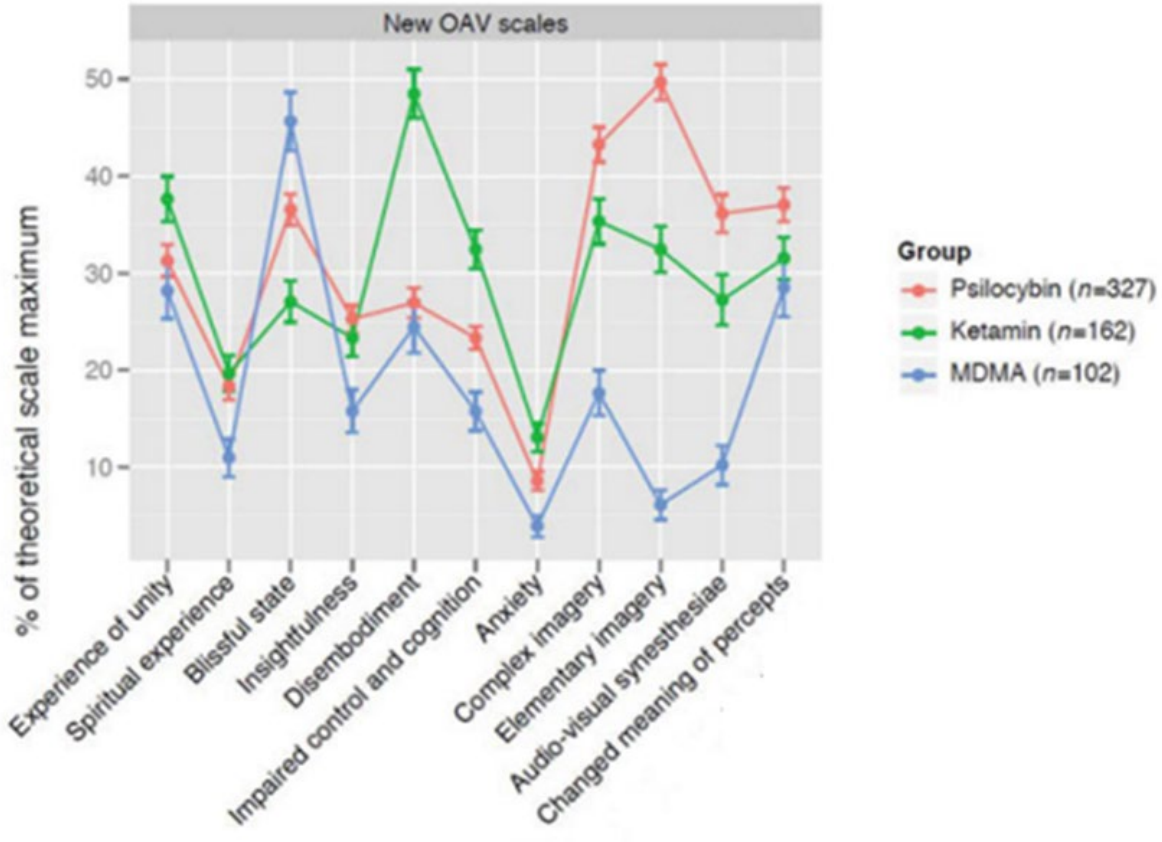


Figure 1.1: Subjective features of acute effects of psilocybin, ketamine and MDMA as measured by the OAV scale. Adapted from Studerus et al. (2010)

Alongside these effects, it is important to highlight previous attempts to characterise the distinctive subjective effects of psychedelics. Psychiatrist Jerome Jaffe highlighted their "capacity reliably to induce states of altered perception, thought, and feeling that are not experienced otherwise except in dreams or at times of religious exaltation" (Jaffe, 1985). Early LSD researcher Daniel X. Freedman emphasised their induction of 'portentousness' — "the capacity of the mind to see more than it can tell, to experience more than it can explicate, to believe in and be impressed with more than it can rationally justify" (Freedman, 1968, p.331).

These descriptions point to what has become known as the 'peak' or 'mystical' experience. While some contemporary researchers avoid the term 'mystical' — perhaps concerned it might undermine perceptions of scientific objectivity — Walter Pahnke (1966) identified no fewer than nine characteristics that psychedelic mystical experiences share with non-pharmacologically-induced mystical experiences: a sense of unity with all things, a sense of fundamental insight into reality that is not mediated by language, a sense of transcending space and time, a sense of sacredness, deeply-felt positive mood, a sense of paradoxicality - of some truths retaining their validity despite violating the laws of Aristotelian logic - an alleged ineffability of the experience, and a temporary duration of the experience that nonetheless tends towards enduring positive changes in attitude and/or behaviour.

Whatever the appropriate name for this dimension of the psychedelic experience, it has been seen to correlate with therapeutic outcomes across a number of treatment indications (Bogenschutz et al., 2015; Roseman et al., 2018; S. Ross et al., 2016), and a substantial number of contemporary researchers believe it to be causally related to clinical improvements (see §1.4.3. below).

The precise nature of the pharmacological and neurophysiological mechanisms of action underlying these subjective effects is a matter of significant scientific debate, far beyond the scope of the thesis. Nonetheless, for what follows, it will be useful for readers to have a basic high-level understanding of some of the key points relevant to the debate about these potential mechanisms.

1.3.2. Basic Pharmacology and Neural Effects

1.3.2.1. 5-HT_{2A} receptor binding

Psilocybin (and its psychoactive metabolite, *psilocin*) shares with the other classic psychedelics a structural similarity to the monoamine neurotransmitter serotonin fig 1.2). It is this structural similarity to serotonin that allows psychedelic substances to act as agonists to varied serotonin receptors in the brain — a process which is understood to drive the characteristic effects of these drugs. Although the classic psychedelics bind at a number of receptors (Rickli et al., 2016), agonism at the serotonin 2A (5-HT_{2A}) receptor is seen to play the largest role in subjective effects: the intensity of psilocybin's psychedelic effects correlate with 5-HT_{2A} receptor occupancy (Madsen et al., 2019; Stenbæk et al., 2021), and are blocked by pre-emptive administration of the 5-HT_{2A} antagonist ketanserin (Holze et al., 2021; Kometer et al., 2013; Kraehenmann et al., 2017; Preller et al., 2017).

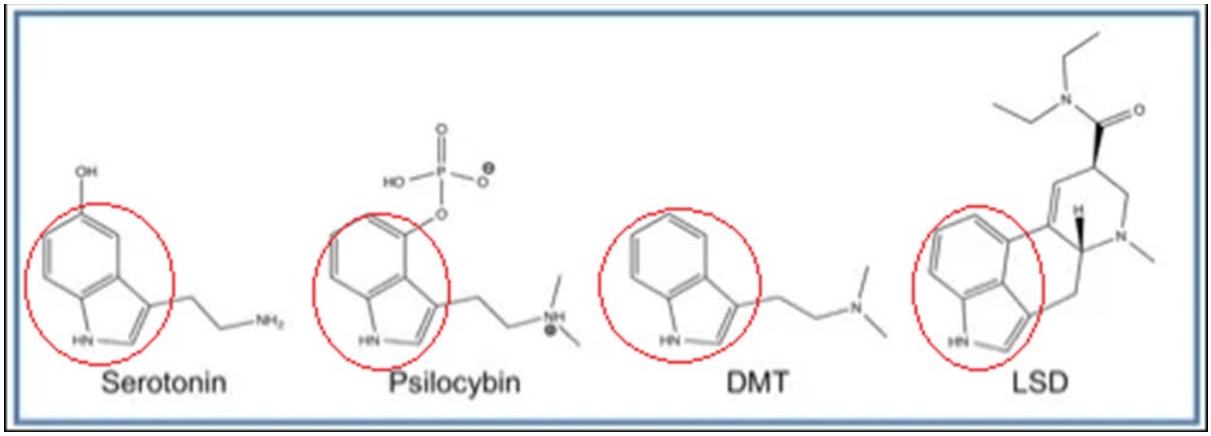


Figure 1.2: Chemical structure of serotonin and three classic psychedelics. The shared indole ring structure is understood to contribute to psychedelics' ability to bind to serotonin receptors in the brain. Adapted from Welsh (2017).

Receptor mapping studies have found high concentrations of 5-HT_{2A} receptors both in the striate and extrastriate visual cortex (López-Giménez et al., 2001; Rakic et al., 1988) —implicated in basic and complex visual processing respectively— and in the higher-order associative areas of the brain (Beliveau et al., 2017). In combination, the implication of these regions in psychedelic pharmacology potentially contributes to the prevalence following administration of both visual hallucinations, and wide-ranging effects across perceptual, cognitive, and affective functions.

1.3.2.2. Glutamatergic effects & network-level changes

While detailed accounts of downstream neural effects are available elsewhere (Carhart-Harris, 2019; D. E. Nichols, 2016; F. X. Vollenweider & Preller, 2020), the most salient additional consequences of 5-HT_{2A} activation by a classic psychedelic include enhancement of the activity of various neuronal networks in the prefrontal cortex via an elevated release of glutamate at the individual cell level (Aghajanian & Marek, 1999; Béïque et al., 2007). This elevated glutamatergic activity is, however, *asynchronous* - while neighbouring neurons typically release glutamate in rhythmic synchrony with one another, the *asynchronous* nature of psychedelic-induced glutamate-release at the single-neuron level leads to disruptions to the normal rhythmic oscillations of cortical neurons, and ultimately to the disorganisation of cortical activity (Carhart-Harris et al., 2012; Muthukumaraswamy et al., 2013).

This disruption of typically coherent cortical activity means that, at the whole-brain level, typically stable networks of functional connectivity undergo *desegregation* and *disintegration* (Luppi et al., 2021; Müller et al., 2018), resulting in increased communication between typically distinct networks and disruption of established ones (Petri et al., 2014). At a first gloss, this network disintegration and desegregation mean that, at a neural level, information processing takes place in ways that are markedly different from ordinary activity (Carhart-Harris, 2019). For example, the functional connectivity of the primary visual cortex under LSD is greatly expanded, suggesting that considerably more parts of the brain contribute to visual processing during acute drug effects than in normal conditions (Carhart-Harris et al., 2016). This heightened connectivity could help explain how distinct psychological functions, including other senses, can influence the visual experience under psychedelics, e.g. the quasi-synaesthetic experience of ‘seeing’ music due to novel connectivity between the auditory and visual cortices (Luke & Terhune, 2013; Pahnke & Richards, 1966), and the induction of eyes-closed visual imagery with autobiographical salience via coupling of the visual cortex and parahippocampal cortex (Kaelen et al., 2016).

1.3.2.3. REBUS: A leading computational account

Beyond this *implementational* account of the action of psychedelics, the most comprehensive *computational* model - the RElaxed Beliefs Under Psychedelics (REBUS) model - situates psychedelic action within a predictive processing (PP) paradigm (Carhart-Harris & Friston, 2019; Clark, 2013). In contrast to traditional approaches to neural information processing (Fodor, 1975; Marr, 1982), PP does not assume a singular 'bottom-up' approach where sensory stimuli are propagated up cortical hierarchies to form complex representations. Rather, the brain generates predictions about sensory causes —that is, beliefs about the world— in a 'top-down' fashion, propagating those predictions downward across cortical hierarchies until they meet incoming sensory data. Any 'prediction error signals' - mismatches between predictions and incoming stimuli - are propagated back upwards, weighted by prediction confidence. Consider a late-night writing session: in dim light, a coat rack might momentarily appear as a silent figure in your peripheral vision. The perceptual correction back to 'coat' represents the reassertion of your high-confidence prior prediction about being alone in the room. The prediction error is explained away, and perception aligns with your existing world model.

According to REBUS, psychedelics simultaneously enhance bottom-up sensory flow while reducing confidence in predictions about reality: hallucinations occur because incoming sensory data exerts greater control over conscious perception. Without strong prior predictions, unlikely interpretations can emerge. Supporting this, participants under LSD display muted neural markers of surprise to unexpected stimuli in 'oddball' experimental paradigms (Timmermann et al., 2018). The model's prediction that 'higher-level' perceptual functions should be more impaired than 'lower-level' ones is supported by findings that contrast sensitivity (a basic, lower-level visual function), but not motion perception (which requires higher-level integration of visual information over time), is preserved following psilocybin administration (Carter et al., 2004).

The explanatory reach of REBUS spans from basic perception to higher-order experience. Weakened priors about object permanence may explain characteristic visual effects like walls appearing to 'breathe'. At a deeper level, ego-dissolution is understood within REBUS as the collapse of our most entrenched prior: the model of self as a unitary, bounded entity (Carhart-Harris & Friston, 2019; Deane, 2020; Letheby & Gerrans, 2017).

1.3.2.4. Neuroplasticity

Beyond their subjective and higher-order brain effects, classic psychedelics have been shown to promote neuroplasticity, the brain’s ability to form and reorganise synaptic connections. Following

psychedelic administration, increased synaptic growth and dendritic complexity has been observed not only in primary neuronal cultures, but also in *in vivo* and *ex vivo* brain tissues (Ly et al., 2018, 2021; Raval et al., 2021), via the release of brain-derived neurotrophic factor-tropomyosin receptor kinase B (BDNF-TrkB). This action has been shown to occur independently of 5-HT_{2A} agonism — a fact with potentially significant implications for theories of how psychedelic-assisted psychotherapy exerts its therapeutic effects (see §1.4.1. below). Moreover, psychedelic administration also increases the expression of genes understood to be implicated in the synthesis of proteins that support neuroplasticity, most notably in the prefrontal cortex (Jefsen et al., 2021; Martin et al., 2014; C. Nichols, 2002).

1.3. Contemporary P-AT

1.3.1. The Contemporary Clinical Trial Model

Having provided an overview of the characteristics of *psychedelics*, I now turn to a fuller account of what I mean by *psychedelic-assisted psychotherapy* (P-AT). In brief, P-AT is any hybrid pharmacotherapy-psychotherapy modality wherein at least one administration of a high dose of a psychedelic substance takes place within a broader psychological treatment regimen. While §1.2.2 above showed that the use of pharmacological aids to facilitate psychotherapy has a history spanning nearly a century, including the use of lower doses of psychedelics, modern clinical research practice has coalesced around the use of higher doses of psychedelics, i.e., those that are likely to engender peak psychedelic experiences. Systematic reviews and meta-analyses of studies incorporating this design indicate positive treatment effects in depressive disorders and symptoms (Fang et al., 2024; Haikazian et al., 2023; Swieczkowski et al., 2025); existential distress in patients with a life-threatening disease (Marchi et al., 2024; Yu et al., 2021), and anxiety symptoms (Goldberg et al., 2020), with strong positive signals of therapeutic effect reported for a much broader range of indications. Importantly though, the sole Cochrane Review of P-AT trials (for "anxiety, depression and existential distress in people with life-threatening diseases", Schipper et al., 2024) found that the certainty of evidence was at best 'mixed', and typically 'very uncertain'. The strict evaluation of bias within these reviews identified that continuing challenges in successfully blinding participants to treatment allocation limits the credibility of findings[12].

[12] However, it should be noted that the certainty of evidence for *many* accepted medical interventions is poor in Cochrane reviews (Fleming et al., 2016; Howick et al., 2022).

At the heart of the contemporary conception of the modality lies a tripartite approach that has evolved from early psychedelic research, encapsulated by the acronym 'PSI' — *preparation, substance administration*, and *integration*.

1.3.1.1. Preparation

In the days and weeks before substance administration, members of the clinical team who will be present during acute drug effects meet with the patient. While conventional psychiatric assessments may be brief and standardised, these preparatory sessions serve multiple crucial relational functions. The primary objectives are to establish a strong therapeutic rapport and alleviate potential apprehensions or concerns. Early researchers found that patients lacking adequate preparation often struggled against their psychedelic sessions, experiencing avoidance and increased emotional dysregulation (Kishon et al., 2024). This attention to relationship building appears particularly important given that psychedelic experiences frequently centre on interpersonal themes, with clinical studies finding that "nearly all participants reported having an experience of love and joy, and these exalted experiences arose primarily through a specific human relationship with another person, whether it was a parent, child, or partner" (Belser et al., 2017, p.363). Similarly to other psychotherapeutic approaches, the establishment of a positive therapeutic alliance is increasingly recognised as important for favourable treatment outcomes in P-AT (Kamilar-Britt et al., 2023; Levin et al., 2024; Murphy et al., 2022).

During these preparatory sessions, patients receive psychoeducation about the structure of the forthcoming dosing sessions, gaining insights into what to anticipate and the likely experiences they will encounter. In addition, patients are equipped with breathing and grounding techniques that they can practise and utilise as needed during the drug sessions, should the experience become overly intense. By making patients feel as safe, comfortable and ready for their upcoming psychedelic experience, preparation serves to optimise 'set' (Garcia-Romeu & Richards, 2018; see §1.2.3. above).

1.3.1.2. Substance

The contemporary clinical model involves at least two substance administration sessions, although this practice has shifted recently (see §1.5.1.). In each session, having been administered a dose of the psychedelic drug, participants recline on a couch or bed in a comfortably appointed room with soft lighting, and are provided eyeshades and headphones through which a specially curated playlist is played. The model procedure for P-AT specifies that throughout the duration of drug effects, the patient

is accompanied by two co-therapists, one male and one female[13]. These features are inherited from early psychedelic trials, developed with the aim of optimising 'setting'. Although patients are permitted to talk to the therapists during the drug administration session, they are encouraged to focus their attention on their 'inward journey', the closed-eye visual hallucinations and visions, autobiographical recollections, and other subjective phenomena that arise due to the drug effects. As such, contemporary practice continues to include early researcher Walter Pahnke's exhortations to 'go inside', and to 'trust, let go, and be open' to the experience (Pahnke, 1969). Contemporary trial practice includes a number of safety precautions, including blood pressure monitoring, and the presence of a prescribing physician to administer rescue medications. The latter typically include benzodiazepines in case of extreme acute anxiety or agitation (Barnett et al., 2025), although these are used very infrequently (Garcia-Romeu & Richards, 2018).

1.3.1.3. Integration

The *integration* sessions that follow any drug administration session serve "to either minimize harms or maximize benefits associated with psychedelic use," and are widely held to be vital to the therapeutic process (Greń et al., 2023, p.31; 2024). While no consensus definition of *integration* exists in the field, and several theoretical models exist (Bathje et al., 2022), these models align in their aim to support patients in processing and making meaning from their psychedelic-induced experiences. It is important to distinguish integration *sessions* from the broader integration *process* of which they are a part. Trials from 2012-8 typically featured 1-3 integration sessions in the days and weeks following each drug session, in which patients discuss their experiences with therapists, who help them identify any insights, explore their significance, and work to assimilate them into their daily lives. Of these sessions, veteran psychedelic researcher Bill Richards has said:

> Drug-free sessions then, of course, continue to be of importance during the weeks following a psychedelic experience. Over and over, one moves one's awareness back and forth from the memory of the experience to the decisions and strategies required in daily living, gradually

[13] This practice is an inheritance from the first wave of psychedelic therapy, during which time Jungian models of psychological change were at the height of their theoretical dominance. According to such perspectives, the psychedelic state can engender both autobiographical and archetypal experiences of 'the mother' and 'the father', such that a male-female therapist dyad provides an opportunity to symbolically re-present therapeutically corrective experiences with these figures. While modern justifications for this approach appeal to providing a sense of safety to patients, especially those who were subject to early sexual abuse, the practice has not been without criticism. There is no robust evidence base for the influence of therapist genders on treatment outcomes, and critics have argued that the heteronormative assumptions underlying the practice risks pathologising sexuality- and gender-diverse communities (Rea & Wallace, 2021; Wagner et al., 2019).

> progressing toward the integration of the insights gained and the implementation of actual changes in attitudes and behavior. (Richards, 2017, p.332)

The broader integration process, however, extends beyond these formal therapeutic encounters, also encompassing ongoing active efforts by the patient to reflect on, apply, and embody the insights gained during psychedelic experiences. Integration sessions will support this process, with therapists guiding patients in finding other complementary activities, including reflection and journaling, mindfulness practices, methods to bring about behavioural change, and finding outlets for creative expression (Aixalà & Bouso Saiz, 2022). Integration may also involve expressive practices like drawing, movement, or role-playing to help process the experience. In some trials, the process of integration is set within a wider-ranging psychotherapeutic treatment plan, wherein the psychedelic sessions are seen to enhance the effects of an already evidence-based treatment such as Cognitive Behavioural Therapy or Motivational Enhancement Therapy (Bogenschutz et al., 2022; M. W. Johnson et al., 2017).

The model outlined above represents neither an optimised nor a perfected mode of practice. Psychedelic-assisted therapy remains a modality very much in its infancy; understanding about its mechanisms of change are limited and imperfect (see § 1.4 below); and the model continues to be adjusted and refined in recent and ongoing studies (§ 1.5.1). Beyond the outline provided above, there are many norms within mainstream psychedelic therapeutic practice that are perhaps better understood as well-established traditions born of clinical observation (Noorani, 2021) than theoretically or empirically robustly-justified choices. The cost- and bureaucratic-restrictions of running clinical trials is such that a full understanding of how to optimise treatment parameters (dose and intervals between administration sessions, level of integration support, choice of psychotherapeutic intervention, and environmental context) will likely only be established long after licensing.

1.4. Potential Therapeutic Mechanisms of P-AT

The last two decades of research has yielded diverse accounts of the therapeutic action of classic psychedelics, couched in the terminology of diverse levels of analysis, including biological, neurocognitive, and psychobehavioural. This diversity in itself is unsurprising, given that accounts of psychopathology itself are likewise explained at different levels. In clinical research contexts, saying that P-AT 'works' for, e.g., depressive disorders, is operationalised as the reduction in clinimetric scores on some validated symptom scale (e.g., the Hamilton Depression Rating Scale; Hamilton, 1967), the construction of which means an improvement in depression may be an improvement in any combination of insomnia, anhedonia, feelings of guilt, suicide, or other symptoms. As such, therapeutically relevant

changes across different patients may reflect the action of one or more pathways targeting different processes (Aftab & Stein, 2022).

Here I provide an overview of the most prominent accounts of therapeutic action.

1.4.1. Biological

Principal among the chiefly-biological accounts of post-psychedelic therapeutic change is that of enhanced neuroplasticity, which has led to the proposal of the term 'psychoplastogens'. This term demarcates the class not by subjective effects, but by shared cellular activity: the rapid promotion of structural and functional neural plasticity (De Vos et al., 2021; Olson, 2018; § 1.3.2.4. above).

The temporal dynamics of this enhanced plasticity are particularly noteworthy. Following psychedelic administration, subjects typically report a distinctive period of positive mood, emotional openness, and enhanced psychological flexibility that persists well beyond the acute drug effects - a phenomenon termed the 'afterglow' (Majić et al., 2015). This subjective state appears to have neurobiological underpinnings: the window of enhanced neuroplasticity following psychedelic administration extends from 48 hours to seven days, creating a period of heightened malleability in neural circuits. Crucially, structural changes that occur during this window - including the formation of new dendritic connections - can persist for at least one month after administration (Calder & Hasler, 2023; Shao et al., 2021). This suggests that the afterglow period may represent a critical window during which environmental inputs and experiences can shape lasting neural reorganisation.

Reduced neuroplasticity is associated with higher symptomatic profiles across psychopathologies. Depression correlates with impaired cortical neuroplasticity, and its remission with restored plasticity (Kuhn et al., 2016; Player et al., 2013). In PTSD and generalised anxiety disorder, pathology is associated with fewer synaptic connections between the prefrontal cortex and amygdala (Liu et al., 2020; Yabuki & Fukunaga, 2019), suggesting reduced cortical control over threat and fear processing. Likewise, addictions are associated with reduced neuroplasticity in the circuits between the prefrontal cortex and the nucleus accumbens, reducing cortical modulation and inhibitory control over addictive behaviours (Kalivas, 2009; Koob & Volkow, 2016). Just as conventional antidepressants are understood to promote neuroplasticity (Casarotto et al., 2021; Castrén & Antila, 2017), exerting a therapeutic effect across a range of pathologies, so do psychedelics - except that they bind to the receptors implicated in plasticity with affinities several orders of magnitude higher than SSRIs (Moliner et al., 2023).

It would be incorrect to infer from this that neuroplasticity is straightforwardly a good thing. In the wrong contexts, neuroplasticity can lead to maladaptive outcomes - as in the development of addiction and OCD, wherein reward circuitry and intrusive thought patterns are excessively rewired (Kalivas & O'Brien, 2008; Van Den Heuvel et al., 2016). Neuroplasticity-inhibiting drugs are being explored for their ability to diminish memory-consolidation, so as to avoid the development of PTSD following traumatic experience (Parsons & Ressler, 2013). Since neuroplastic changes are sculpted by environmental inputs and experiences (Cramer et al., 2011), the quality of the environment becomes significant - it may determine whether enhanced plasticity leads to adaptive or maladaptive neural reorganisation.

1.4.2. Neurocognitive

The REBUS model (§1.3.2.3., Carhart-Harris & Friston, 2019), which proposes that classic psychedelics 'loosen priors', i.e., weaken the dominance of unconscious assumptions about the nature of reality that the brain uses to model the world, can also be used to account for psychedelics' transdiagnostic efficacy. Many psychopathologies can be characterised by the strength of maladaptive assumptions about how the world works, as in the negative cognitive bias seen in depression (Beck, 1972). Similarly, anxiety disorders can involve unrealistically rigid priors—specifically, exaggerated expectations about both the likelihood of encountering feared stimuli and the severity of potential consequences of that encounter (Aue & Hoeppli, 2012; Aue & Okon-Singer, 2015). In those who have experienced life-threatening events, it has been proposed that the high salience of these events produces a strongly weighted prior to support its pre-emptive detection in the future, leading to PTSD symptoms such as flashbacks (Kube et al., 2020); a suggestion indirectly supported by a relative inability to update beliefs in response to good news when people are under stress (Garrett et al., 2018). The weakening of such maladaptive priors may enable more adaptive belief-updating. REBUS also explains psychedelics' context-sensitivity: with high-level predictions weakened, immediate environmental inputs have greater influence on experience and belief formation than they might otherwise do. As yet there has been little direct experimental testing of the REBUS model, although one small (n=11) study of healthy individuals found that confidence in negative self-beliefs decreased four weeks following psilocybin administration, with those decreases in confidence predictive of increases in well-being.

1.4.3. Psychobehavioural

A number of competing, though not necessarily exclusive, explanations of psychedelics' therapeutic efficacy are grounded at the levels of the psychological, including aspects of the acute subjective experience, and shifts to psychological traits and behaviours in the sub-acute and long-term stages.

Significant associations between mystical experiences and therapeutic outcomes have been reported across multiple indications: depression and anxiety in cancer patients (Griffiths et al., 2016; Richards et al., 1977; S. Ross et al., 2016), treatment-resistant depression (Roseman et al., 2018), and substance dependencies (Bogenschutz et al., 2015; Garcia-Romeu et al., 2015). However, the longest-term follow-up study (4.5 years post-treatment) found enduring therapeutic effects but no correlation between mystical experiences and long-term changes (G. I. Agin-Liebes et al., 2020). Whether this finding reflects a lack of statistical power - half of participants had died since the original study - or because of engagement with other salutary changes in the interim, remains unclear.

Although the mystical experience following psychedelic administration has been well-characterised (1.3.1.), the correlational studies between mystical experience and improved outcomes leave the mechanism of action here as somewhat of a black box. The overlapping construct of *awe*, characterised by the perception of vastness - a stimulus far larger than the self, and the need for accommodation, to adjust mental structures to integrate that experience, has been proposed as the mechanism underlying post-psychedelic therapeutic change (P. S. Hendricks, 2018; Keltner & Haidt, 2003). The experience of awe has been associated with enhanced meaning in life, increased self-transcendence, enhanced satisfaction with life, and increased generosity and pro-social behaviours (Chirico & Gaggioli, 2021; Krause & Hayward, 2015; Piff et al., 2015).

Of the many live psychobehavioural explanations for psychedelics' transdiagnostic therapeutic action, perhaps the most versatile is its potential for increasing *psychological flexibility* (Bond et al., 2011; Close et al., 2020; Watts & Luoma, 2020), "the capacity [of people] to develop skills recognising and adapting to various contextual demands, shift their mindset or behaviors during individual and social experiences, maintain balance across important life domains, and learn to be open to, aware of, and committed to behaviors that are congruent with their values" (A. K. Davis et al., 2020). The construct of psychological flexibility comprises six components - *acceptance*, willingness to engage fully with unwanted experiences without resistance; *contact with the present moment*, being fully aware of the here and now, '*self as context*', keeping perspective of oneself within one's experience; *defusion*, the ability to avoid getting stuck in distressing thoughts; *committed action*, maintaining behaviours in line

with values and goals; and *values*, staying connected to valued principles to give direction to behaviour (Rolffs et al., 2018).

Higher levels of psychological inflexibility are associated with higher levels of depressive and anxiety-related symptoms, as well as greater overall psychological ill-health (Bond et al., 2011), while increases in psychological flexibility predict improvements in depression and anxiety during psychotherapy (Twohig & Levin, 2017) alongside a range of clinical outcomes in other conditions and other measures of quality of life including self-compassion, affective well-being at work, and greater relationship satisfaction (Daks & Rogge, 2020; Hayes et al., 2006; Yadavaia et al., 2014, p.2014). Indeed, a number of behavioural therapies, including cognitive-behavioural therapy (CBT) and Acceptance and Commitment Therapy (ACT), place openness to new ways of seeing the world, thinking, and behaving at the core of their goals. In a psychedelic context, increases in psychological flexibility have been found to mediate the relationship between acute effects of psilocybin and (i) depression and anxiety (A. K. Davis et al., 2020) and (ii) racial trauma symptoms among People of Colour (A. K. Davis, Xin, et al., 2021). Meanwhile, in healthy participants at ayahuasca retreats, increases in psychological flexibility mediate the effect of factors of the acute experience and long-term positive mood (Agin-Liebes et al., 2022).

Other proposed psychological mediators of long-term therapeutic change following psychedelic administration include the constructs of emotional breakthrough and psychological insight, each of which returns explanatory focus to the very characteristic of psychedelics that earned them their name - their ability to make clear the typically unseen or unacknowledged facets of the mind. While the two constructs are highly conceptually and empirically related, distinguishing between *emotional breakthrough* - an affective process during acute drug effects, and *psychological insight* - a reflective, cognitive process in the post-acute phase, is best demonstrated by reproducing items from the recently validated scales for each (Peill et al., 2022; Roseman et al., 2019):

I faced emotionally difficult feelings that I usually push aside.
I achieved an emotional release followed by a sense of relief.
I experienced a resolution of a personal conflict/trauma.

Table 1.2. Sample items from the Emotional Breakthrough Inventory (EBI; Roseman et al., 2019)

I have had important new insights about how past events have influenced my current mental health and behaviour.
I have learned important new ways of thinking about my 'self' and my problems.
I have become more conscious of aspects of my 'self' that I used to ignore or not be fully aware of.

Table 1.3. Sample items from the Psychological Insight Scale (PIS, Peill et al., 2022)

Temporally, emotional breakthrough can be conceived of as the overcoming of psychological resistance to consciously facing emotionally challenging memories or feelings, which itself can facilitate psychological insight: improvement in understanding of one's own history, trauma, habits and needs. This relationship between breakthrough, insight, and therapeutic benefit has substantial heritage in psychodynamic theory, which posits that enhanced self-understanding improves management of psychopathology and enables adaptive responses to future stressors (Jennissen et al., 2021; Johansson et al., 2010; Rosenblatt, 2004). Consider the P-AT smoking cessation participant who attributed his quitting to the insight that "to smoke at all was to be 'a smoker'" (Noorani et al., 2018).

Finally, it may be that the main factor driving long-term improvements in symptom severity following psychedelic use is the well-replicated finding of behaviour change, which frequently comprise lifestyle changes that are supportive of good overall health (Teixeira et al., 2022). A cross-sectional study representative of the US population (n=2,822, Simonsson et al., 2023) found that lifetime classic psychedelic use was associated with healthier diet- and tobacco-related behaviour, and a greater likelihood of having a healthy BMI. Although this study is only correlative, and failed to control for all socioeconomic variables associated with health behaviours, the proposal is supported by some causal evidence: in a qualitative study of participants in a tobacco cessation trial, Noorani et al. (2018) found evidence of behaviour changes that are evidenced to support positive mental well-being, including increased gratitude (Bohlmeijer et al., 2021); spending more time in nature (Lackey et al., 2021); and engaging in artistic pursuits (Caddy et al., 2012). Watts et al. (2017), in a qualitative study of patients in a psilocybin trial for treatment-resistant depression, found that 'nearly half' of participants reported spontaneous improvements to their lifestyle, including 'diet, exercise, and cutting down on alcohol' (p.13). A US survey of 343 people whose alcohol consumption reduced after psychedelic use[14] found that over half also reported improved diet and increased exercise as a result of their psychedelic experience (Garcia-Romeu et al., 2019).

[14] Of this number, only 10% reported using psychedelics *in order* to reduce or quit alcohol consumption.

Rather than attempting to adjudicate between the merits of mechanistic accounts pitched at different levels of analysis, or evaluate their relative explanatory completeness and potential, I finally turn to challenges in implementing and scaling P-AT, as well as key outstanding debates in P-AT which are germane to the ethical analyses of the second half of the thesis

1.5. Current Challenges in Implementation and Outstanding Debates in P-AT

1.5.1. Resource implications of contemporary P-AT

Irrespective of the therapeutic potential that P-AT may have, it faces significant implementation challenges due to its resource intensive nature. While psychedelic drugs are relatively inexpensive—and may become cheaper with licensing, rescheduling, and economies of scale—the main cost lies in clinician time. Standard psychiatric treatment paradigms are brief and comparatively low-cost. A typical psychological treatment for anxiety or depression under the NHS is an 8-session course of hour-long Cognitive Behavioural Therapy (NHS Digital, 2022), while psychiatric pharmacotherapy is administered via monthly - or less frequent - medication check visits with a psychiatrist or GP. In comparison, a 6-12 hour psychedelic substance administration session, attended by two therapists with advanced degrees (with a physician on standby in case of the need for medical intervention), as well as multiple preparation and integration sessions, represents a significant resource commitment that payers such as the NHS in the UK, and chiefly insurance companies in the US, may be unwilling to meet.

Responses to these resource pressures broadly fall into two categories: operational modifications that seek to optimise the health economics of delivery while maintaining core therapeutic elements, and more fundamental conceptual shifts in how P-AT should be understood and implemented.

Numerous avenues for operational streamlining are being explored. These include the use of only one therapist during drug administration sessions (Agrawal et al., 2023); simultaneous dosing of participants with one physician present (Marseille et al., 2023; Rucker et al., 2022); reduced qualification requirements for the clinician(s) present in administration sessions (Shnayder et al., 2023); and the use of group sessions for preparation and integration (Anderson, Danforth, Daroff, et al., 2020; Shnayder et al., 2023). Some trials have experimented with single administration sessions rather than the traditional two or more (Raison et al., 2023; Von Rotz et al., 2023), or with shorter-acting psychedelics

to reduce session duration (D'Souza et al., 2022; Reckweg et al., 2023). Each of these modifications aims to reduce resource intensity while preserving the essential therapeutic framework of P-AT.

More radical are proposals that reflect deeper conceptual shifts in how P-AT is understood. Some have gone so far as to suggest that the field dispense with the term 'psychedelic-assisted psychotherapy' entirely, arguing that minimal clinical experience is required for those providing support during an administration session (Goodwin et al., 2024; though see also Gründer et al., 2024). Such proposals reframe the role of clinicians from therapists to monitors, representing a fundamental reconceptualisation of P-AT, moving away from its hybrid pharmacotherapy-psychotherapy nature toward a more purely pharmacological model.

1.5.2. Must psilocybin always assist psychotherapy?

The title of this section is taken from a 2024 opinion piece led by the Chief Medical Officer of commercial drug development company Compass Pathways, which argues that "the effects observed thus far in the best controlled studies of psychedelic treatment must be attributed to the drug itself and not to psychotherapy" (Goodwin et al., 2024). This claim finds some support in naturalistic evidence: population studies controlling for mental health covariates have found reduced odds of suicidality, psychological distress and major depressive episodes among psilocybin users (P. S. Hendricks et al., 2015; Jones & Nock, 2022a). Since less than 5% of psychedelic users report administration in the presence of a therapist or health professional (Glynos et al., 2023; n=1,435), these benefits appear achievable without formal therapeutic support.

Survey data further supports potential benefits from unsupported use. Self-medicating users (n=1,967) rated psychedelics as more effective than clinician-provided treatments, citing greater symptom relief and quality-of-life gains (Mason & Kuypers, 2018). Another survey of 3,364 self-selected participants who had self-medicated with LSD or psilocybin mushrooms reported a range of positive outcome items relating to well-being, psychiatric symptoms, social-emotional skills and health behaviours, with improvements enduring for at least four weeks in half of participants (Kopra et al., 2023).

However, this same survey revealed concerning rates of adverse outcomes: 22% of respondents reported negative effects including mental confusion, disconnection from reality, persistent worry, and emotional dysregulation. For over a quarter of those affected, these difficulties persisted beyond one month, with 13% reporting problems lasting longer than six months. These findings raise a crucial distinction in the debate about psychotherapy's necessity: the question concerns not just efficacy, but also safety. While Goodwin et al. (2024) suggest only 'a responsible person' rather than therapeutically trained staff need

be present, critics have argued that this position sits uneasily with Compass' own trial practices, in which the 'psychological support' model explicitly draws from evidence-based psychotherapies (Gründer et al., 2024; Tai et al., 2021).

The role of therapeutic support in treatment efficacy remains an open empirical question. Goodwin and colleagues highlight emotional breakthrough as a mechanism of therapeutic action independent of psychotherapy, citing research showing it strongly predicts antidepressant response (Murphy et al., 2022). Yet this same study found therapeutic alliance predicts emotional breakthrough, suggesting an more intricate relationship between relational and pharmacological factors than simple additivity.

Without factorial trials systematically comparing combinations of psychedelic administration and psychotherapy, their respective contributions cannot yet be definitively parsed. However, given psychedelics' enhancement of neuroplasticity and the corresponding importance of the post-administration environment, a precautionary approach favouring therapeutic support appears warranted.

Emerging trial data, while limited, offers some support for this approach. Compass Pathways' phase IIb depression trial, which employed reduced therapeutic support, showed diminished efficacy and higher rates of severe adverse events compared to earlier studies (Goodwin et al., 2022). Similarly, MindMed's LSD anxiety trial (n=20) with minimal psychotherapeutic component required emergency sedation for one patient experiencing acute delusions (MindMed, 2022; NCT03153579).

Such preliminary findings, while inconclusive, raise crucial questions about the necessary therapeutic support for safe and effective P-AT. This debate has two aspects. First, there's a fundamental disagreement about mechanism: whether therapeutic effects derive primarily from pharmacological factors, as Goodwin and colleagues suggest, or whether psychotherapeutic elements play an essential role in both efficacy and safety. Second, there's the practical question of resource allocation: P-AT's current model is resource-intensive, creating pressure to reduce therapist involvement to improve scalability and reduce costs. This economic pressure exists in tension with patient experiences. As Earleywine et al. (2024) note, there is irony in "discharging suffering patients when they might most relish the chance to share insights with an adept listener": an observation supported by evidence that many participants continue working to process and incorporate their experiences long after formal trial endpoints (Noorani, 2019, p.35; Schwarz-Plaschg, 2022, p.6), as well as broader patterns of post-trial support-seeking that may indicate significant unmet psychotherapeutic needs that warrant closer attention (Jacobs, Murphy-Beiner, et al., 2024; O'Donnell et al., 2024; see also §5.3.2).

These competing imperatives—therapeutic efficacy and safety, and economic feasibility—present a central challenge the field must resolve to develop sustainable approaches to P-AT.

1.5.3. Is the subjective experience necessary for therapeutic effect, or an epiphenomenon?

Abstracting away the mechanistic details of the various brain-based accounts outlined above, it can still be asked whether the subjective experience of classic psychedelics has any causal role in their enduring therapeutic benefit (Olson, 2021; Yaden & Griffiths, 2021). The extent of the mystical experience, or some component thereof (such as 'oceanic boundlessness'), has been found to be predictive of therapeutic benefit across a number of treatment indications (Garcia-Romeu et al., 2015; Griffiths et al., 2016; Ko et al., 2023; Roseman et al., 2018; Weiss et al., 2024). The thesis that the subjective experience is not necessary to therapeutic benefit would certainly strike many people who have experienced symptom improvement following psychedelic administration as implausible: qualitative accounts of P-AT trial participants abound with narratives of specific phenomenological contents being causally relevant to their recovery, such as insights into, and revised perspectives on, past trauma, the experience of unconditional love, the feeling of acceptance that death is inevitable and not to be feared, or the insight that 'to smoke at all was to be 'a smoker' (Noorani, 2018, p.760).

Despite this apparent connection, there remains space for doubt. Confabulation - the generation of coherent, internally consistent, and relatively intuitive falsehoods to account for one's own behaviour - is a well-established phenomenon (Hirstein, 2009), even among healthy people (Wheatley, 2009). For the former smoker described above, there is no way to independently verify the motivational force of the insight gained during psilocybin administration as *causing* the downstream smoking abstinence. It *may* be that post-hoc, a newfound disinclination to smoke despite a longstanding habit needed to be explained somehow, and that this insight provided the most plausible candidate account that was accessible and coherent. Moreover, those sceptical of the causal relevance of the subjective experience point to participants who have a 'full' mystical experience with no concomitant therapeutic benefit, those whose symptoms improve despite the lack of such an experience, and the wholly correlational nature of the evidence linking any subjective experience and therapeutic benefit (Olson, 2021) - indeed, it may be that mystical experiences are simply a good, if imperfect, biomarker of the 5-HT_{2A} activation that brings about clinical benefit through other mechanistic pathways.

A reliable empirical test for the causal relevance of the subjective will likely have to wait for the development of non-hallucinogenic analogues of classic psychedelics, an enterprise that has been

granted significant funding from the US Defense Advanced Research Projects Agency (Cameron et al., 2021; DARPA, 2019) and has begun to generate positive signals in preclinical models (V. Lewis et al., 2023). Such drugs, were they of comparable clinical efficacy to classic psychedelics, would almost certainly change the landscape of psychedelic medicine significantly: as outlined above, the bulk of the costs associated with the normative model of psychedelic-assisted therapy is clinician time, which might be practically eliminated if drugs could be produced without any subjective effects: without 'trips', there is no need for 'trip-sitting'; without insights or mystical experiences, there is ostensibly nothing needing integration. Such drugs might be supplied much as SSRIs are today, with much better scalability and accessibility than P-AT. But such an increase in accessibility is not without potential trade-offs. As outlined above, enhanced neuroplasticity without appropriate psychological support may carry its own risks. Neuroplasticity represents capacity for change rather than inherently positive adaptation - its therapeutic value depends entirely on the experiences and environmental inputs that shape that plasticity. This biological reality suggests that even "tripless" variants may still require some form of therapeutic support to ensure positive outcomes, though ultimately this is an empirical claim that would merit careful attention.

Contemporary pressures to retrofit P-AT —whether through reduced therapeutic contact or the development of non-hallucinogenic analogues— reflect a broader tension between treatment optimisation and healthcare system constraints. However, the evidence reviewed in this chapter suggests that attempts to cleanly separate pharmacological from psychological elements of the treatment may be fundamentally misguided. The acute subjective effects of psychedelics frequently centre on profound interpersonal experiences, while their enhancement of neuroplasticity creates a window of heightened environmental sensitivity that extends well beyond drug metabolism. As healthcare systems prepare for widespread implementation of psychedelic therapy, crucial questions emerge about necessary infrastructure for safe and effective treatment. The interviews conducted for this thesis, examining the experiences of some of the first patients to receive modern psychedelic therapy, reveal how insufficient attention to these psychological and social dimensions can lead to significant challenges in patients' post-treatment trajectories. The ethical analyses that follow examine three key implementation challenges highlighted by these experiences: the provision of post-trial support, the influence of patients' social contexts on outcomes, and the development of more comprehensive frameworks for capturing the full spectrum of treatment outcomes.

2. P-AT as an ethical enterprise

2.1. Introduction

This chapter provides a focused examination of key ethical considerations in P-AT. Rather than attempting an exhaustive review of all ethical issues in psychedelic medicine (for overviews of broader scope, see McGuire et al., 2024; Poppe & Repantis, 2024), it concentrates on considerations that are foundational to understanding P-AT as an ethical enterprise. In doing so, the chapter engages with significant contributions and discussions in the nascent field of psychedelic ethics, while establishing the necessary groundwork for the novel empirical ethical analyses that follow in subsequent chapters. As Cheung et al. (2025) contend, P-AT is 'distinctive, but not exceptional' - while a number of ethical challenges overlap with other therapeutic modalities, certain features of P-AT create atypical or heightened ethical considerations that warrant careful examination.

This review examines issues in P-AT organised by three core themes, analysed at both practical and theoretical levels. The chapter begins by examining patient vulnerabilities in P-AT (§2.2), which are heightened relative to typical psychotherapeutic modalities. The acute effects of classic psychedelics create distinct vulnerabilities that extend beyond typical therapeutic contexts, affecting patients' capacity for autonomous decision-making, boundary maintenance, and protection of their interests during treatment.

Analysis then turns to therapeutic relationships and professional ethics (§2.3), exploring how vulnerabilities intersect with and shape clinical encounters. Here, I examine how P-AT therapists conceive of the modality in ways that put pressure on traditional psychotherapeutic boundaries and professional norms, and the ethical significance of this difference. Particular attention is paid to transferential dynamics and the contentious role of touch in P-AT, examining how these features challenge conventional clinical boundaries while raising questions about necessary adaptations versus potential risks to patient welfare.

The final theme addresses uncertainty within P-AT (§2.4), both in securing valid informed consent, and in the conceptualisation of therapeutic outcomes. This section examines how the transformative nature of psychedelic experiences challenges conventional frameworks for informed consent, as well as examining the implicit normativity in how we measure and value different types of therapeutic change. The latter uncertainties intersect with broader questions about the goals of mental healthcare and the appropriate scope of medicine.

The review's scope encompasses both immediate clinical concerns and their broader conceptual implications. While examining specific challenges in clinical implementation - from touch protocols to oversight mechanisms - it also engages with the theoretical frameworks needed to address them. Issues of informed consent in P-AT, for instance, require both practical protocols and theoretical engagement with questions of transformative experience. Similarly, debates about therapeutic outcomes in P-AT implicate both measurement practices and competing conceptual models of health and therapeutic change.

2.2 Vulnerability and Protection in Psychedelic Treatment

2.2.1 Special vulnerabilities

P-AT introduces distinct vulnerabilities that extend beyond those typically encountered in mental healthcare. While all patients engaging in psychotherapy experience some degree of vulnerability, the outsized alterations in consciousness, cognition, and emotional processing induced by psychedelics create specific challenges for patient protection and autonomy. These vulnerabilities are particularly noteworthy as they are not merely incidental to treatment, but are deliberately induced as part of the therapeutic process itself.

2.2.1.1 Vulnerabilities in advance of P-AT

Even prior to the commencement of P-AT, there are potential intersecting vulnerabilities that need to be attended to. As noted by a range of psychedelic researchers (M. Barber et al., 2024; Petranker et al., 2020; Yaden, Potash, et al., 2022), recent media coverage of P-AT has often been uncritically enthusiastic, sometimes presenting the treatment as a potential mental health panacea. This has likely contributed to an oversubscription of interest from prospective participants for planned P-AT trials but may also lead participants to overestimate likelihood of benefits and underestimate risks.

The risk of unrealistic expectations is most significantly borne by participants whose mental health conditions have been treatment-resistant or difficult-to-treat. Such participants may view an allegedly revolutionary therapy as their 'last hope', with significant potential for profound disappointment and demoralisation if anticipated treatment benefits are not realised (Gukasyan, 2023). This heightens the risk of consent to participation being given only because of what Appelbaum et al. (1982) term 'therapeutic misconception' - where participants conceive of treatments delivered as part of research as

equivalent to normal healthcare. But in the context of a still-experimental treatment that has been subject to considerable media hype (Yaden, Potash and Griffiths, 2022), even where prospective participants are not confused about the nature of research trials, they may still have unrealistic expectations about effectiveness, due to insufficient understanding of material information about likely outcomes.

Such misalignment between expectations and reality can compromise valid informed consent regardless of concerns about the therapeutic misconception (Allmark & Mason, 2006; J. Halpern et al., 2019; Minogue et al., 1995). In context of last-resort treatment-seeking, participants may also weigh risks in ways that appear irrational due to desperation, further complicated the consent process.

The impact of pre-session materials and preparation deserves particular attention when considering vulnerabilities in advance of acute drug effects. In a study of participants in a P-AT trial for tobacco cessation, (Devenot et al., 2022a) demonstrated that trial materials presented to participants before drug sessions can be "visually rendered within the imaginal content" (p.375) of their acute subjective experiences, with immediate and enduring impacts on their self-identity (*qua* 'smoker' or 'non-smoker'). Although this finding coheres with broad understanding about the influence of 'set' on acute and enduring outcomes following psychedelic administration, and in this instance was used towards a desired treatment goal, it suggests that vulnerability to influence can begin well before drug administration. This vulnerability may be intentionally or inadvertently used to less salubrious ends.

To address these intersecting vulnerabilities, clinicians must pay particular attention to communicating the state of the available evidence while underscoring the limits of current understanding and the still-experimental nature of the treatment during the consenting process. Participants need to develop realistic expectations of the intervention, balancing potential benefits against both known and unknown risks. This is particularly crucial given how pre-session materials and preparation can shape not just expectations, but the very content of participants' subsequent experiences.

2.2.1.2. Vulnerability during acute effects

The most conspicuous vulnerabilities induced during P-AT occur during acute drug effects, wherein patients are liable to experience impaired executive function (Basedow et al., 2024), heightened suggestibility (Carhart-Harris et al., 2015; Duerler et al., 2020), and impaired verbal communication (Sanz et al., 2021). Respecting patient autonomy in this context demands not only safeguarding bodily autonomy, but also protecting against undue influence on thought and reasoning (‘cognitive autonomy’).

Considering the latter, Kochevar (2024) introduces the concept of 'epistemic vulnerability' to demarcate the heightened susceptibility to environmental influence under psychedelics, affecting sensory, affective, and cognitive domains. This "radical vulnerability", however, as Kovechar acknowledges, is "arguably central to models of psychedelic benefits" (p.9): the same mechanisms that may enable therapeutic change also create risks that require careful management. *Per* the REBUS model (see §1.3.2.3), patients in the acute psychedelic state are more liable to revise their beliefs, such that "therapists can to some degree influence the direction of revisions through the bottom-up input they produce (e.g., therapeutic setting, verbal interactions)" (Villiger & Trachsel, 2023, p.3), a process which can continue through the integration process, which therapists can also exercise influence over.

This openness to therapeutic suggestion, however, is liable to also make patients easier to manipulate by unscrupulous practitioners (Barber & Dike, 2023). Outside of clinical contexts, exploitation of epistemic vulnerability has been used to perpetrate financial abuse (Adams & Evans, 2023), as well as by a number of cults to "indoctrinate members and amplify their allegiance to the group" (Evans & Adams, 2024). Within the context of regulated P-AT trials, a number of practices can reduce the risk of such exploitation, including the careful screening of therapists, the use of therapist dyads, and video recording to discourage inappropriate behaviour (McGuire et al., 2024; Rajwani, 2023).

Such practices have not, however, been sufficient to prevent examples of the gravest misconduct and abuse of individuals in heightened states of vulnerability. Regrettably, it is not hard to find examples of serious physical and sexual violations within underground P-AT (Harrison et al., 2025). While the extralegal and unregulated nature of underground therapy limits the avenues and structures for accountability and redress, the same misconduct is not absent from clinical trials (McNamee et al., 2023). In leaked footage from one phase 2 clinical trial of MDMA-assisted therapy, two trial therapists were recorded appearing to pin down, spoon, and kiss a participant, who attempted to resist but was overpowered (L. K. Ross & Nickels, 2022). The participant, who was seeking trauma therapy following a history of sexual abuse, went on to engage in a sexual relationship with one of the therapists while she was still enrolled in a clinical trial - a relationship she characterised as exploitative and abusive. Neither the existence of a trial sponsor code of ethics for therapists, nor the recording of the session, prevented these events from occurring. This case demonstrates that oversight mechanisms must go beyond simple documentation or written policies to be truly effective in preventing misconduct. Robust oversight requires multiple layers of protection, including careful therapist screening, ongoing supervision, clear reporting pathways for violations, and meaningful consequences for transgressions. Most importantly, these mechanisms must be actively maintained and regularly evaluated rather than treated as mere procedural checkboxes.

While such violations are reported across medical and psychotherapeutic modalities (Alpert & Steinberg, 2017; Capawana, 2016; DuBois et al., 2017), the heightened vulnerability experienced during psychedelic states, wherein patients have a decreased capacity to assert their autonomy, and to object to or even recognise boundary violations (Azevedo et al., 2023), amplifies the risk.

2.3 Therapeutic Relationships and Professional Ethics

While cases of misconduct might be attributed straightforwardly to 'bad actors' who need to be excluded from the P-AT community, this potentially reductive view obscures other salient features of the modality that warrant some examination. The therapeutic relationship in P-AT presents challenges beyond conventional clinical encounters, shaped by the alterations in consciousness and heightened vulnerability discussed in the previous section.

2.3.1 Transference and countertransference

P-AT appears to generate more intense transferential dynamics compared to typical psychotherapeutic relationships (Anderson, Danforth, & Grob, 2020; Brennan et al., 2021; Fisher, 2000; Maggio et al., 2023; Palitsky et al., 2025). Transference refers to the unconscious process whereby clients project feelings, often stemming from early familial and romantic relationships, onto their therapist. For instance, a patient may partially relate to their therapist as they once did to a parental figure, complete with the associated expectations, anxieties, and patterns of relating. Countertransference describes the complementary process, i.e. the therapist's own unconscious emotional reactions and projections toward the patient.

While these dynamics are present in all psychotherapeutic relationships, they can be heightened in P-AT, and "skills in attachment theories and transference-countertransference analysis" are suggested as a key competence in psychedelic therapist training, regardless of practitioners' standard modalities of practice (Passie et al., 2022; Penn et al., 2024; Phelps & Henry, 2021). Intensified transferential dynamics likely stem from several intersecting factors: during acute drug effects, patients frequently experience a dissolution of self-boundaries, union with the world, and heightened feelings of connection to others (Forstmann & Sagioglou, 2025; Lebedev et al., 2015; Smigielski et al., 2020). P-AT trial participants have rated their psychedelic sessions among the most meaningful experiences of their lives, frequently ranking them alongside major life events such as the birth of a child or death of a parent (Griffiths et al., 2006; Søgaard Juul et al., 2023; Sweeney et al., 2022). In the context of so intense an experience, it is easy to understand why, in a qualitative study of participants undertaking P-AT for

treatment-resistant depression, “many reported feeling bonded to their guides, saying they had been through something substantial together” (Watts et al., 2017, p.550).

In a survey of 23 underground psychedelic therapists, practitioners reported three predominant forms of transference: “those that involved sexual desire, regressed states of boundary-testing, or ‘guru-projections’, in which the client ascribes great wisdom or power to the practitioner” (Brennan et al., 2021, p.10). Importantly, respondents noted that the intensity of such projections could evoke equally powerful countertransference in unprepared therapists, potentially leading to boundary violations. Early psychedelic researcher Sidney Cohen warned that “the ability to induce the transcendental state is a heady and powerful endowment. Only well-adjusted therapists without personal needs to play God will be unaffected by the potency inherent in the situation” (Cohen, 1970, p.152). Given the inherent power imbalance between a therapist and patient, as well as the enhanced vulnerability of patient’s during acute drug effects, it is incumbent on the therapist to thoughtfully protect professional boundaries, and to “be irreproachable in their conduct with patients, particularly with regards to monitoring their countertransference responses” (Penn et al., 2024; p.605).

Although the psychedelic state is commonly described as ‘boundary dissolving’ (Jacobs et al., 2023; Letheby & Gerrans, 2017), pressure on therapeutic boundaries extends beyond the acute drug experience. The prevalence of ‘dual relationships’, in which a therapist “assumes a second role with a client, becoming social worker and friend, employer, teacher, business associate, family member, or sex partner” (Kagle and Giebelhausen, 1994, p.213), appears particularly high in underground P-AT settings (Brennan et al., 2021). These can include friendships, spiritual teacher-student relationships, or involvement in shared psychedelic communities. While the frequency of such boundary crossings may partially reflect the countercultural context of underground practice, it may point to something intrinsic in the psychedelic therapeutic process itself.

Pressures on boundaries emerge even in regulated trial contexts. Palitsky et al. (2025) found that both P-AT trial participants and therapists frequently desired continued contact after formal treatment concluded. Though this mutual desire was reported to stem from therapeutically relevant concerns - therapists wanting to be involved in follow-ups to ensure patients were doing well, and patients wanting continuity of care and a seamless transition to ongoing integration. However, as one therapist noted, such ongoing relationships “might be taken advantage of by unscrupulous facilitators” (p.9). Given these inherent challenges in psychedelic therapeutic relationships, robust professional structures are essential. The field needs to develop and articulate clear, transparent codes of conduct for psychedelic work (cf. American Psychedelic Practitioners Association & BrainFutures, 2023; McGuire et al., 2024),

including well-defined accountability structures for receiving reports of misconduct, investigating violations, and implementing appropriate penalties. However, formal rules alone are insufficient. The complexity of therapeutic relationships in P-AT demands the development of professional cultures that actively engage with ethical challenges as they arise in practice.

Regular clinical supervision with supervisors experienced in managing complex transferential dynamics is valuable for minimising risk, allowing therapists to process and receive guidance on challenging clinical situations before they develop into boundary violations. Peer consultation groups provide additional forums for discussing ethical dilemmas and maintaining professional standards These structures serve not just as safeguards against misconduct, but as spaces for collective ethical deliberation that can help the field develop approaches to managing the particular challenges of psychedelic therapies (Taylor, 2024).

2.3.2 Touch

While physical contact between therapist and patient is generally discouraged in conventional psychotherapy, touch is widely employed in P-AT, particularly in underground settings. In Brennan et al.'s (2021) study of underground therapists, the majority of practitioners interviewed considered "touch [to be] an essential part of their work" (p.12). Although incorporated into manuals and protocols for clinical trials (Back et al., 2024; Ching et al., 2022; Guss et al., 2020; Watts, 2021), the use of touch remains hotly debated (Devenot, Tumilty, et al., 2022; Insua-Summerhays & Jacobs, 2025; Luoma et al., 2024; Neitzke-Spruill et al., 2025).

Neitzke-Spruill et al. (2025) offer a taxonomy of various forms of touch in P-AT, including *safety touch*, aimed at preventing harm and preserving wellbeing (e.g., preventing a fall, helping participants walk to nearby toilets), *procedural touch*, for the purposes of routine clinical or research practices, *supportive touch*, intended to provide grounding for or communicate empathic caring to patients (as in a comforting hand placed on the shoulder, or holding a patient's hand during intense moments), *therapeutic touch*, including massage or somatic therapy to facilitate healing, and *sexual touch*, whether initiated by the therapist or the patient.

While a consensus has been established about the permissibility of safety touch and impermissibility of sexual touch (Back et al., 2024; Jacobs et al., 2024a; McGuire et al., 2024), there remains disagreement about the propriety of supportive and therapeutic touch (Devenot et al., 2022b, Brennan et al., 2023; Marks et al., 2024). One lens through which this debate can be illuminated is that of *bodily integrity rights*, which Herring & Wall (2017) argue is conceptually distinct from autonomy. While autonomy

concerns decision-making about one's body, bodily integrity protects against unwanted interference with the body itself – the point where subjective experience meets the objective world. This distinction is particularly significant in psychedelic states, where the boundaries of bodily experience may become fluid or permeable (cf. Belser et al., 2017, p.15).

Within this lens, the complexity of touch in P-AT emerges precisely because different forms of touch engage different aspects of patients' rights. Safety touch might be justified by the exceptional circumstances of preventing harm, but supportive or therapeutic touch requires more substantive *justification* than mere consent, especially given the altered state of consciousness. Even touch that would be innocuous in ordinary circumstances might engage with a patient's sense of bodily integrity during psychedelic experiences, during which the integration of self with the external world can already be in flux.

Given the risk and reality of boundary violations like those described above, as well as the general vulnerability induced by acute drug effects, it is fitting that the use of touch in P-AT is subject to careful ethical scrutiny. Proponents of more engaged touch point to participant affirmations of its therapeutic value (Back et al., 2024), while the MAPS manual (for MDMA-assisted therapy) asserts that "withholding nurturing touch when indicated can be counter-therapeutic" (Mithoefer, 2017). A participant working through issues relating to neglect or abandonment, for example, might experience the refusal of requested supportive touch as a re-enactment of early relational wounds, which may compromise therapeutic progress. These considerations point to a potential therapeutic double-bind, wherein both the provision and withholding of touch carry distinct risks that may be better to be carefully weighed rather than categorically resolved.

However, it remains the case that there is a dearth of formal evidence about the impact of touch or its withholding in P-AT. As such, Devenot et al. (2022b) argue for a precautionary approach to touch, arguing that "an environment that lacks defined boundaries provides shelter for predatory behavior as well as increased opportunity for unintentional transgressions": the risk of misattuned, counter-therapeutic, or grossly inappropriate touch is minimised if there are general prohibitions of non-safety touch.

The impaired executive function and increased vulnerability during acute drug effects has led to a norm of using a 'two-stage' model of consent for touch (Brennan et al., 2021; Nietzke-Spruill et al., 2025). Therein, patient values and preferences regarding non-safety touch are established during the (sober) informed consent process, and, if the patient consents to such touch, consent is sought again during drug effects. Recent proposed refinements of this model involve the early exploration of patient preferences

in the case that they change their mind (from refusing to welcoming touch) mid-session, and the establishment of shared non-verbal signals asking for touch to be provided or halted (McGuire et al., 2024; Neitzke-Spruill et al., 2025). Advocates suggest this approach "respects participant autonomy while trying to avoid making clinical interactions overly sterile, impersonal, and bureaucratic" (Neitzke-Spruill et al., 2025, p.34).

While these procedural safeguards are valuable, they don't address a more fundamental question: whether touch is necessary for achieving therapeutic aims in P-AT. This question shifts our ethical analysis from considerations of autonomy to those of beneficence—moving from whether patients can consent to touch to whether touch actually serves their therapeutic interests. The ethical permissibility of any medical intervention requires meeting both standards: respect for autonomy through valid consent and promotion of patient welfare through demonstrated therapeutic benefit. While proponents of touch in P-AT have endorsed the need for further research, this has been asymmetrical, focusing only on the impacts of touch, rather than comparative evaluation as to whether its purported benefits can be achieved through other means (Luoma et al., 2024). This narrow focus risks prematurely codifying touch practices without adequate justification, particularly given the existence of established alternatives in therapeutic practice.

Contemporary psychotherapy demonstrates that emotional containment and grounding can be achieved without physical contact, even when working with patients in states of acute distress, or processing emotionally challenging material. Alternative methods developed in other therapeutic contexts can create supportive environments while avoiding the risks associated with touch. These include imagery work, application of sensory supports like weighted blankets, or the use of intermediate objects (such as a 'schema rope' or scarf held at either end) that allows physical connection and a non-verbal communication channel while maintaining boundaries and giving patients control over engagement levels. The success of non-touch approaches in managing intense emotional states in other therapeutic contexts suggests that the field should carefully evaluate whether touch offers unique benefits that cannot be achieved through lower-risk alternatives (Insua-Summerhays and Jacobs, 2025).

The need to evaluate alternatives to touch is particularly pressing given the complex ways that psychedelic states alter sensory processing and psychological boundaries. Even minimal physical contact may be experienced with amplified intensity or imbued with heightened meaning beyond what is therapeutically necessary or beneficial. Moreover, common therapeutic dynamics—such as patients' desire to please their therapists or fears of abandonment—may lead patients to accept or request touch that they later experience as boundary-violating, making it crucial that therapists not mistake apparent

consent for genuine therapeutic indication. Until we better understand these dynamics and have formal evidence comparing touch and non-touch approaches in P-AT, Devenot et al.'s (2022b) call for a precautionary approach appears warranted.

These considerations suggest several practical implications for the field. First and foremost, formal research comparing touch and non-touch methods of support in P-AT are needed, examining both immediate impacts and longer-term outcomes. Second, if touch is to be incorporated into treatment protocols, clear guidelines must extend beyond simple anatomical restrictions (e.g., "only touch from elbow to shoulder") to account for the altered processing of social and sensory information during psychedelic states. Touch that is innocuous while sober may be experienced differently under acute drug effects. Finally, P-AT practitioners should be trained in non-touch methods of providing support and containment, ensuring that touch, if used, represents a considered therapeutic choice rather than a default response to patient distress.

2.4 Navigating Uncertainty in Consent and Outcomes

2.4.1. Informed Consent, Non-Clinical Changes, and the Epistemic Challenge from Transformative Experience

The atypical acute and long-term effects of psychedelic administration both present challenges for the practice of informed consent, which seeks to safeguard patient autonomy and support patient-defined goals for treatment (Berg et al., 2001, ch.14; Sheather, 2011). Subjective effects during psychedelic experiences can include profound perceptual and cognitive changes, including alterations to sense of self and reality (Studerus et al., 2011). These effects are not only hard to anticipate but can be challenging for clinicians to comprehensively convey to psychedelic-naive prospective patients, rendering it difficult to secure sufficient understanding required for valid informed consent. Aday et al. (2024) documented major life changes attributed to, or influenced by, naturalistic psychedelic use including changes to life goals, religion and spirituality, eating habits, political views, and marital status. The potential for longer-term influences on these domains, as well as metaphysical beliefs (Timmermann et al., 2021), personality (Weiss et al., 2023), and values (Kähönen, 2023) present particular challenges for deciding whether to undertake treatment.

This challenge can be understood through the framework of 'transformative experiences' (Paul, 2014) - experiences that are both *epistemically* and *personally* transformative. An experience is epistemically transformative when it involves subjective qualities that can only be understood through firsthand

experience. It is personally transformative when it alters one's core values, preferences or worldview. Having one's first child exemplifies both aspects - the experiential qualities cannot be fully conveyed through description or analogous experiences (epistemic transformation), while the event typically leads to substantial revisions in values and priorities (personal transformation). P-AT exhibits both forms of transformation: the acute psychedelic experience represents a significant alteration of consciousness that cannot be adequately described in advance, while clinical evidence indicates that P-AT can lead to lasting alterations in personality, beliefs, and behaviour - including shifts in the very values and priorities that inform treatment decisions (Jacobs, 2023).

Considering the unusual subjective effects and downstream side-effect profile of psychedelics, Smith & Sisti (2021) propose a consenting process which is "enhanced relative to that of informed consent procedures used to prescribe other psychotropics" (p.3). A third of UK nationals who would not consider a psychedelic-based treatment referenced their unwillingness to undergo a psychedelic 'trip' (Jacobs, 2021), suggesting that features of psychedelic treatments that are atypical in medicine are highly salient in patient decision-making processes, and must be included in any valid consenting process.

Expanding on Smith and Sisti's 'enhanced consent', many bioethicists call for the development of diverse resources to better communicate the effects of psychedelic treatment, including preliminary low doses to 'test the waters', access to testimony from similar users, multimedia educational materials and virtual reality to simulate some of the acute effects (Appelbaum, 2024; Jacobs, Earp, et al., 2024; Marks et al., 2024; Villiger & Trachsel, 2023). While acknowledging the limitations in describing psychedelic phenomenology, Marks et al. (2024) propose that such limitations be explicitly discussed with patients while maintaining 'good-faith efforts to fully inform' them.

However, elsewhere I argue (Jacobs, 2023) that even enhanced consent procedures cannot fully address the transformative nature of psychedelic treatment. Informed consent processes are meant to support patients in rationally deciding whether undertaking a potential treatment is *right for them*. But a *rational* choice cannot be made to undertake an experience that involves both *learning* something that can only be learned through direct experience, and *changing* in response to that experience. If the subjective quality of a psychedelic treatment is fundamentally inaccessible before the fact, and I cannot foresee *who* I will become or what I will value afterward, my consent cannot be properly 'informed'. The severity of the challenge of transformative experience to informed consent is subject to ongoing debate (Egerton & Capitelli-McMahon, 2023; Kious et al., 2024; Villiger, 2025). Though that debate cannot be resolved here, it is useful to forestall one criticism of the position I have defended.

Villiger (2024) argues that taking this epistemic challenge too seriously risks creating a form of "rational paternalism" - if we accept that patients cannot give informed consent to transformative treatments due to their inherent epistemic limitations, this would seem to create an obligation for physicians not to perform such treatments at all. This would perversely transform informed consent from a tool for promoting patient autonomy into a barrier preventing patients from accessing potentially beneficial transformative therapies. This line of reasoning, however, rests on a false dichotomy: the available options are not limited to informed consent or prohibition. Even if we accept that transformative treatments create significant epistemic barriers to fully informed consent – without necessarily concluding that valid consent becomes impossible – medicine already recognises numerous contexts where standard informed consent processes may be inadequate or require modification (such as in emergency medicine or paediatric care) yet has developed alternative legitimising frameworks (presumed consent, proxy consent) for intervention. The alleged impossibility of securing informed consent (as opposed to refusal to grant consent) need not automatically prohibit treatment, but rather may indicate the need for different frameworks to ethically ground these interventions.

Practical challenges in informed consent for P-AT compound these theoretical concerns. Reviews of informed consent forms for psychedelic trials have found that they may be lacking regarding highly salient features of psychedelic therapies, including the use of touch (Harrison, 2023) and the prospect of long-term changes to personality, values and worldview (Rouhe, 2022). While these features should be acknowledged during the consenting process, quite which of the many potential outcomes should be highlighted remains unclear. As for any intervention, clinicians should strive to inform without overwhelming patients (O'Neill, 2003). Detailing every possible complication, however minor and rare, could paradoxically diminish autonomous decision-making by inducing patients to focus on irrelevant information or be swayed by the sheer number of negative possibilities rather than likely benefits.

This challenge of balancing disclosure against overwhelm takes on additional complexity in P-AT due to psychedelics' suggestibility-enhancing effects. As described above, material introduced to patients in advance of drug-assisted sessions can shape acute experience and patient understanding. As such, disclosure of potential outcomes of psychedelic use, crucial to safeguard patient autonomy, may inadvertently make some outcomes more likely by contributing to patient expectations and 'set'.

Moreover, while the signing of a consent *form* may be a one-off process that precedes an intervention, informed consent remains important throughout treatment. Under the acute effects of psychedelics, a patient's decision-making capacity – itself a key requirement of informed consent – can be compromised, complicating how a clinician should respond to some patient requests, including, as

discussed above, therapeutic touch which the patient had not consented to prior to the session, or for the termination of the session itself with rescue drugs (Lee et al., 2024).

As with many dimensions of P-AT practice, researchers and clinicians contemplating best practice for informed consent should retain a sense of epistemic humility: in alerting prospective patients about the limitations of our current understanding of psychedelic effects, and in avoiding the premature concretisation of consent practices (Appelbaum, 2024).

2.4.2. Conceptualising Therapeutic Change

When asked by a journalist 'if it worked', one participant in a P-AT trial for depression recalled that she…

> …felt like he had hurled an old, familiar, two-dimensional question into my now very three-dimensional world. And I told him my life was richer…And when my depression reemerged - and it did- it wasn't that it had gotten any smaller, but rather, that the space around it had grown much bigger. And somehow, being held by that blessed, blank space compelled me to hold my own suffering, and others', in new ways. He paused, and then quipped, "So I guess it didn't work" (R. Peterson, 2020).

This exchange surfaces an important tension in P-AT: outcomes that patients find deeply meaningful and valuable may not align with conventional metrics of therapeutic success. The journalist's quip highlights how our frameworks for evaluating treatment outcomes may fail to capture, or even dismiss, what patients themselves consider meaningful change[15]. This raises important questions about how we conceptualise therapeutic benefit in mental healthcare.

These questions take on practical, rather than theoretical significance as researchers explore developing non-subjective psychedelic analogues that might produce similar clinimetric improvements without the characteristic altered states of consciousness. Such developments require us to examine not just what we measure, but what we value in mental healthcare.

[15] Consider too the finding mentioned in the preface from the qualitative study of P-AT for tobacco cessation participants: "Quitting smoking was often reported as one of the least important effects of the study for participants in retrospect" (Noorani et al., 2018)

2.4.2.1. The Challenge of Measurement

As of February 2025, there has only been one head-to-head trial of P-AT versus an established mental health treatment - the study by Carhart-Harris et al. (2021) of escitalopram vs. psilocybin therapy for major depressive disorder (n=59). While the trial found no significant differences between psilocybin therapy and escitalopram on the primary outcome measure (the QIDS-SR-16, a brief self-report tool for quantifying depression severity), the secondary outcomes, though not corrected for multiple comparisons, all pointed in favour of psilocybin therapy. Among the statistically significant secondary outcomes were other measures of depression (including the clinician-administered Hamilton Depression Rating Scale (HAM-D-17) and Montgomery-Åsberg Depression Rating Scale (MADRS), and measures of experiential avoidance, anhedonia, work and social functioning, and 'flourishing'[16].

The lack of corrections for multiple comparisons does increase the risk that (some of) the statistically significant secondary outcomes may be spurious false positives. That all secondary measures trended in favour of psilocybin, however, is noteworthy and is indicative of a pattern rather than chance. Moreover, respondents in qualitative studies of psychedelic treatments for psychiatric disorders, outcomes consistently report personally meaningful outcomes at follow-up, including: revised or reidentification with forgotten life priorities (Belser et al., 2017; Gasser et al., 2015), increased sense of meaning or purpose in life (Swift et al., 2017) expanded emotional repertoires (Watts et al., 2017), feelings of self-compassion and love (Malone et al., 2018; Renelli et al., 2020), increased aesthetic appreciation (Watts et al., 2017; Noorani et al., 2018), and improved relationships (Belser et al., 2017; Watts et al., 2017; Noorani et al., 2018).

While clinimetric improvement remains crucial - people suffering from a psychiatric disorder want to know that a prospective treatment will reduce their symptoms, and regulatory bodies rightly require robust evidence of such reduction - the apparent regulatory irrelevance of these other valued outcomes warrants examination. Our choices of outcome measures, though they may be presented or treated as objective scientific tools, are not value-neutral. They embed assumptions about what constitutes therapeutic success and what kinds of outcomes matter in mental healthcare.

[16] Higher scores on the Flourishing Scale (FS, Diener et al., 2009) indicate stronger endorsement of the following statements: *I lead a purposeful and meaningful life*; *my social relationships are supportive and rewarding*; *I am engaged and interested in my daily activities*; *I actively contribute to the happiness and wellbeing of others*; *I am competent and capable in the activities that are important to me*; *I am a good person and live a good life*; *I am optimistic about my future; people respect me*.

2.4.2.2. Competing frameworks for understanding health

Different theoretical frameworks for understanding health suggest different criteria for evaluating therapeutic interventions. The medical model, focused on the absence of disease or infirmity and the restoration of 'normal' functioning, privileges symptom reduction as measured by standardised clinical scales. From this perspective, the primary outcome measure in Carhart-Harris et al. (2021), the QIDS-SR-16, appropriately captures what matters most: reduction in depressive symptoms to within normative ranges.

But other models of health are available. The holistic model of health adopted by the World Health Organisation (WHO) defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (World Health Organisation, 1948, p.10). This broader conception validates the significance of outcomes like increased sense of life meaning or purpose and could account for P-AT trial participants valuing non-symptom-related outcomes highly (Noorani et al., 2018). The social model of health, emphasising how environmental and structural factors shape health outcomes, draws attention to how interventions affect people's capabilities and functioning as understood within their social context (Guzys & Arnott, 2014). This framework helps explain why improvements in work and social functioning might be equally or more important than symptom reduction for some patients.

Historical precedents can show how dominant therapeutic models have been successfully challenged and overturned. The disability rights movement has challenged how medicine conceptualises 'normal functioning', underscoring how medical models of disability obscure how social and environmental factors create or amplify impairment (Barnes et al., 2020; Koch, 2001). This critique helped shift focus from 'fixing' individuals to addressing systemic barriers to participation and flourishing. Similarly, the palliative care movement successfully argued that quality of life considerations were as important as survival metrics, challenging the assumption that extending life should always be medicine's primary aim, and in doing so substantially reshaped end-of-life care (Saunders, 2001). These precedents suggest that questioning conventional metrics of therapeutic success can lead to more patient-centred clinical practice.

2.4.2.3. Non-subjective psychedelic analogues and the scope of medicine

These competing conceptions of health, and which treatment outcomes to emphasise, intersects with the earlier discussion about vulnerabilities in P-AT in the context of non-subjective psychedelic analogues. As explored in the last chapter, these (so far embryonic) treatments have the potential to

significantly reduce resource demands relative to P-AT. But by eliminating the acute psychotropic effects that induce heightened vulnerability, they could also theoretically provide clinimetric benefits while avoiding risks of exploitation, complex boundary negotiations, and resource-intensive safety requirements. This aligns with perspectives that medicine should focus narrowly on treating pathology rather than facilitating other outcomes. In rejecting a call for P-AT to be the default treatment even if non-subjective psychedelic analogues performed similarly in symptom improvement (Yaden, Earp, et al., 2022), Peterson & Sisti (2022) argue, "physicians do indeed have positive obligations to promote patient health, but those obligations do not require them to provide non-medically relevant experiences on the grounds that they could be meaningful or existentially transformative. Medicine is not in the business of self-transformation."

This disagreement mirrors a longstanding debate about psychiatric treatment more broadly, about the relative roles of medication and psychotherapy. While medication alone may demonstrate similar clinimetric efficacy compared to psychotherapy (Cuijpers et al., 2013), many patients report additional benefits from psychotherapeutic approaches that may justify their higher resource utilisation. The question of whether meaning-making, insight, and broader personal growth lie within medicine's proper domain takes on particular salience in mental healthcare, where narrative restructuring and meaning-making can play crucial roles in recovery (Llewellyn-Beardsley et al., 2019).

The boundaries between the clinical applications of psychedelics and society at large are porous, and as such the developments within biomedical research and practice do not happen in an ethical vacuum (Noorani, 2021). Disagreements about what constitutes legitimate therapeutic outcomes intersect with broader questions of medicalisation, access, and drug policy. While healthcare payers may be sceptical of funding P-AT's additional costs for the sake of non-clinimetric but nonetheless valued outcomes, restricting psychedelics to purely medical contexts raises additional ethical concerns. If the personal transformations reported in P-AT - enhanced life meaning, expanded emotional repertoires, deepened interpersonal connections - are indeed valuable, they are presumably valuable regardless of psychiatric status. Yet making these goods available exclusively through medical channels while maintaining policies of prohibition elsewhere creates an odd scenario where having a psychiatric condition becomes a privileged position regarding access to certain kinds of meaningful experiences and valued goods. This could incentivise 'symptom shopping', seeking psychiatric diagnoses primarily to access these goods, or pressure clinicians to expand diagnostic categories to accommodate demand, potentially contributing to the medicalisation of normal human experiences and desires for growth (cf. Conrad, 2007; J. E. Davis, 2020).

2.5 Conclusion

The institutionalisation of altered states of consciousness as a therapeutic mechanism creates ethical challenges that require us to refine our understanding of safeguarding patient autonomy, professional boundaries, and the nature of therapeutic change. This chapter's analysis demonstrates how the specific features of psychedelic treatments - deliberately induced alterations to perception and cognition, heightened transferential dynamics, and potential for precipitating non-clinical changes in patients - present distinctive challenges for ethical practice.

The heightened vulnerability in P-AT extends beyond typical concerns about whether consent is sufficiently informed. Even before drug administration, evidence that pre-session materials can shape subsequent experiences points to specific forms of influence that must be carefully managed. During acute effects, altered states affect not just decision-making capacity but also patients' ability to recognise and resist unwanted influence. This vulnerability continues through integration, as patients enter what Kochevar terms a state of 'epistemic vulnerability'.

This altered capacity for boundary maintenance intersects directly with challenges around therapeutic relationships. While intensified emotional experiences and psychological intimacy of P-AT may create pressure for more embodied forms of therapeutic support, examination shows how these features can make touch particularly risky. This creates a specific therapeutic challenge: both providing and withholding touch carry distinct clinical risks. Evidence from other areas of psychotherapy that emotional containment and support can be achieved through other means suggests that alternatives to touch might serve therapeutic aims without exacerbating the risks of misattuned intervention.

The historical record of abuses in both underground and clinical settings demonstrates that formal oversight mechanisms alone cannot prevent misconduct. Video recording of sessions, written codes of ethics, and even the presence of co-therapists proved insufficient to prevent a serious boundary violation in one clinical trial of MDMA-assisted therapy. This points to the need for robust professional cultures that actively engage with ethical challenges as they arise in practice, supported by meaningful accountability structures.

The examination of therapeutic outcomes reveals how P-AT challenges basic assumptions about mental healthcare. When patients find significant value in outcomes their clinicians considered incidental, or when broader life changes are prized as highly or higher than symptom reduction, this exposes

competing frameworks for understanding therapeutic benefit. The disability rights movement and palliative care movement provide instructive precedents - both successfully challenged conventional metrics of therapeutic success, reshaping clinical practice to better reflect patient-centred outcomes. Similar evolution may prove necessary in P-AT, particularly as the development of non-subjective analogues puts additional pressure on these competing conceptions of therapeutic benefit. If similar clinimetric improvements could be achieved without consciousness alteration, the field, regulators and healthcare payers must grapple explicitly with how to weigh different types of therapeutic change.

Just as those movements demonstrated how centring patient perspectives can reshape our understanding of what constitutes good clinical practice, developing appropriate frameworks for ethical practice in P-AT requires careful attention to the lived experience and priorities of patients who have undergone treatment. While clinimetric improvement remains crucial - people suffering from psychiatric disorders want to know that a treatment will reduce their symptoms - qualitative studies suggest that participants often value outcomes that receive substantially less attention than treatment effect sizes.

A striking gap in the current literature is the relative scarcity of patient perspectives on the actual lived experience of P-AT. While researchers have extensively documented clinical outcomes and proposed theoretical frameworks, far less attention has been paid to how patients themselves understand, interpret, and navigate the complexities of this novel treatment modality (for important exceptions, see Watts et al., 2017; Noorani et al., 2018; Palitsky et al., 2025). Without these perspectives, our understanding of P-AT's ethical dimensions remains incomplete.

The foregoing review of existing ethical frameworks and identified challenges serves as groundwork before examining patient experiences. Having established this conceptual foundation against which to situate the lived experiences of participants, we are better situated to identify both where patient perspectives confirm existing ethical concerns and, perhaps more importantly, see entirely new dimensions that current frameworks fail to capture.

These considerations point to the value of speaking directly with those who have undergone P-AT, to better understand the ethical dimensions of this novel therapeutic modality from the perspective of those most affected by it. The empirical research described in the following chapters addresses this gap by centring the experiences of former trial participants, identifying specific ethical challenges that emerge from their narratives, and using these insights to develop frameworks that better serve future patients.

3. Methodology

3.1 Introduction

This chapter, which discusses my chosen methodology for the primary research component that follows, is an emblematic microcosm of the integrated empirical-ethical approach that characterises the thesis at large. The account below is necessarily both descriptive and normative in nature: descriptive in outlining what I did and how I did it, and normative in defending why these choices were appropriate given the aims of the research.

It begins by describing the philosophical foundations that support the wider project of *empirical* ethics, the marshalling of social scientific methodologies to support and enrich ethical reasoning about real world matters. While this interdisciplinary approach has become increasingly prevalent over the last two decades, sometimes described as the 'empirical turn' in bioethics (Borry et al., 2008), the midwives of this development met strong resistance about the coherence and very possibility of an *empirical* ethics. As empirical ethicists continue to face objections born of the selfsame philosophical impulses, I characterise the forms of this resistance and outline argumentative responses to it.

Mindful of the status of qualitative research in an area which is principally quantitative and clinical in nature, I next motivate and defend the value of qualitative research methods in general, and of my originally chosen approach of Grounded Theory in particular. My research was originally envisioned to develop a Grounded Theory of 'non-clinical changes' in participants following P-AT trials, with a view to generating theoretical insights to ground ethical deliberation about P-AT as a clinical modality. However, during process of interviewing my participants, former trial P-AT participants, three important realities became apparent: (1) such changes were often difficult for members of my sample to articulate, or they disavowed that any such changes had happened to them; (2) some participants only realised certain changes had occurred through the process of being interviewed[17]; and (3) most crucially,

[17] The difficulty some participants experienced in articulating changes, and the emergence of awareness during interviews themselves, itself constitutes an interesting finding about the nature of P-AT experiences. But I had intended to understand the impact of these changes on their lives, and developing a robust theoretical account of how these changes impact participants' lives would be challenging when based on extemporaneous reflections on a phenomenon that had only just come to their attention. I additionally judged that, in this context, participants might feel pressure to generate or elaborate upon changes to meet perceived researcher expectations.

the semi-structured interviews revealed ethical issues that were more salient to participants and/or myself, and more important than those covered by my original research intention.

Methodological responsiveness to the data as it emerges is an important feature of qualitative research (Lim, 2024) and is supported by a range of established frameworks for knowledge generation (Charmaz, 2014; Levitt et al., 2017; Maxwell, 2013; Ravitch & Carl, 2021). The under-reporting in the P-AT literature of the ethical dimensions that became apparent during interviews pointed to the value of a shift in research methods. Documentation of methodological evolution is essential for transparency and rigour in qualitative research (Maxwell, 2013), and so I justify the rationale for the methodological evolution undertaken, both in general, and toward a case-based approach, which has an established pedigree as *casuistry* in bioethics. After outlining the final methodological framework chosen, I describe the more practical research methods employed to gather data, as well as the more standard considerations of reflexivity and research ethics practices undertaken.

3.2 Empirical Bioethics: Philosophical Foundations

3.2.1 The 'Empirical Turn' in bioethics

The ‘empirical turn’ described above represents both a methodological and a philosophical shift in how bioethics approaches complex problems in healthcare and medicine. Rehmann-Sutter and colleagues (2012, p.436) motivate this turn by appeal to the intuitive idea that, “in order to provide meaningful advice or helpful clarifications, ethicists must know something about the experiential landscape of the given situation of the practitioner involved.”

Many approaches to combining empirical and ethical work have emerged, with one systematic review identifying as many as 32 distinct approaches (Davies et al., 2015). Although multiple typologies of these approaches have been attempted (Kon, 2009; Sugarman et al., 2009), for present purposes it serves to articulate a driving ethos that unites them. Borry et al. (2008) characterise the breadth of approaches neatly by describing “empirical ethics [not as a] methodology for doing ethics, but a basic methodological attitude to use the findings from empirical research in ethical reflection and decision-making” (p. 39-40).

They articulate this shared attitude by reference to some of the assumptions that unite empirical ethicists, including myself:

1. That studying people's 'actual moral beliefs, intuitions, behaviour and reasoning yields information that is meaningful for ethics'
2. That 'the methodology of the social sciences … is a way (and probably the best way) to map this reality'
3. Denial of 'the structural incompatibility of empirical and normative approaches', and
4. The propriety of integrating 'empirical methodology or empirical research in the process of ethical reflection' (p.39)

For P-AT research, where many ethical dimensions remain underexplored and at a preliminary stage of understanding (Jacobs et al., 2024a), this empirical turn offers valuable methodological resources. The novel nature of these therapies, combined with the often deeply personal nature of their effects, makes careful attention to lived experience particularly crucial for developing appropriate ethical frameworks.

However, this integration of empirical and ethical work has faced persistent philosophical challenges. At the heart of these challenges are fundamental questions about the relationship between facts and values; how descriptive data - about what *is* - can inform normative conclusions - about what *ought* to be done. To establish the legitimacy of empirical ethics as an approach, I now turn to this philosophical challenge and outline how empirical ethicists have responded to it.

3.2.2 The fact/value distinction

The fact/value distinction, in ethics described as the is/ought problem, is attributed to the logical empiricist David Hume, who, in a short paragraph of his *Treatise on Human Nature* (1740), draws attention to an apparent logical fallacy deployed among his contemporaries - namely, the production of an evaluative or normative conclusion from a set of descriptive premises. More concretely, there appears to be an insurmountable distance from a set of statements about how the world *is* to how the world *ought to be*. To introduce a toy example, the normative conclusion that it is *wrong* to electrocute Simon, on the basis that electrocuting humans kills them and Simon is a human, is not logically valid - the conclusion does not logically follow from the premises. Logical validity in this instance can only be reached with a further enthymematic, or invisible-but-necessary premise that is itself normative - i.e., that it is *wrong* to kill humans.

It bears considering that it seems like *no* further purely descriptive information about the situation can lead to the conclusion that it is wrong to electrocute Simon. No amount of enrichment of the descriptive

account alone - about the nature of electricity, or about humans, will suffice to bridge the gap between the *is* of the situation and the *ought*. Appealing to the psychological distress of Simon's loved ones, for example, does not provide normative force not to electrocute Simon, without the addition of a normative premise like 'it is *wrong* to cause actions that bring about psychological distress'.

This principle, about the apparent separateness of is and ought, held significant sway over meta-ethical theorising for much of the time since Hume. As such, the empirical turn, which heralded the introduction of social science methods, characterised by descriptive data-gathering, into the process of ethical reasoning, was met with suspicion. Such scholarship was seen as little more than the generation of swathes of descriptive statements about how the world *is*, and as such of limited value to the business of ethics in articulating *oughts*.

A number of responses to this argumentative move suffice to rescue empirical ethics as a worthwhile and justifiable scholarly endeavour (Solomon, 2005). Most plainly, an empirical ethicist can shrug off the charge of incoherence or impossibility by acknowledging that they themselves can provide the normative premise(s) needed to reach normative conclusions: the objection to empirical ethics from the fact/value distinction is only strong enough to support the conclusion that empirical ethical work, to be coherent, cannot consist *only* of empirical work.[18] The sorts of ethical challenges that are of interest to empirical ethicists, including the best norms of practice in healthcare settings, involve far more complicated scenarios than the permissibility of electrocuting humans. Philosophical ethicists are (or, should be) interested not only in logically *valid* arguments, but rather in *sound* arguments, i.e., arguments in which the premises logically entail the conclusion, where additionally the premises are in fact *true*. Using social scientific methods of data-gathering may never by themselves generate normative conclusions, but they can ensure that the descriptive premises are accurate and relevant, and so able to bear sufficient weight to support the normative conclusion.

There is some debate about whether such research properly counts as *empirical ethics* (McMillan & Hope, 2008), and this approach has been characterised merely as philosophical ethics using social science as a handmaiden (Haimes, 2002), i.e., a mundane example of using facts to support an argument. But this characterisation flatters philosophical ethics, and denigrates the social sciences. It flatters philosophical ethics by assuming it knows what facts it needs to make sense of a normatively-valenced scenario. It denigrates the social sciences by under-appreciating the richness of the data it can uncover:

[18] "No sane defender of empirical bioethics is likely to suggest that we unreflectively use empirical data to determine what we morally ought to do" (Ives & Draper, 2009, p.254).

empirical work can identify and document *unacknowledged ethical problems* within some context of interest[19] (Bosk, 1999; Chambliss, 1997), reveal mistaken assumptions about the relevance of principles to moral agents (Freedman, 1993) or underlining the relevance of otherwise neglected ethical principles (Leget et al., 2009). With each of these outcomes, the fact/value distinction is accepted, but there are important ethical discoveries that have been made possible by virtue of the judicious use of social scientific methods.

3.2.3 Thick ethical concepts

A more sophisticated response to the fact/value distinction, and one more pertinent to the current study, is to reject the idea that social scientific methods can only generate descriptive observations, as they can also engage directly with moral norms. Such a response effectively amounts to a rejection of the absolute nature of the fact/value distinction, a philosophical position that first became prominent in the mid-twentieth century (Foot, 1958; Murdoch, 1957). This position depends on the development of another distinction, namely that between 'thin' and 'thick' ethical concepts. Whereas many of the standardly explored concepts in moral theory (e.g., 'good', 'right', 'ought') are clearly evaluative in nature, other normative terms (e.g., 'honest', 'rude', 'generous') seem to be simultaneously descriptive and evaluative. In calling Iris a *good person*, I am making an evaluative claim, but one that provides little descriptive content, since there are many attributes that might justify such a claim, and it is unclear which I have in mind. In comparison, in calling Iris an *honest* person, I make a claim with *both* descriptive and evaluative content. For the claim 'Iris is honest' to be true, certain facts must obtain - about Iris' tendencies towards truth-telling and avoiding deception. But the description as *honest* does more than state a fact. It also carries a normative component, evaluating Iris positively. As these tendencies are describable, detectable facets of the world, they are in principle able to be determined by empirical methods[20] (McMillan, 2016, p.27). However, the descriptive facets of Iris' behavioural tendencies do not exhaust a proper understanding of it. A social scientific researcher studying *honesty* cannot simply frame their study in terms of truth-telling and deception, but must appreciate the normative valence of honesty - i.e., that it is (under normal conditions) considered *good* - to properly understand its role in research participants' lives (Sayer, 2011).

[19] As happened in the present thesis.

[20] Here, for the sake of succinctness I suppress the question of the epistemological commitments and positioning of social science methodologies - a consideration I discuss below (§3.3.2).

Anthropologists of ethics and morality have successfully navigated the fact/value distinction in practice through careful attention to both observable patterns and cultural meanings, examining the "partial, perspectival, situated, affective, embodied, horizon-defined" aspects of moral experience (Mattingly & Throop, 2018, p.483) that take shape through practical engagement with lived experiences within specific social worlds. In Singh's (2013) study of children's experience with ADHD medications, thick ethical concepts like 'good behaviour' or 'being oneself' are not so much abstract universals, but take on specific meanings within particular institutional and relational contexts - understanding these concepts requires examining how they are articulated and enacted within actual social practices and relationships (cf. Mattingly, 2014).

This understanding proved methodologically crucial for the current study in two principal ways. Firstly, it supported the evolution towards a case-based analysis (3.4) when it became clear that participants' accounts of post-trial experiences could not be adequately captured through coding alone. For example, when one participant contrasted 'operating on an *existing* kind of level, not really *living*', this represented both an observable situation (her daily routine and behaviours) and a moral evaluation of what constitutes a life well-lived. Case studies preserved this integration of descriptive and evaluative elements that might have been fragmented by other approaches. Moreover, sensitivity to 'thick' ethical concepts informed data collection by highlighting the importance of allowing participants to articulate their own moral understandings. Rather than imposing predefined categories of 'good' or 'bad' outcomes, interview questions explored how participants made sense of their post-trial experiences within their specific social contexts.

3.3 Initial Methodological Framework

3.3.1 Grounded Theory Selection and Rationale

Having defended the validity of an empirical ethics approach, it remains necessary to ground a *particular* method appropriate for the research aims of the present study, since the choice of method, and the epistemological constraints that it imposes, strongly constrain 'what can be seen, how it is seen, and, therefore, what can be known' (Singh, 2016, pp.71-2). Although some studies in empirical ethics use quantitative measures (De Casterlé et al., 2004), they present significant limitations for my purposes. Quantitative methods necessarily operate through predetermined variables and standardised measures, which require specifying in advance precisely what aspects of experience are worth attending to: reliance on predefined questionnaires and scales mean that potentially interesting dimensions of

experience that are not anticipated by these instruments remain invisible to analysis. This constraint is particularly problematic when investigating novel therapeutic modalities such as P-AT, where the full range of ethically significant experiences may not yet be well understood.

Instead, qualitative research is needed to generate what social science researchers call 'thick' descriptions, which do not simply outline participant action and behaviour in a clinical, 'objective' fashion, but are also imbued with an understanding of the context of the behaviour, including the web of context and meaning that participants attribute to those behaviours[21] (Ponterotto, 2015). Such thick description is essential for ethical analysis, as it captures not only what changes occur following psychedelic therapy, but how these changes are experienced, interpreted, and integrated into participants' lives - dimensions that often carry significant moral weight and resist quantification.

Grounded Theory (GT) (Charmaz, 2000; Glaser & Strauss, 2017; Strauss & Corbin, 1998) was initially selected as the methodological framework for this study due to its particular strengths in investigating complex social phenomena. First, GT has been identified as especially suitable for investigating phenomena for which the has been relatively little research (McCann & Clark, 2004; Wuest, 2007), or for when theory is not yet available to explain a process (Creswell & Poth, 2016, ch.4). As such, it is suitable for addressing the relative paucity of scholarly knowledge, on the subjective experiences of value, attitude, and personality changes following a psychedelic experience. Unlike some qualitative approaches, GT seeks not just to *describe* a social phenomenon, but to *generate a theory*, an abstract analytical schema of that phenomenon (Cresswell and Poth, 2016, Ch. 4). This approach seeks neither to test some extant theory or set of hypotheses against empirical data, but rather to generate theory ‘grounded’ in data, moving from accounts of the phenomenon provided by experience, towards a generalised explanation of it.

The iterative approach central to GT methodology is particularly suited to investigating complex experiential phenomena like post-psychedelic changes. Core to GT's approach is what Cresswell & Poth (2016, p.64) call a 'zigzag' process: rather than conducting all data gathering before retreating to analyse the complete dataset, researchers gather data from a small number of participants, analyse it, and return

[21] Consider the difference in how the behaviours of the players and several thousand spectators of the World Cup final might be described by an alien with no concept of sport (“twenty-two humans repeatedly propel a spherical object between poles while thousands of others seated and standing around them emit sounds"), versus a football commentator's account rich with tactical understanding, historical context, and appreciation of the emotional and cultural significance of each moment. The alien provides objectively accurate but 'thin' description, while the commentator offers a 'thick' description that captures the meaning and significance of the events to those involved. (This example adapted from (Dennett, 1987), who uses it towards different ends).

to the field to gather more information, with questioning amended in light of the analysis. This continues through a process of 'constant comparison', including 'theoretical sampling' - choosing additional participants based on what is thought most informative to continue theory development. Common patterns that emerge across multiple participants can be progressively abstracted into higher-level conceptual categories, ultimately allowing the development of abstract theoretical constructs that can explain the original patterns of the data. This methodological flexibility, allowing engagement with emerging data through its iterative approach, was crucial given the exploratory nature of the original research focus on post-psychedelic non-clinical changes. GT's emphasis on letting theory emerge from the data, rather than testing pre-existing hypotheses, provides space for unexpected findings and novel theoretical insights, which proved important as the research evolved beyond its initial focus.

3.3.2 Constructivist Grounded Theory

Since its initial development in the 1960s, Grounded Theory has generated more than 3,650 journal articles, including both research studies and papers elaborating upon and developing the methodology itself (Mills et al., 2006). The breadth of its uptake has led to a diversification of approaches in its use, which draw from distinct philosophical and epistemological paradigms. Among these, I chose Charmaz's Constructivist Grounded Theory (CGT; Charmaz, 2014) as the approach most congruent with my own philosophical sensitivities. As such, it is appropriate to provide an articulation of those of my own commitments that relate to the research process.

I suggest that the diversity of people's personal histories, psychological temperaments, interests and biases, and the different meanings they ascribe to the actions and phenomena, mean not only that people can perceive reality in different ways, but that two people can encounter the same phenomenon and *experience* it differently. This challenges the notion that our shared social reality can be construed as a wholly objective phenomenon, since it is not clear how we can justifiably privilege one person's experience of a phenomenon over another's. It seems beyond the powers of social scientific methods to directly measure an objective social reality, or to identify a singular objective truth in many social matters: the varied perceptions of some phenomenon, alongside the complexity involved in interpreting the web of meanings that people attach to phenomena, render the pursuit of such objectivity ill-guided.

This particular epistemological stance is particularly relevant when studying psychedelic experiences and their aftermath, the meanings and significance of which may be deeply personal[22].

Turning more directly to the research process, I recognise that I, as a researcher, can only gather data by means of a social activity - i.e., talking with my participants. Recognition that understanding is co-constructed through the research process is central to CGT. I, too, have a particular personal history, temperament, set of interests and biases, so any data forthcoming from my conversations with participants will unavoidably have some of my 'fingerprints' on it, since that data is "created from shared experiences and relationships with participants" (Charmaz, 2014, p.239). As such, in the study that follows I am not strictly speaking 'collecting' data that exists in the world independently of my asking questions, but I am 'generating' data or 'co-constructing' it: Another researcher with identical aims and using an identical methodology, but a different history and set of biases, would likely generate different data. This CGT perspective rejects the positivist notion of objective findings passively emerging from data (characteristic of early GT schools), instead embracing abductive reasoning - a form of inference that moves between observation and theory to generate novel explanatory insights. Unlike purely inductive approaches that claim to build theory solely from data, or deductive approaches that test pre-existing theories, abductive reasoning acknowledges the value of researcher insight in forming possible theoretical explanations and accounts of observed phenomena. This approach allows me to productively draw upon my broader experience in psychedelics while remaining grounded in participant data (Timmermans & Tavory, 2012).

3.4 Methodological Evolution

3.4.1 Emergence of Distinct Ethical Considerations

Despite the original focus on 'non-clinical changes', it became progressively clear over the course of my first six interviews that a change in focus was warranted. Although such changes were identified in my early sample, conversations with two participants made it clear that the 'non-clinical changes' described in chapter 2 were not relevant to their own trial experiences. For two others, my line of questioning (see initial interview schedule below, §3.6.2) was found to be interesting and engaging, but largely because the process of the interview itself was the first time that they had become aware of the

[22] For instance, many people interpret the content of their psychedelic experience in supernatural or otherwise non-naturalistic terms. Regardless of the truth, or indeed verifiability, of such meanings loaded onto experience, these meanings nonetheless inform and direct people's thinking and behaviour, and it is people's thinking and behaviour that is of principal interest to bioethical reflection, rather than the source of them.

changes that they had undergone. In early memos (see §3.6.2 below) I flagged two important considerations: (i) the apparently opaque nature of these changes to the participants themselves is suggestive of a relatively low salience to the participants themselves. Of their experience following P-AT, these non-clinical changes were not simply peripheral considerations that were untroubling to them, but were rather not considered at all. As well as suggesting, perhaps, a diminished ethical *salience* of these changes for contemplation of P-AT practice, (ii) there was also a risk that interrogation about the nature and meaning of these changes, on the spot, might be overly subject to social desirability bias, acquiescence bias, or other demand characteristics - making their data a risky basis on which to develop a theoretical account of these changes.

Most fundamentally, some interviews revealed ethical concerns that were not only more salient to participants than the 'non-clinical changes' I had set out to investigate, but also largely unexamined in the existing literature. The open-ended nature of my initial question ("Thinking about how you saw the world before you took part in the study, and how you saw it afterwards, does anything stand out?") allowed participants to naturally gravitate toward what mattered most to them about their experience. That these spontaneous narratives highlighted ethical dimensions unreported by the wider clinical literature suggested not just their importance to participants, but also a significant gap in current understanding of P-AT's ethical implications[23]. One of bioethics' key contributions towards clinical practice is a horizon-scanning function, "identifying potential problems before they will actually emerge in reality" (Sutrop, 2004, p.vi). The discovery of these previously underexamined ethical issues prompted me to reorient the focus, and therefore methodological approach, to the study.

3.4.2 From GT to case study ethics

The emergence of these unanticipated ethical dimensions as central to participants' accounts presented specific challenges to the original GT framework that sought to develop a theory of post-psychedelic non-clinical changes. The ethical issues that arose were relatively independent, casting doubt on the assumption that a unified theory could adequately capture their details. GT's emphasis on moving toward theoretical abstraction through constant comparison risked obscuring precisely those contextual details and narrative elements for individual participants that were necessary to understand the ethical salience of the challenges they faced following their trial experience.

[23] The realities that led to the methodological evolution mirrors an important aspect of psychedelic therapy itself: the importance of 'letting go' of preconceptions and being open to the emergence of the unknown, the unexpected, or challenging material (Watts & Luoma, 2020; Wolff et al., 2020).

This methodological challenge suggested the value of case study ethics, which has an established pedigree in bioethical reasoning (Strong, 2013). Rather than seeking to generate abstract theory, case studies allow the preservation of contextual richness that is crucial for understanding how an ethical challenge has arisen in a particular situation. The emergence of the challenges identified during interviews was unanticipated and as yet undescribed by the literature, and I judged it better to allow the experience of the relevant participants to speak for itself, rather than risk being lost in a more aggregated theoretical analysis. The case study approach is developed more fully in § 3.5, where I outline its methodological foundations and how it was implemented in this research. For now, it suffices to note that this evolution was not merely a response to practical difficulties with the original GT framework, but rather reflected a deeper alignment between the emergent ethical focus of the research and an established tradition of bioethical inquiry.

3.4.3 Evolving research design

The shift in methodological approach described above is supported by established frameworks for qualitative research design and evaluation. The initial theoretical support for such a shift is itself embedded in CGT, the developer of which describes it as "inductive, indeterminate, and open-ended. An emergent method begins with the empirical world and builds an inductive understanding of it as events unfold and knowledge accrues" (Charmaz, 2008). Charmaz's emphasis on 'theoretical agnosticism', remaining open to theoretical possibilities while conducting empirical work, provided a foundation for my methodological flexibility. When it became evident that my original CGT approach was inadequate to fully capture where the data was leading me, this principle enabled me to adapt my methods accordingly. This responsiveness to data and iterative refinement of research focus represents not a deviation from the spirit of CGT but its appropriate application in practice.

This openness to emergent findings align with Levitt and colleagues' (2017) recommendations for 'methodological integrity', which provide additional theoretical foundation through their emphasis on two core processes: fidelity to the subject matter, and utility in achieving research goals. Both aspects are enhanced by the shift to case study ethics, demonstrating how Charmaz's theoretical agnosticism can lead to methodologically sound evolution.

Regarding fidelity, case studies were necessary to preserve the particularities, rather than shared features, that were necessary to understand how the emergent ethical challenges arose. The original CGT framework, despite its constructivist orientation, risked fragmenting precisely those details that

made the ethical significance of participants' experience understandable. Case studies, in contrast, allowed the preservation of the complexities that gave rise to ethically salient dimensions of experience. This preservation of the particular likewise supported utility, since a case study approach, but not CGT, enabled analysis that could inform future practice. Importantly, Levitt et al. argue that methodological integrity is established when research designs support research goals, respect researchers' approaches to inquiry, and are tailored to the characteristics of both subject matter and researcher. These criteria are well met by the move to a case study approach, since (i) it better supported the emergent goal of bringing to light underappreciated ethical dimensions of the patient experience in P-AT; (ii) maintained alignment (or, did not contravene) with my espoused constructivist commitments, and (iii) allowed me to leverage my training in both empirical methods and philosophical ethics.

As Janesick (1994, p.215) notes, an overfixation on undertaking research as a rigid set of procedures - what he terms *methodolatry* - can impede, rather than enhancing research quality. The methodological evolution outlined here exemplifies the opposite approach: a principled flexibility that responds to emerging data while maintaining theoretical and methodological rigour.

3.5 Final Methodological Framework

The methodological evolution described above led to an approach grounded in case-based ethical reasoning with deep roots in bioethics (Strong, 2013). While case study research takes various forms across the social sciences, this thesis specifically employs case-based analysis, treating cases not simply as illustrations, but as the fundamental units of ethical inquiry and understanding. This methodological evolution allowed for a deeper examination of specific ethical challenges that emerged organically from participant narratives, providing a natural progression from the initial Grounded Theory approach as the research focus sharpened toward specific ethical dimensions of P-AT.

3.5.1 Case Study Ethical Analysis

Case study research is best characterised as an approach or strategy rather than a method in itself, as case studies can employ various data generation and analysis techniques as the research context demands. What unites case studies is their focus on an in-depth study of one or a limited number of cases. This focus on depth over breadth is particularly valuable for the current project, given the aforementioned nature of the salient ethical issues identified as often subtle, complex, and deeply embedded in participants' lived experiences.

A case study approach is especially suited to investigating ethical challenges in novel therapeutic contexts. As Ives and Draper (2009, p. 251) observe, it permits 'encounters with experience' - "positioning oneself so that one can understand, as far as possible, how an ethical problem affects peoples' lives...[t]he advantage of this is that it contextualizes a problem and sensitises one to the needs and experiences of those most affected by it." This contextual understanding is crucial when examining emergent treatments where the full range of ethical considerations may not yet be apparent.

The complex nature of P-AT specifically, including its novel mechanism of action and potential to rapidly catalyse psychological change, means its ethical dimensions may not map neatly onto familiar frameworks developed for conventional treatments. Where traditional approaches might assume clear distinctions between drug effects and psychotherapy, or between treatment and personal transformation, P-AT's hybrid nature challenges these boundaries.

Early patient experiences can reveal ethical tensions that are not visible in trial data alone. The lived experience of undergoing P-AT and integrating its effects into one's life may generate considerations that standard clinical measures cannot capture. For instance, changes in worldview or relationships that fall outside conventional outcome measures might nonetheless carry significant ethical weight. Case-based analysis allows examination of how challenges emerge from the interaction of therapeutic mechanisms, healthcare structures, and lived experience—all crucial elements for developing appropriate ethical frameworks for this emerging treatment modality.

In the present research, I conducted in-depth interviews with ten former P-AT trial participants, but provide detailed analysis on just three cases that most clearly illuminate different aspects of the post-trial experience. So selective a focus requires justification: isn't this simply cherry-picking the cases that support whatever argument I wish to make, regardless of their representativeness across participants or even within my own small sample? This criticism misunderstands the purpose of case studies. I make no claims about representativeness or statistical generalisability. The selection is not arbitrary or merely convenient, but rather follows established case study methodology where cases are chosen for their potential to reveal important theoretical insights (Yin, 2009), focusing on specific instances where existing frameworks and assumptions about P-AT may need to be reconsidered or revised. Just as early safety studies in medicine focus particular attention on adverse events even when rare, ethical analysis should attend to potential challenges even if they are not universal.

3.5.2 Situating case study research as knowledge generation

Accordingly, the cases included in this thesis ultimately serve as 'vouchers' rather than 'clinchers' (Cartwright, 2007): they support theoretical possibilities, rather than establish statistical certainties. A small number, or even a single, case in which a particular ethically salient occurrence arises cannot definitively establish anything. But a phenomenon need only appear once to warrant inclusion in the analytical map of the territory under study. Indeed, the single cases can be sufficient to demonstrate that:

a) This type of ethical challenge *can* arise in the context in P-AT (because it already *has*);
b) Current frameworks for practice may not adequately address it (because these challenges arose in trials following current frameworks for practice); and
c) Future trial designs should consider it.

Importantly, *consideration* of the material presented in these case studies does not mean that practice should be inverted on the basis of a single participant's experience. Despite my efforts at careful rigour, I may have misconceived the nature of the case at hand. Responses to the experiences outlined here may require costly or effortful adaptations to practice, and it would be prudent to undertake further research to establish the validity of my findings, as well as the precedence of the salient occurrences identified.

Case studies, while not generalisable in a statistical sense, reveal important possibilities that require attention as the field develops. Like early safety studies in medicine that focus particular attention on adverse events even when rare, ethical analysis should attend to potential challenges even if they are not universal among participants. Dismissing ethical considerations merely because they do not affect the majority of participants would risk perpetuating blind spots in treatment protocols and participant protections.

The knowledge generated through case studies takes a distinct form from that produced by the clinical and experimental paradigms that have dominated recent psychedelic research. Rather than seeking the *statistical* generalisability that quantitative researchers are familiar with, the case studies aim for what (Stake, 1978) terms *naturalistic* generalisability. Naturalistic generalisation of a case study is dependent on the engagement of the reader or user of the research. The target reader especially, those engaged in psychedelic research of their own, need to get *their* fingerprints on this research. I have provided thick descriptions and experiential accounts of the cases at hand. Naturalistic generalisation happens when the account resonates with the reader's own context, being "epistemologically in harmony with the

reader's experience and thus to that person a natural basis for generalisation" (Stake, 1978), p.5 - a tacit recognition of similarity rather than a formalised process. Close reading of my case studies may permit readers - either prospective patients or psychedelic therapists - to reflect on the similarity to their own experiences and circumstances, drawing what lessons they may for their own context and purposes.

My own role as researcher in this knowledge generation process warrants acknowledgement. Subjectivity - on the parts of both the participants and the researcher - is ultimately inevitable in approaches like the one chosen. Subjectivity from the participants is *desirable*, especially where the research questions attend to lived experiences and people's subjective interpretations of them, which typically cannot be captured by quantitative methods alone. Subjectivity from the researchers is *unavoidable*, since the main instrument for data generation is the researcher themself. However, in acknowledgement of this, qualitative researchers engage in *reflexivity* (Morse et al., 2002; see § 3.7 below): critical self-reflection and the acknowledgement and attention to personal biases that may influence interpretations of research. As outlined above, *I* have chosen to draw attention to and analyse three ethically-inflected dimensions of P-AT that I have deemed salient and worthy of attention. The choice of cases is ultimately driven by my own biases, temperament, and interests and professional history in psychedelic research and bioethics. My 'fingerprints' are all over the research that follows, as they are all over the preceding chapters. But it is important to acknowledge that this is not a unique characteristic of my study, nor a shortcoming to be mitigated. Every researcher, regardless of the objectivity they aspire to, inevitably shapes the research process with their own perspectives, assumptions, and experiences.

3.6 Research Methods

3.6.1 Participant recruitment

As of 2025, P-AT continues to advance through clinical trials for depressive and addictive disorders, with several Phase III trials ongoing but not yet completed. Despite significant research progress, psilocybin and most psychedelics remain classified under the most restrictive categories of controlled substances in most jurisdictions worldwide. Although Oregon has implemented a state-regulated non-clinical 'supported adult use' psilocybin services program since 2023, and Colorado has begun developing similar frameworks, the primary route of access to therapeutic P-AT continues to be through clinical trials and expanded access programs.

Since psychedelic experiences are understood to be strongly influenced by *set and setting*, it was desirable to recruit participants who underwent P-AT in a setting as similar as possible to what will be experienced in the principal (i.e., licensed medical) route of therapeutic access. While future clinical delivery may see some variation in treatment protocols compared to research settings, medically administered P-AT will bear far stronger resemblance to the protocols developed during clinical trials than to other modes of psychedelic administration.

The target population was therefore former participants in clinical trials of psilocybin-assisted therapy. This choice was driven by several methodological considerations. While there is qualitative research about life following psychedelic use among recreational and spiritual users (Dollar, 2021; Uthaug et al., 2022), and such users represent a far larger pool of potential interviewees than those who have undergone P-AT in a trial context, these are importantly different populations. The set and setting differs markedly between clinical and non-clinical contexts. The 'setting' of a clinical room in a research hospital, in the context of a legally sanctioned medical trial, creates a fundamentally different container than retreats or private spaces. More crucially, the (mind)'set' of trial participants is distinct: they are not healthy individuals seeking personal growth or spiritual insight, but rather people burdened with medical conditions of sufficient severity that they volunteered for experimental treatment. Given that 'set' is understood to influence psychedelic experiences, I excluded from participation those who had taken psychedelics for recreational or spiritual purposes: clinical trial participants share with future patients the decision to undergo P-AT for the purposes of treating a health condition, and so likely overlap in their hopes and expectations about getting well.

The recruitment strategy comprised two main channels. The primary route was through the Psychedelic Participant Advocacy Network (PsyPAN), an organisation that provides support to trial participants and maintains connections with this geographically dispersed and difficult-to-access population. This was supplemented by social media outreach shared through professional networks in the psychedelic research space. This dual approach helped ensure both targeted access to the relevant population while also allowing for broader reach.

The empirical research included ten participants who had undergone psilocybin-assisted therapy trials for various conditions including major depressive disorder, treatment-resistant depression, alcohol use disorder, and bipolar II disorder. Standard demographic information and basic clinical measures were collected during participant onboarding and interviews, though these were not intended for statistical analysis and are not included in empirical papers. This diversity of indications was intentionally sought to examine how similar therapeutic processes and ethical considerations might manifest differently

across different populations and trial contexts. Moreover, recruiting across different conditions meant engaging with participants treated at different research centres, which can have their own distinct approaches to the P-AT model outlined in §1.3. As Gearin & Devenot, (2021, p.918) observe, contemporary research contexts actively incorporate cultural signifiers that reflect different orientations to practice. At NYU, for instance, "clinical researchers have ritualized the dispensation of psilocybin by using a ceremonial chalice, and dosing sessions take place in a medical office decorated with landscape paintings, books of art and mythology, aboriginal 'tchotchkes,' a statue of the Buddha, and a glazed ceramic mushroom." Recruiting across different clinical conditions and research centres was seen as a virtue, allowing a scope of focus that was sensitive to core challenges of P-AT rather than artifacts of particular research protocols or institutional cultures.

The current study does not seek to make claims about incidence or prevalence, but rather to identify and analyse ethically significant dimensions of the post-trial experience. As discussed in §3.5.2, a phenomenon only needs to appear once in the sample to warrant inclusion in the analytical map. The final sample of ten participants, from which three detailed cases were selected for in-depth analysis, provided sufficient rich data for the careful ethical analysis intended, while remaining manageable within the constraints of doctoral research.

One aspect of my relationship with participants is worth noting for methodological reasons: namely, that I engaged with them as a researcher independent from any of the clinical trial teams. Although direct affiliation with P-AT research sites might have facilitated recruitment, this independence offered a noteworthy advantage. Participants speaking with original study researchers or their therapists might reasonably feel pressure to provide positive feedback due to social desirability bias or concerns about disappointing those who provided their care. This separation likely created a more balanced power dynamic during interviews, where participants could feel greater freedom to share honest experiences, including negative or critical perspectives about their trial participation, without fear that this might disappoint or offend their former therapists or harm ongoing therapeutic relationships.

3.6.2 Data Generation

The principal mode of data generation for this study was semi-structured interviewing. This method was chosen due to the nature of the content to be discussed: psychedelic experiences are frequently ranked among the most personally and spiritually significant in participants' lives, and the meaning-making that follows them often involves deeply personal reflection. As such, the confidential setting of

one-to-one interviews was deemed more likely than group discussions to provide the comfort and security needed to facilitate open and genuine responses (Gaskell, 2000).

Initial interviews lasted approximately 90 minutes and followed a set of open, non-directive questions, thematically arranged according to the following guide:

a) Stand-out impressions

- E.g., *"Thinking about how you saw the world before you took part in the study, and how you saw it afterwards, does anything stand out?"*

b) Person

- E.g., *"Did you notice any changes following the drug sessions with regards to your habits of thinking, concentration, or cognition?"*

c) (Social) world

- E.g., *"Have you found some things or people in your life to be more or less important following the drug sessions?"*

d) Characteristics of person-world interactions

- E.g., *"Have you noticed any changes with regards to your focus on your inner thoughts vs your current experience and surroundings?"*

e) Existential stance - second-order evaluative relations to themselves, or the changes they have noticed

- E.g., *"Which of the changes that we discussed today are the most important or significant to you? Why?"*

The last scheduled questions were also intended to provide open space for the participant to volunteer any aspects of their post-trial experience that they wanted to share

- E.g., *"Is there anything that you expected to be asked today that we haven't discussed? Is there anything you hoped you would be asked about today that we haven't explored?"*

The semi-structured approach, with ad-hoc follow-up questions to allow interviewees to express themselves fully, permitted a genuinely exploratory approach to the topic of inquiry. This format

allowed for meaningful comparison of different participants' responses while providing opportunity for novel and unanticipated material to be discussed at length. The initial study design had planned for systematic second interviews with all participants. However, as the research evolved toward a case study approach (see § 3.4), this was modified. Follow-up interviews of 40-60 minutes were conducted with two participants where additional exploration of specific ethical dimensions was warranted.

Given the geographic dispersion of the target population, interviews took place over videoconferencing software. Although previous research suggested that rapport-building could be hampered when conducting research interviews online (Hay-Gibson, 2010), the widespread dependence on videoconferencing during pandemic lockdowns has familiarised significant proportions of the wider population with these means of communicating. Recent research has demonstrated that quality qualitative research can be undertaken through online platforms (Boland et al., 2022; Keen et al., 2022; Torrentira, 2020).

All interviews were recorded with participant consent and transcribed verbatim (details below). Field notes were taken during and immediately after each interview to capture initial impressions, emerging themes, and reflexive observations about the interview process itself. These notes formed part of the broader audit trail (discussed in § 3.7.2) and helped inform the evolution of the interview approach over the course of the study. The combination of verbatim transcripts, field notes, and iterative reflection on the interview process helped ensure a rich dataset while maintaining methodological rigour.

3.6.3 Data Analysis and Validation

Interview transcripts were analysed using the software package Delve. The analysis process evolved alongside the broader methodological development of the study. Initial analysis began with descriptive coding of the first tranche of transcripts, one at a time, generating a significant number of code categories. As commonalities across interviews became apparent, the coding structure was assessed and refined to increase coherence and clarity: some codes were collapsed into others, while sets of conceptually related codes were collated under encompassing themes.

However, as outlined in § 3.4, the emergence of distinct ethical dimensions in the data prompted a shift from the original Grounded Theory approach toward case study analysis. This evolution required a different analytical focus - from seeking patterns across all participants to identifying and deeply examining specific cases that illuminated important ethical considerations. Previous coding work remained valuable but was repurposed to support the identification and analysis of ethically salient cases.

Several quality assurance measures were employed to enhance the rigor of the analysis:

1. Expert Supervision: Although the nature and restrictions of doctoral research meant that it was not feasible to recruit additional coders, regular discussions with an expert in qualitative methods during supervision sessions provided an elementary check against the risk of bias associated with single-coder analysis. These discussions involved reviewing coding approaches, examining interpretations of key passages, and critically discussing the selection and analysis of cases.
2. Triangulation (Bans-Akutey & Tiimub, 2021; Heale & Forbes, 2013): Where possible, supplementary interviews were conducted with participants' loved ones and carers. These additional perspectives helped validate and enrich understanding of the cases selected for detailed analysis, particularly regarding changes and challenges described by participants.
3. Participant Validation (Lindheim, 2022): Participants whose experiences were selected for detailed case analysis were invited to review draft case descriptions (see Ch. 4). This process served to verify the accuracy and completeness of my characterisation of our conversations, while ensuring participants were comfortable with their level of anonymisation. In one instance, this led to moderate revisions to enhance anonymity and correct minor misunderstandings. Participants responded positively to this validation process, noting that it made them feel respected, provided new insights into their experience, and offered a valuable opportunity to reconnect with their thoughts several months after the interview.

These quality assurance practices align with established approaches in qualitative research, helping to ensure both the trustworthiness of the analysis and the ethical treatment of participant data. The combination of expert supervision, triangulation with additional informants, and participant validation provided multiple checks on the interpretive process while respecting the participatory nature of qualitative inquiry. ‘Reflexivity’, that is, the critical examination of the role of the researcher in the research process, is recognised as a critical feature of qualitative research (Morse et al., 2002). Seen as a *concept*, reflexivity refers to the recognition of researchers as active participants in the research process (Lambert et al., 2010), a notion which is partially acknowledged in the development of this thesis by referring not to ‘data collection’, as is typically standard, but rather ‘data generation’. Leaving aside ontological questions of the *reality* of the phenomenon of inquiry, it is acknowledged that the social and psychological processes of interest to me make up part of a social world, that can only be accessed (and investigated) socially (Ackerly & True, 2010; Morse, 1991). Wherever a phenomenon of inquiry has a subjective or social aspect, there will be a need for *reflexivity* - a recognition of the

necessarily partial and biased interpretations of both the research participants and the researcher themselves.

3.6.4 Case selection construction

From the ten participants interviewed, three cases were selected for detailed analysis. This selection followed Yin's (2009) criteria for critical cases - those that are particularly revelatory of the phenomena under study. The selection was deliberate rather than arbitrary, guided by my aim to illuminate distinct ethical dimensions that have received insufficient attention in existing P-AT literature. I specifically sought cases that revealed how P-AT's distinctive features—its hybrid pharmacological-psychotherapeutic nature, profound subjective effects, and potential for rapid psychological change—generate ethical considerations that may not arise with conventional treatments. This selection strategy deliberately privileged novelty, identifying previously unexamined challenges specific to P-AT rather than reiterating established ethical concerns already well-documented elsewhere.

Other salient issues emerged across interviews but were not selected for deep analysis because they were less distinctive to P-AT or already well-represented in existing literature. The selected cases, individually and in conjunction, best demonstrated issues requiring careful consideration as the field moves toward clinical practice.

The seven interviews that did not become detailed case studies were set aside for several reasons. Three participants reported minimal challenges or concerns following their trials, making their experiences less revelatory of the ethical dimensions this thesis aimed to examine. Two interviews, while containing relevant material, covered similar thematic ground to the selected cases without offering substantially novel insights that would justify additional detailed analysis. The remaining two participants experienced challenges that, while salient to them personally, were judged as more readily explicable through existing ethical frameworks than revealing distinctive features of P-AT that warranted extended examination. The three selected cases were chosen because they were judged to have the highest ‘revelatory’ potential (Stake, 1995), i.e., they most clearly illuminated previously underexplored ethical dimensions while representing different aspects of the P-AT experience.The case descriptions follow a consistent structure designed to provide readers with both comprehensive context and narrative depth. Each opens with a concise contextual background, establishing demographic information, the trial participated in, and pre-existing mental health challenges. A broader exploration of the participant's pre-trial context, including their treatment history, life circumstances, and relationship to their diagnosed condition follows. The cases then unfold through a chronological narrative structure, though this

linearity is complexified by temporal layering that weaves together present reflections on past experiences, comparisons between different periods, and anticipated futures. This layered approach helps contextualise how participants make sense of their experiences over time, a feature that becomes particularly salient in Chapter 7, as shifting interpretations of experience comes to complicate adverse event reporting in P-AT trials.

In using this structure, I aimed to satisfy Stake's (1995) exhortation to provide readers with a vicarious experiential understanding of each case, before drawing out and examining the theoretical significance of participant experiences in the chapters that follow. The anonymisation procedures outlined above serve to safeguard the privacy of my interviewees in the face of detailed description of a handful of individuals, as did the participant validation of draft case descriptions.

3.7 Reflexivity

3.7.1 Researcher positioning

Reflexivity as *process* refers to a continuous practice of self-reflection on the researcher's part to acknowledge the values and perceptions that guide the development of the research: recognising their pre-existing knowledge and perspectives, social background, and 'positionality', their stance in relation to the social and political context of the study (Rowe, 2014, p.628). I provide a fuller positionality statement in Appendix 1, but in brief, this includes my own experience with psychedelics both as an adjunct to spiritual practice and as a mental health intervention, my interpretation of the meaning(s) of psychedelic experiences and the 'non-clinical side effects' that made up a significant part of the initial inquiry of this thesis. Moreover, professional engagement with psychedelics for some six years as an analyst, researcher and consultant has meant being embedded in, and engaging with, the heterogeneous 'psychedelic community' for a considerable fraction of my adult life. This background provides valuable context for understanding participant experiences but has naturally led to particular beliefs about appropriate models of practice and regulation of psychedelic medicines.

3.7.2 Ongoing reflexive practice

The goals of engaging in reflexivity are to "make the relationship between, and the influence of the researcher and the participants explicit" (Jootun et al., 2009, p.45) and to clarify the "influence that the researchers exert, either intentionally or unintentionally, on the findings" (p.42). Since my own positionality would naturally evolve over the course of data gathering by the process of continued conversations about psychedelics in my broader personal and professional life, and likely due to

developing researcher-participant relationships and the conversations that make up my research data, it is appropriate to engage in reflexivity as an ongoing feature across all steps of the research process (J. Hughes & van der Riet, 2012), rather than a one-off event. As well as writing an initial positionality statement (Appendix 1) before the beginning interviews, a snapshot of reflexivity at a crucial point in the research process, the continuous reflexive process is well-served by the process of *memoing*, which serves as an 'audit trail' (Lincoln & Guba, 1985): a means to track the evolution of interpretations and analytical decisions, document emerging insights and thoughts about how to understand the data, and record 'reflexive moments' where I spot that personal experience or bias might be influencing analysis.

3.8 Ethical Considerations

All data collected for the study was collected, stored and handled according to internal University regulations and Best Practice Guidance, so as to be in line with the Data Protection Acts of 1998 and 2018. Participants were informed that they had the right to withdraw consent for the use of their data up until the end of the collection period in November 2023.

The wellbeing of participants was a central ethical consideration throughout the research, given both the sensitive nature of the interview topics and the potentially vulnerable state of participants who had undergone experimental therapy for mental health conditions. Prior to interviews, participants received clear communication about interview topics and the nature of what would be discussed, allowing them to make an informed decision about participation. The participant information sheets explicitly noted that discussions might cover sensitive personal experiences and emotions related to their trial participation. Protections during interviews were established from the design stage: the semi-structured interview format was chosen partly to allow participants control over how much they shared about potentially sensitive experiences, while the choice of one-on-one interviews, rather than group discussions, provided a more contained environment for discussing personal experiences. Before and during interviews, participants were explicitly reminded of their freedom to pause or end interviews at any time without prejudice. While I encouraged participants to speak freely, they were reminded they were not obligated to make disclosures or participate in discussions that made them uncomfortable.

Recordings of interviews were made over password-protected videoconferencing calls, for online interviews. This digital data, along transcriptions of interviews and incidental emails from participants, were stored on password-secured Oxford University drives, with a deletion date set at 10 years after the

conclusion of data collection. To secure against data loss, copies of anonymised transcriptions were stored locally as encrypted word document files on a password protected laptop.

In all disseminated outputs from the research, including this thesis, participants were assigned a pseudonym, with potentially identifying details omitted or altered to preserve anonymity. Names of family members, friends, and others mentioned in interviews were pseudonymised, although mentions of study staff, including therapists and guides, were retained.

A unique consideration arose from participant recruitment through PsyPAN, which provides peer support networks for trial participants. The possibility existed that study participants might discuss their participation with others within the network. While such freely-chosen disclosure was deemed ethically unproblematic and potentially beneficial for recruitment, I maintained strict boundaries around participant information, never disclosing who had or had not chosen to participate in the interviews.

3.9 Moving from Method to Analysis

The methodology outlined above provides the foundation for examining three distinct analytical themes that emerged from the case studies. Each theme illuminates different ethical dimensions of P-AT that warrant careful consideration as the field moves toward clinical implementation. Three case descriptions are presented, followed by analyses of their ethical significance.

The first analysis examines questions of ***post-trial access and care***, highlighted particularly through Helen's experience of insufficient integration and support following the trial, leaving her feeling "ripped open, left with all the mess and having to deal with it on my own." Her case, alongside others', raises important questions about researchers' obligations to trial participants following study completion, particularly given the distinctive characteristics of psychedelic intervention. The second analysis centres on the role of what early psychedelic researcher Betty Eisner termed 'the matrix' - ***the socio-ecological environment from which patients come from, and to which they return***, following P-AT treatment. Eleanor and Aaron's contrasting experiences following their trials, one supported by an understanding partner and the other facing resistance from both partner and community, demonstrate how features of participants' matrices can, in the context of administering a plasticity-enhancing and environmentally-sensitising drug, potentially amplify or diminish the impact of their post-psilocybin experiences. The final analysis examines the complex territory of ***adverse events*** in P-AT, moving beyond standard

clinical categorisations to consider the nuanced, sometimes ambivalent nature of challenging experiences that can follow psychedelic administration. This analysis particularly benefits from the case study approach, as it allows close examination of how participants interpret and integrate difficult experiences over time.

These analyses do not exhaust the ethical considerations raised by P-AT (see, for example, other work developed concurrently with this thesis: (Cheung et al., 2024; Insua-Summerhays & Jacobs, 2025; Jacobs, 2023, 2025; Jacobs, Earp, et al., 2024; Jacobs et al., 2023). Nor do they represent the only possible interpretations of the gathered data. Rather, they represent three particularly salient themes that emerged through the iterative process of data generation and analysis described above. The case study approach allows each theme to be examined with the contextual richness necessary for understanding how these ethical challenges manifest in participants' lived experience.

4. Case descriptions

The following three case studies offer windows into varied trajectories following P-AT trial participation. Eleanor's journey reveals her navigation toward authentic living despite ongoing emotional challenges; Helen's story illustrates initial therapeutic promise followed by frustration and distress; and Aaron's narrative demonstrates complex symptom improvement alongside broader life turbulence following his psychedelic experience. While each case contains elements relevant to all three ethical dimensions examined in subsequent chapters, they collectively highlight phenomena that warrant deeper exploration. These detailed accounts provide the phenomenological foundation for the analyses that follow, though they are not offered as empirical proof of causal relationships, but rather as illustrations of ethically salient experiences deserving careful consideration as P-AT continues to develop.

4.1 Eleanor

D1 (‘Eleanor’) is a professional woman in her early 40s who participated in a trial of psilocybin-assisted therapy for treatment resistant depression in late 2019, following several years of SSRI use for major depression with a comorbid anxiety disorder. She considers the trial intervention to be a successful treatment, and of the number of non-clinical changes she attributed to the trial, she feels “generally very positive… I felt very much like [the trial] was a stimulus for a lot of big changes in my life.”

Eleanor described her life before participating in the trial as “very mundane, operating on an *existing* kind of level, not really *living*.” This pattern she attributes to her prior tendency to prioritise doing what she imagined other people would approve of, rather than properly engaging with her own values for deciding what to do with her life: “I think my life prior to the trial was always very sort of externally determined, you know, ‘what do your parents think? What [does] society think?’...do ‘*the right thing*’.” This period was marked by a struggle to find fulfilment, despite her best efforts. It is not so much the case that Eleanor had no inkling about how she might have liked to have lived, but rather that she was either unwilling or unable to properly engage with this:

> "My entire life has been sort of not doing the things I wanted to do…which I didn't have the courage or confidence to engage with…I had these glimmers prior to the trial of things I wanted to pursue, which I kept on batting away"

In contrast, she reports that the trial "definitely gave me the stimulus to start following my passions; it gave me the courage and confidence to get out there." 'Getting out there' for Eleanor included committing to find time to dance, starting a business, and finding work as a facilitator at a psychedelic retreat, each of which are activities she derives satisfaction from. She ties this post-trial willingness to 'get out there' to her experiences 'going into difficult places' during acute drug effects and recognising that she was able to manage them. "I came out with an idea of like, well I want to do the things I've always wanted to do now." When asked where she thought this newfound confidence to do these things *came from* - considering the risky nature of starting a business or retraining to perform a novel kind of work - she spoke of her experiences during the acute drug effects, an increased "comfort with all the uncertainty in the world", a willingness to do things in spite of fear, and a sense of joie de vivre:

> "What I learned is that your worst possible nightmare is probably not as bad as you make it out to be… Sometimes it's the fear of doing things or the fear of a certain outcome, which is actually more crippling than just doing the thing or experiencing the loss or just experiencing. Post-trial after sort of going into difficult places and maybe realising I'd be OK doing that…I came out with an idea of like, well, I want to do the things I've always wanted to do now"

In contrast to her life pre-trial, Eleanor now feels she keeps "getting this invitation at the moment from life, from chaos. Maybe [I] just need to accept it. I think maybe I'm redefining my relationship to chaos in the world. Or maybe, maybe not finding it as terrifying, just trying to see it as part of the process." Eleanor characterised this attitude as antithetical to depression - that this perspective on the world was constitutive of not being depressed: "it's not about being static and paralysed, which is a lot of what depression is for me. Paralysed by indecision, concern, anxiety, and just not doing anything. Now the idea is *do something*. Show up in your own life. *Do the thing* - irrespective of the outcome."

Despite this positive shift, Eleanor's life after the trial has not been smooth sailing. Within months of her trial participation, she was tested by a number of particularly challenging life stressors, including financial insecurity, a (non-psychiatric) hospitalisation, and the onset of the COVID-19 pandemic. She described this shift as going from 'the cocoon of the trial' to the 'brutality' of 'everything falling apart' and being "in free fall for three months" without her "usual crutches" of SSRIs to support her. However,

her personal insights during acute drug effects about "the causes of my depression," and clearly seeing "what [emotional baggage, problems, and responsibilities] were mine and what weren't mine," led to a more pragmatic attitude towards life's challenges. She reduced her previous hyper-self-criticality and shifted to a proportional sense of responsibility, differentiating between what she could control and what she couldn't, moving away from a tendency to internalise guilt for past choices.

> "I was really, really upset with…the situation. But [then I started] realising, 'no, actually, you know what, *this* is what you can't control but *this* is what you can control… not taking it all upon myself and saying 'Oh, I deserve this' or 'this is all my doing'. So, I started sort of realising, I guess, what was circumstantial and separate to me and then was able to meet it and then choose a response as opposed to just, I guess, being triggered and reacting automatically."

The most salient change that Eleanor reported was an increased awareness of, and direction of attention to, her body. This was evidenced by a recurring use of somatosensory metaphor during the interview. Reflecting on the dosing session and the months that followed, she described "the very tangible feeling of depression being an ill-fitting black coat…again, it's a touch thing, about how constricting and clumsy and awkward it felt - [this sense] has come with time that I can now notice the difference." This attention to sensation has also led to changes in her (non-metaphorical) dress: "[with] clothes, like, synthetic feels uncomfortable. Scratchy clothing doesn't work any more… [I now want] softer clothes and prettier clothes."

With this recently developed somatosensory and interoceptive sensitivity, Eleanor described "feeling more at home in [my body] ...I felt like that wasn't me prior to the trial. I was just walking around in some kind of weird meat suit, but I'm really coming into myself a bit more now". This heightened bodily sensitivity has led to a number of behavioural changes, including dietary shifts and increased daily activity that led to significant weight loss. These shifts represent alterations from Eleanor's pre-morbid preferences: previously, she would, if possible…

> "...have had a tablet or intravenous shot of something and that's nutrition done for the day, a purely utilitarian thing. Whereas now it's like, 'ooh, wouldn't that be nice?' ***I'm definitely enjoying those senses a lot more***".

Eleanor has found value in this increased somatic sensitivity beyond straightforward enjoyment of sensory stimulation, including a greater ability to mentalise her own psychological state by attending to physiological signals. Having discontinued SSRIs following the trial, "while depression might be gone, anxiety has ramped up, [and] I'm very aware of feelings in my body. Now I can feel a tightness in the chest, or tummy tied up in knots…and I think that's a good thing. I'm trying to really, really feel what my body's saying to me, how am I feeling in this encounter, in this situation?"

Eleanor's newfound sensitivity extends beyond her own body to other people she comes into contact with, reporting an empathic attunement to her family, friends and colleagues, but also to strangers when out in public: "I find myself trying to put myself in their heads and wonder what their world looks like…these are random strangers, and I just have to - *wow* - almost spine-tingling moments where I feel really deeply connected." Eleanor largely sees this as a beneficial shift. Having taken on work as a facilitator in a psilocybin retreat (a non-clinical context in which psychedelic users typically outnumber sober supporters at a ratio of 4-5:1), both retreatants and supervisors have commented on her high level of emotional attunement. She recalls one occasion when she alone saw a need for a supportive intervention.

> "There was somebody really struggling in their journey, but it was invisible. Somehow I really picked up on it because of her stillness. It was a frozenness - she's just lying down, but it's like she's stuck. She's not in a good place, even though she looked perfectly calm. I think that sort of [perception] is what's been amped up."

This empathic sensitivity comes with its own challenges: it "isn't with me 100% of the time; it comes in waves. And it's incredibly powerful every time it pops up, and it pops up in random places at random times… Sometimes I think I just need to go back on the [SSRIs] to mute some of this, because it's just intense - you know, it can be quite overwhelming at times…sometimes it just feels like I'm feeling too much." At a number of points, conversation returned to Eleanor's ambivalence about her increased emotional sensitivity, which she sometimes felt ill-equipped to handle, in her view because of her long-term use of SSRIs: "it's a whole new skill set, especially in my case, [as I've] been medicated for 20-odd years; I just don't have the tools."

The decision to recommence the use of SSRIs, or not, following psilocybin therapy was seen as significant for a number of respondents, as it can symbolically mark whether the trial treatment was 'successful' or not, with corresponding effects on the overall evaluation of the trial experience. In

Eleanor's case, a steady influence in the decision not to restart SSRIs was the supportive encouragement of her husband. "My husband definitely thinks that this is the right path or journey or that things are better, especially when things are more challenging." When the intensity of emotional sensitivity (to both positive and negative affect) became so overwhelming as to lead Eleanor to reconsider SSRIs, "he's always unequivocally supportive of not doing that. He's like, no, keep going, just take one more step…I think he genuinely sees that there's happiness in me…and there have been moments of a sparklingness, and I've really felt alive and connected and inspired. And that makes the hard times worth it, I guess."

Eleanor also credits her trial experience with positively perceived shifts in her patterns of relating to others. This is in part because of her heightened somatic sensitivity, which she credits with broadening her thinking style: before the trial, she would be "aware of others from a place of anxiety or people-pleasing, whereas now I'm just more aware of others, because I feel more interconnected, and I'm just reading my own body, and I'll read other people's responses to me." With this attention to her own responses, she reports being more able to confidently discern which interactions and relationships are energising, and which are draining. Rather than trying to expend as much energy as possible maintaining a large number of friendships, she has adjusted her social energies to focus on those relationships she finds nourishing. For Eleanor, these are the relationships that are grounded in authenticity and in sharing the emotional content of life: "it almost sounds like I'm [intent on] narrowing down on a few people [. But] it's not about narrowing or closing down. It's about opening more deeply - really wanting to bear witness to somebody's real journey, not what they project." Reflecting on her previous relational style, she characterises her past priorities as "a lot of people-pleasing, fawning behaviour, and really wanting to make sure everyone's alright because if you're OK, I'm OK." In comparison, the new importance that Eleanor places on authenticity in relationships has made her more willing to tolerate interpersonal discord if it is the price of honesty.

Eleanor's attitude of tolerance for discord, alongside her forbearance in the face of the sometimes-chaotic nature of the world is representative of a broader acceptance of the characteristic experiential variance of life, which is also seen in her relationship with her depressive symptoms after the trial:

> "I definitely don't judge them as harshly any more…my initial response would be, oh this isn't right I need to fix it, make it go away. Excise it, remove it. But no, it's more of a relationship and understanding that it's there and then it'll pass… I think what makes my depression get

entrenched is when I'm not accepting it, when I'm not accepting the difficulty, and I rail and the process of railing extends it."

As with other phenomena, Eleanor also interprets her symptoms through the prism of her body: now, her thought process when she notices depressed mood is "my body's telling me things aren't okay...well, then rest and regroup and somehow things resolve and then you pick up and carry on. So I think my downs are a bit shorter than they had been." At the close of our discussion, Eleanor speculates whether the reason for her 'treatment-resistant' depression is that she had been incorrectly diagnosed, with her symptoms actually emerging as a trauma response that needed to be addressed before the depressed mood could clear.

"I don't feel comfortable calling myself depressed - it doesn't feel like a label that fits any more. Yeah, it feels like I've outgrown that ill-fitting coat, and put it down."

4.2 Helen

AN1 ('Helen') is a woman in her early 30s who participated in a trial of psilocybin-assisted therapy for a long-standing anorexia nervosa in late 2021. Prior to this, she had a long history of mental health challenges, including a diagnosis of obsessive-compulsive disorder from age 11, and the first manifestation of eating disorders at age 13, and a later diagnosis of autism. She had been under the care of a specialist eating disorder team for several years without any previous successful treatment - her father reflected that, "with Helen, nothing's ever worked for her over the years. All the treatments, for anything, really". She views the trial intervention as unsuccessful in reducing her symptoms and holds mixed feelings about its broader impacts on her life, which include a complex aftermath of heightened internal conflict and a deepened sense of loss.

Throughout her interview, Helen drew attention to the hope that she experienced following the second of her three psilocybin doses, after which she felt a sense of optimism that she would be able to make enduring shifts to her highly routinised lifestyle, a lifestyle within which she felt she had little ability to act outside of the 'allowed' list of food choices and activities.

> "I would say in the month or so after I wanted to change things. I was feeling more… that things were possible rather than going 'oh, no, I can't do that. I'm not even going to try'...There was more positivity in the planning for different things"

> "[Previously] I wouldn't have thought about doing those sorts of things, it would have been literally just do what I do every day and rigidly thinking I can't do anything different"

Helen's father offered a similar assessment of this shift following the second dose, reflecting that she was "talking more, trying new things - a definite change. I felt very uplifted because previously she'd been in a very dark place… It was very hard to talk to her but [after the second session] it was almost like getting the old Helen back." Helen herself identified two distinct motivations for trying to change her behaviour: (i) a positive motivation driven by her recollections of the joy she experienced from a variety of activities in her premorbid state, and her wish to recapture it; and (ii) a negative motivation driven by an insight into the long-term consequences of not changing her current, restricted behaviour patterns, which she tied to a vision of her own funeral during her second dosing session.

> "I keep going back to the funeral - one of the big visions is my funeral and people saying 'what a waste' and everything… So every time I follow the eating disorder voice and I don't try to move forward, I feel like we're slipping away, time is slipping away"

This period of positive motivation was, however, short-lived. Helen estimated a period of some three weeks after the second session when she was in the most positive mood she had been for years, and was motivated to pursue pleasurable activities outside of her typical prescriptive patterning, including a trip to the seaside which would have been impossible for her before the trial. She relates that her father, who accompanied her on that trip, "said he'll never forget that day…how I was different and was positive, and he just said I was completely different." The positive motivation then began to dissipate. She struggled to channel the drive for different experiences, and experienced a diminution of the pleasure of new activities, feeling anxious at the mismatch between the enjoyment she anticipated and what she felt:

> "I tried to do new things, and I went away for three weeks and tried to do new things. Quite shortly after, none of those things stuck really... It was quite overwhelming the amount of things I wanted to do, and my brain was like 'wow, what could I do?' It was just too much."

> ""I didn't enjoy it. I just felt stressed. I thought I might feel connected to how I felt when I was younger and did these things…But it didn't feel…particularly pleasurable …I just felt tension and stress around it. I think there was a disappointment that it didn't feel very…I didn't feel great or feel those positive things that I felt [before the eating disorder]. Well, what's wrong? Why, why am I not?"

While the positive aspect of her motivation to change faded away, Helen's negative feelings about maintaining in her disordered eating patterns - guilt and anxiety that she is wasting her life - remained salient, leading to an internal conflict she struggled to resolve: a lack of wherewithal to change maladaptive behaviours, and a heightened distress at her inability to change. She describes this internal conflict as a battle between two 'voices' or 'sides' within her that represent the drives *to continue with*, and *to change*, her maladaptive patterns.

> "I didn't feel strong enough to deal with the eating disorder side, so that got louder because this other bit is daring to try something different and wanting to do something different, so it starts shouting louder too. So I've now got these two sides that are very strong - it's quite painful if

> you've got one part going, 'why the hell are you following your eating disordered habits and thoughts?'' And then you have … [the eating disordered side insisting that you follow those patterns]. It's almost made it more painful because I've got both thoughts stronger"

The initial impact of the second psilocybin session was a relative weakening of the maladaptive voice and strengthening of the salutogenic voice. Of the maladaptive voice, she said, "I guess initially [after that session] it felt less important. And smaller, but it just felt less…Yeah, it shrunk in size, so it felt more defeatable…But unfortunately it seems to have got bigger again and almost louder. But the other side still hates those behaviours, and now…it feels like it's more of a waste what I'm doing and I hate [performing the ED behaviours] more."

The stress, as well as the lack of enjoyment that Helen experienced during activities that should be pleasurable, in combination with the objections from the maladaptive voice, ultimately meant that she started to try less and less to change her behaviours:

> "It's just so stressful. So the bit of my brain that's awoken is saying 'you need to do these things'. But then it doesn't feel great, and the eating disorder voice gets angrier. So I've kind of stopped. Why am I doing it if it's not pleasurable and it just makes my eating disorder voice angry?"

This has led to her to revert to her pre-trial behaviour patterns, a situation which is in some respects subjectively more distressing for her than before. After reverting to maladaptive patterns, in part because of the objections of the eating disorder voice, she still experiences pain from the frustrated wish to make changes following the trial.

> "It's like a war going on in my head. At least before [the trial, the part of me] that had any hopes and stuff and wanted change was just squashed down, so it wasn't so painful…Before, you just did the [eating disordered] behaviours. Now, every time I do it, I'm reminded how much this is a waste. It's hard enough dealing with the behaviours, and the panic and stress associated with that, but now I've got this bit saying 'you're wasting your life' every time you do it."

Reflecting on the psilocybin sessions themselves, Helen "felt good after them, initially, I kind of experienced it as good, even the trauma. It felt cathartic." The new activities following the trial that she has been able to sustain are related to the drug experiences: learning about neuroscience, and seeking

to recapture how she felt following the psilocybin sessions through mindfulness, sound baths, and music.

> "I'm doing meditation and I'm trying to do that daily…and the sound baths. Now I'm trying to get back to that state that I felt…"

> "I do try to return [to the feeling of the drug session], but sometimes I can't…Even if it's a bit painful [to return to those feelings with music], it almost feels cathartic to do it."

Her sentiment towards the psilocybin sessions themselves was positive, relating that she has been considering other routes to securing further experiences: "I know it's not great, but I have been looking…But then it's a matter of where do I find these drugs? Do I go abroad, which is very difficult for me…Do I try and grow it? These obviously have legal difficulties, actually doing it and getting the right doses and safety." Asked if she would participate in another trial if the opportunity arose, she had clear plans about how she would approach it differently. "Definitely. This time, I would be getting psychedelic therapists and other therapists set up ready to catch me afterwards," a sentiment echoed by her father.

Despite positive feelings towards the drug sessions themselves, pointing towards a belief that the modality itself could be useful, Helen felt that she was inadequately prepared for what would come after the trial, and not properly supported by the study team in making the most of the brief period of improvement. "I feel there was promise there, and hope - it just wasn't used. I didn't know what to do with it…I didn't feel I had enough help to try and tackle the behaviours and change." She felt the integration sessions provided as part of the trial protocol were insufficient, "I was just thrown out of the trial with no plans…I kind of thought, well, yeah, but now what do I do with this?...What do I do now when I go home? I'm not really being helped with guidance." Likewise, she reports her father, her identified next-of-kin for the study, was given a brief psychoeducation session with the study team, but

> "He felt he didn't really know what to do, either. He could just see me completely like so positive and wanting to do things, and he didn't know what to do or how to channel that. He feels he didn't have enough specific guidance of what to do…He thinks if they'd said 'her brain might be really different, she might be really open to therapies and different things', he would have tried to get some arranged or some booked…He didn't feel prepared at all. "

Speaking later to Helen's father, he related that they had sought further guidance from the trial team:

> "We did raise it with the person who was our contact. Didn't get much help back from them… Helen described it - 'she felt she'd been left in the lurch' - She described it as having open heart surgery and being left with her chest open … I sort of felt [the trial team] were very sympathetic, but there wasn't any sort of help from them."

Ultimately, Helen was provided with a list of private integration therapists to support her with the challenges arising following her trial participation. Regrettably, this support was outside of her ability to pay. Her father reflected on the recruitment period, saying that "we didn't think too much - probably unwisely - about the time after [the trial]. And they didn't really make much comment on what happened afterwards…Perhaps they should provide therapy rather than direct you to it, because…it's quite expensive. Not everyone can afford to, and I certainly couldn't."

The limited opportunities to undergo psilocybin sessions in controlled contexts, coupled with her frustration at developments following the trial, have left Helen doubtful of the overall value of the trial to her:

> "I feel incredibly disappointed, like it was my last chance or that I wasted it because I think I could have changed so much. But I didn't, and it's like you slipped away because it disappeared within about two months, that feeling and that openness… Now I don't know. Is it worse to experience the positive and now have that taken away - or not, taken away, but… not able to access that any more? It's almost like more painful than if I hadn't experienced that."

While her father "sort of felt [the trial team] were very sympathetic, but there wasn't any sort of help from them," Helen was mindful to stress that she did not feel mis-sold by the team: "they did it ethically and they told me, it's not a cure, and this is just a trial." But in the broader societal context of psychedelic therapies, "obviously, the media kind of hype it all up…you can't help but absorb a bit of that hope," meaning that her lack of enduring improvement "makes you feel like a failure." At times she "would say that the behaviours have got worse rather than better", and that occasionally she felt that "I wish I'd never done it. It was just not worth it. It's like, I've been ripped open, left with all the mess and having to deal with it on my own. And it's unbearable."

Just as Helen felt underequipped to make the most of the fleeting benefits from the trial, likewise she feels that the psychic 'mess' uncovered in the wake of the trial - the heightening conflict between the two drives pointing towards and away from behaviour change - is a challenge that she cannot face alone:

> "It kind of feels unfair that I would be expected to pay quite a lot of money to see a therapist, which I wasn't really warned I might need. This is not cheap. It could be a hundred pounds or something a session…I just feel a bit resentful that it's been awoken in my brain and I've been churned up a bit and…Well, emotions have resurfaced, and now I have to…try and sort it out myself"

4.3 Aaron

D5 (‘Aaron’) is a professional man in his early 50s who was in the midst of a depressive episode of several years’ length when he participated in a trial of psilocybin-assisted therapy for major depressive disorder. He described his pre-trial state as “irritable, not feeling, socially isolating,” acknowledging that his “depression didn’t come out of nowhere,” pointing to early childhood experiences of neglect in an “emotionally dysregulated household.” Aaron “had been through therapy over and over through the years”, and although he had experienced symptom relief from standard pharmacotherapies in the past, these were accompanied by intolerable side-effects. At the time of his entry to the trial, he “had tried the [commonly prescribed antidepressants] again, and they didn’t work…nothing.” At the point of entering the trial, Aaron was “getting desperate…[and] in denial - I was suppressing how bad it was…I was shut off in my room for like a good year.” Asked about his mindset going into the trial, he reported daily, but fleeing, suicidal thoughts, applying to the trial as a last-ditch attempt to improve. His therapeutic response to the psilocybin was striking and immediate, characterising it as an instantaneous remission, but his post-trial experience was one of significant challenge.

Aaron’s social experience prior to his entry onto the trial was marked by a challenging isolation. A long-standing member of a sobriety support group, he had met his partner in sobriety, and credited his move to sobriety to the diminution of previous depressive episodes. However, in the depressive episode that led to his trial participation, he had “hit a wall” with the value of participating in meetings, and ultimately stopped attending out of a sense of futility about them: “I was going to meetings, going to meetings, going to meetings, but it’s just like, *this is not fucking working any more*. I don’t have any desire to drink, but everything else in my life is fucking disastrous. So eventually I just stopped going because… I would come out feeling worse.” Concerned about his risk of relapse, the group pressured him to return, leaving Aaron feeling an oppositional social atmosphere of “me against the rest of my sober community and my wife.”

Against this backdrop, Aaron’s partner was sceptical, and strongly resistant to his participation in a trial which involved a drug of abuse. Aaron reports that they “were not supportive of me doing this, [the trial] was very, very triggering for them.” Ultimately this manifested in her refusing to collect Aaron from the study site following his drug session, a point typically marked by environmental sensitivity and emotional fragility. He reports that she had assented to his participation on the understanding that “I don’t want the kids to see you like that, and you have to pretend like it didn’t happen.” Her refusal

to engage was a source of significant distress for Aaron, and was an axis around which a large part of his post-trial challenges revolved. He reflected that "if she had… just been there and believed [in] me, it would be a completely different world right now…the simple difference that would have made if my partner had met me to pick me up and take me home."

Aaron's therapeutic response to the psilocybin experience was immediate, and immediately conspicuous: "in one single session - full remission." On the day of his first dosing, the apparently instantaneous relief from his symptoms for the first time in several years drew his attention to the stark contrast between the two states of mind. "I didn't realise how much I was [hiding the extent of my symptoms] to myself," later remarking that he had been underreporting the extent of his depression "because I didn't realise how bad it was until its absence."

When asked about the trajectory of his mental state after the trial, Aaron described a typical healthy mindset, which is neither devoid of negative thoughts or feelings, nor completely beholden to them. He reflected that, while such thoughts and feelings had not remained completely absent in the two years up to our interviews, they were vastly muted in their intensity and salience. Pressed further about the qualitative differences in his mental states following the trial, Aaron described tendencies towards increased self-compassion, and greater psychological autonomy from previously automatic depressogenic thought patterns.

> "'*[Aaron] bad'* used to be very, very prevalent… But the self-chastising is just not the same. I tend to be a person that's notably hard on myself. But the qualitative difference between then and now, it's an alien planet, almost…It's not as if I'm free of compulsion or reactivity or something, but somehow it seems much more conscious now…It's not like it's exactly a choice, but it's not *not* a choice"

> "It's less severe, it's less frequent. In the immediate aftermath, it was completely absent. And then after it slowly gained momentum…But the severity is different and the impact is different, and it's just so significantly less weighted now than it used to be… I don't ascribe to it the value that I used to somehow… It's almost as if it's a false premise, and I can [look at the same cognitive and behavioural patterns that led to depression]... and I can somehow just see, *OK, that's just part of the old overweighting*"

Reflecting on why, in contrast to some participants, Aaron's symptomatic relief was so enduring, three features were apparent from our conversations. The first is that he continued self-medication with psilocybin every few months out of a steadfast refusal to risk relapsing, as well as seeking out conventional psychotherapy. Although not entirely satisfied with the therapist who "wasn't psychedelically informed," he acknowledged that this post-trial psychotherapy should be credited with the resolution of some longstanding psychological challenges. In the years prior to the trial, Aaron had learned and used a breadth of practices to keep previous depressive episodes manageable, and he was confident that his access to this repertoire of skills allowed him to make the antidepressant effect of the trial enduring. Finally, Aaron was evidently the most driven of all my interlocutors to engage in an exercise of sense-making about his experience. In the two years between his trial and our conversation, he had engaged in systematic and comprehensive self-education about psychedelics. Throughout our interviews, he referenced a large number of physiological, neurological, and psychological accounts, including less widely-reported and sometimes decades old research, about their mechanisms of action, leveraging his understanding of these to frame his experiences.

Despite the therapeutic success of the trial in terms of symptom reduction, Aaron's experience following the trial was marked by personal challenges that were a significant source of distress for him. As was the case for a number of participants, the onset of the COVID-19 pandemic, and the resultant lockdown policies, regrettably coincided with the period following Aaron's trial participation, heightening the challenge of settling into life after his psychedelic experience.

As is often the case, during the acute drug effects Aaron experienced significant psychological insight about himself, including early relational influences on his sense of himself and the world, as well as profound subjective material of a transpersonal nature. But his ability to unpack these experiences and talk them through was hampered by his partner's resistance to engage with Aaron about the trial. This was made all the more trying for Aaron to manage, given that a significant dimension of his psychological insight during the trial related to being able to understand and articulate sources of dissatisfaction within his relationship. "I deeply started addressing that (there are many things that) I am not happy with in my relationship. It doesn't mean that I didn't love my spouse, [just that] all the things that I was dissatisfied with were suddenly in my face." He described that things "that I'd been suppressing about our relationship were not suppressible anymore," but "there was this really dismissive attitude from them, of hoping that this was just a phase I'd be passing through." Although he did not directly attribute his depression to his relational difficulties, he suggested that they were a contributing

factor, with the “issues in the relationship [becoming] a kind of status quo that had been dragging me under.”

With the lockdown curtailing other social engagement in which he might work through these challenges, Aaron related that “the isolation, or the separateness is intensified when I’m not around people that can relate…I’m inside, and I’ve got no one to talk to about any of this.” It was during this period that Aaron went online in seeking help to make sense of these changes. “When I was in the greatest distress around this? Pretty fresh out of the program.” With the restrictions in being able to find someone to talk to about his experience within his extant social networks, Aaron connected online to others who were engaged in psychedelic use, research and advocacy to better make sense of his experience. “Within the broader psychedelic community, there’s this whole larger affinity based on this shared collective experience of piercing the veil, as it were.” Finding this new community allowed Aaron to accept the rift that had grown between him and his sober community, and to embrace those parts of himself - including psilocybin use- that had contributed to the rift. “I kind of stopped caring what they think, … and I guess I stopped being ashamed of being a weirdo… Yeah, OK, I get that I’m not like you, but I also see things that you don’t and should.”

But this newfound connection to the psychedelic community also came with its challenges. Aaron connected with, and quickly became intensely romantically engaged with, another member of the community. Exploration [in our discussion] of this material was emotionally challenging for Aaron, but something he felt was particularly important for the purposes of the research - “it just felt like something particularly representative of this whole thing, and I wanted to portray this as honestly as possible.” Although this relationship provided an outlet for his pronounced need for connection in the context of his broader sense of isolation, the nature of that context meant that the connection was an admixture of profound happiness and anguish. Aaron held a strong sense of fidelity as a key component to his self-identity, alongside a commitment to his family, and an unwillingness to subject them to the ordeals of separation. Likewise he was unwilling to subject the other person to the pains of being sidelined in an extramarital affair. This situation was novel territory for Aaron, and he struggled to make sense of his emergent feelings - unsure if they were ‘real’ or an artefact of his intense psychedelic experience, and the ensuing enhanced openness and sense of connection. “I really tended to hijack every researcher I could find. Like, is this normal? Does this happen? Is this just me? Right. Really needing to know. Like, is this exposing defects of character, or is this an aspect of myself I've suppressed so deeply? Seeing no ideal resolution, ultimately Aaron broke off contact with this person, a decision which he stands by but nonetheless left him “sobbing for a month.”

Asked how he feels about this dimension of his post-trial experience, Aaron reported that he doesn't "think that's a bad thing. I don't think any of this feels like a bad thing. It actually feels like quite a good thing. Um. It's just. Intricate and the level of raw intimacy it opens up within." Having discussed the issue with underground practitioners in the space, he relates that "the other one I hear is people going through this, and then like wives leaving their husbands…they said the only time they've ever been threatened with suits is from ex-spouses who say, what did you do to my to my darling?"

At the time of our conversations, Aaron had not experienced a depressive episode following the trial, and though he had found a more even keel relationally with his wife, he reflected that he is still "completely in limbo now." Although his depression hasn't returned, he points to a singular challenge of psychedelic therapies as "when it unburies stuff, un-automates stuff." Nonetheless, he concludes that "in spite of everything that's happened, you know, I wouldn't trade it for anything in the world. Not for a single second, but we have to prepare people for what that space in there is like."

These narratives provide the foundation for examining three critical dimensions of P-AT in the chapters that follow: the provision of post-trial access and care (Chapter 5), the influence of participants' socio-ecological contexts on therapeutic journeys (Chapter 6), and the challenges of adequately capturing adverse events in P-AT trials (Chapter 7). Through these analyses, I aim to show how these lived experiences can inform more ethically robust approaches to P-AT research and practice.

5. Post-trial Access and Care[24]

5.1 Introduction

The nature and extent of duties owed by clinical researchers to participants at the conclusion of a trial are subject to much scholarly discussion. This centres around the continued provision of an experimental clinical intervention at close of trial. Variously grounded by appeal to *non-exploitation*, *reciprocity*, *beneficence* and *nonmaleficence*, some international codes of ethics (e.g. The WMA's Declaration of Helsinki, the Council for International Organizations of Medical Science's (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects) include requirements for the provision of post-trial access (PTA) of effective treatments (Mastroleo, 2016). While these requirements are legally codified in some countries, no such arrangements are in place in jurisdictions where psychedelic trials have been carried out.

The experiences of my interviewees suggest that individuals in such trials can go on to take on risks associated with further psilocybin use, as well as taking on additional expenses in psychotherapy, or suffering for their inability to do so. Whilst acknowledging the limits to the generalisability of the case study methodology adopted in this thesis, I submit that the experiences of my participants highlight ethically salient phenomena that warrant further scrutiny as we consider the future development of P-AT. I thus draw on these experiences to help illustrate distinctive features of P-AT trials that significantly strengthen the case for post-trial provision.

This chapter proceeds as follows: I begin by outlining the established principles and frameworks through which claims of post-trial obligations on the part of researchers are typically understood. I then make the positive case that three characteristics of P-AT generate a stronger case for post-trial researcher obligations than in typical pharmacotherapy trials: the availability of psychedelics through unregulated channels, which creates a non-standard risk profile for participants; the unpredictable and ongoing nature of psychedelic-initiated psychological processes, which do not simply conclude at the arrival of a trial endpoint; and the unusual depth and intensity of therapeutic relationships in P-AT that are intentionally cultivated by researcher-therapists, which I argue generates distinctive moral entanglements between them and participants.

[24] Material from this chapter has been published in *Neuroethics* as 'When the trial ends: The case for post-trial provisions in clinical psychedelic research' (Jacobs, Murphy-Beiner et al., 2024).

These features, I contend, as well as the nature of P-AT as a hybrid pharmacotherapy-psychotherapy modality, necessitate reconceptualising post-trial provision beyond simple post-trial access (PTA) to the investigational drug, which is the predominant focus of post-trial obligation discourse. Instead, I advocate for a broader framework of post-trial access and care (PTA/C), that recognises the relatively complex therapeutic needs of P-AT participants.

Having established the positive case for post-trial obligations in P-AT trials, I examine and respond to several potential objections, before sketching out directions for implementing expanded post-trial support that are not only to the benefit of trial participants, but would also advance the expertise and infrastructure needed for a well-functioning psychedelic healthcare system.

5.2 Justifying Post-Trial Access

The question of what obligations researchers have to trial participants after a clinical study ends has generated substantial scholarly discussion. A systematic review identified 235 distinct arguments for and against ensuring post-trial access (PTA) to study interventions (Sofaer & Strech, 2011). While much of this literature focuses on research conducted in low and middle-income countries, where power differentials heighten risks of exploitation (Schroeder, 2008), the core ethical principles apply more broadly. Rather than attempting an exhaustive review, I outline the main ethical principles and associated arguments through which post-trial obligations are typically justified.

Non-exploitation requires that research participants receive *fair* benefits for assuming the risks and burdens involved in trial participation, and that researchers do not take unfair advantage of participants (Millum, 2011; Wertheimer, 2010); accordingly, considerations of fairness are foundational in concerns about exploitation. This principle holds that researchers have an obligation to provide PTA where the costs participants bear in association with their contribution to the trial are disproportionate to the benefit they receive from trial participation without PTA. Notably, Helen voiced concerns about fairness in our interviews, and her concern about fairness can plausibly be parsed as a concern about exploitation. Consider for example her remark that "it feels kind of unfair that I would be expected to pay quite a lot of money to see a therapist, which I wasn't really warned I might need." One interpretation of this remark is that Helen felt that unfair advantage was taken by her lack of awareness of the need to pay for therapy after the trial. However, while all stakeholders might agree that participants deserve to receive 'fair benefits', determining *what* constitutes a fair benefit for trial participation can be contentious.

Reciprocity suggests that participants, who are indispensable to the research process, deserve to share in its benefits. This goes beyond mere compensation, but rather, "involves a more holistic recognition that research participants represent a sine qua non of clinical research, and that the essential nature of their contribution warrants some special gratitude or recognition, over and above the potential benefits inherent in a given research design" (Lavery, 2008, p.701).

Arguments from *beneficence* contend that researchers have positive obligations to promote participant welfare where possible. Since researchers are often clinicians, some argue this creates duties to provide ongoing beneficial care (Hutt, 1998; Laughton, 2007; Zong, 2008). However, the scope and limits of beneficence obligations in research contexts remain debated. Unlike clinical care, where the primary goal is patient welfare, research aims to generate generalisable knowledge, a goal that can come into conflict with maximising welfare (F. G. Miller & Brody, 2003).

In distinction to beneficence, *non-maleficence* focuses on the obligation not to cause harm, as opposed to the positive obligation to provide benefit. The non-provision of PTA following a trial may can cause harm to participants, whether by the worsening of health status, or by emotional or dignitary harms (Mitchell et al., 2023) such as feelings of grief, frustration and extreme disappointment - affronts to personhood that, while intangible, warrant ethical consideration. The distinction between causing harm and failing to prevent it is philosophically complex, and the boundaries of the obligations imposed by non-maleficence are contested. In the PTA literature, some argue that PTA should be provided because participants should not have worse health after the trial than during (Laughton, 2007; Macklin, 2004), and others because participants should not have worse health after the trial than before it (Sachs, 2010).

Finally, some ground obligations in the unique *fiduciary relationship* between researchers and participants. Richardson and Belsky's (2004) "partial entrustment" model suggests that participants grant researchers limited discretionary authority over aspects of their health during a trial, creating a moral obligation to address needs arising within the scope of that entrustment. Such obligations are limited in scope, shaped by the specific vulnerabilities participants face, the extent to which they are dependent on researchers for their health needs, and the nature of the study itself.

Nonetheless, it remains the case that implementation of PTA in any trial, let alone P-AT, faces significant challenges. Beyond a scarcity of the resources required to implement PTA, fundamental disagreements persist about the extent of obligations imposed by the principles and duties outlined above. Some, for example, maintain that obligations extend only to what was explicitly agreed upon during informed consent. Mandating extensive post-trial provisions could render many valuable trials financially infeasible, potentially delaying important advances in treatment development. Before

turning to these reservations, I will make the case that three distinctive (if not unique) features of P-AT trials make the case for PTA in this context particularly strong.

5.3 Three Distinctive Features of P-AT Trials

Having mapped the ethical terrain in which discourse around post-trial obligations takes place, I now examine how atypical features of P-AT trials interact with these, and other ethical principles, arguing that they generate atypically strong obligations for post-trial provision. The case studies highlight two immediately apparent characteristics that complicate standard approaches to thinking about post-trial obligations: the availability of psychedelics through unregulated channels, as evidenced by participant's post-trial search for further psilocybin; and the ongoing nature of psychedelic-initiated psychological processes, illustrated by Helen's struggles with unresolved therapeutic material. A third feature was discussed by some of my interviewees but not those in the chosen case studies, but nonetheless will be familiar to psychedelic therapists (see, for example, Brennan et al., 2021): the unusual depth, vulnerability and intensity that can characterise psychedelic therapeutic relationships.

5.3.1 Psychedelic access "in the wild"

Perhaps the single most striking theme that emerged across my conversations, including with the case study subjects, is the willingness amongst my participants to initiate further use of psilocybin following their trial participation. All three of the participants presented in the previous chapter made attempts to procure further psilocybin, of whom two were successful. Eleanor in particular found such use valuable, volunteering that "dare I say, the most healing experience has actually been doing it in a group context with [a Dutch retreat provider], that sort of changed everything for me, like glued everything [together]".

There has been little formal or direct reporting of the prevalence of self-initiated post-trial drug use in clinical trials of P-AT, although one early study in treatment-resistant depression found that five of 19 participants (~26%) disclosed post-trial use of psilocybin (Carhart-Harris et al., 2018). In my interviews, 6/10 reported such use, including self-administration, as well as participation in psilocybin retreats both illicitly, and in jurisdictions where this is legally permitted. Two more, including Helen, investigated

the prospect but were ultimately put off by perceived lack of safety. One of these waited a period of several years until another P-AT trial for which they were eligible was launched.

While repeated use of a controlled drug might be characterised as problematic drug-seeking behaviour, this framing is inappropriate in the context of P-AT trials. Classic psychedelics such as psilocybin are not regarded as dependence-forming: they neither induce the same reinforcing behaviours as opiates, stimulants or cannabis in humans, nor is self-administration witnessed in animal models (D. E. Nichols, 2016). Moreover, the texture of the conversations conducted with participants did not indicate addiction or dependence, but rather intentional efforts to sustain or recapture clinical benefit. Asked about his decision to self-medicate at regular intervals following study participation, Aaron spoke with conviction that "no way I was going to let that [i.e., relapse] happen."

Access to experimental treatments after trial completion typically depends entirely on the trial sponsor, whether through enrolment in further trials or formal compassionate use programs (J. E. Miller et al., 2017). This creates a binary situation: participants either receive the drug through official channels, with the associated sponsor oversight and medical supervision, or they cannot access it at all. P-AT trials present a fundamentally different scenario because psilocybin, unlike most investigational drugs, can be obtained through other means. As seen in Aaron's case, participants who experienced benefits during the trial may pursue these alternative routes despite their associated risks. This availability outside official channels creates distinct challenges for both researchers and participants that are rarely encountered in typical clinical trials.

For P-AT trial participants seeking further psilocybin experiences, three main routes present themselves. Each is associated with nontrivial legal and/or safety risks (Jacobs, Murphy-Beiner, et al., 2024), and it is for this reason that trial researchers do not condone their exploration (Watts et al., 2017, p.553). The first, procurement via the black market, exposes participants to harm from adulterated or mis-sold products. While self-cultivation can minimise these risks, the legal and downstream social risks associated with possessing controlled substances remain, including the loss of employment and educational opportunities, and the impact of custody and family relations. Regardless of the route of procurement, self-administering psilocybin outside of the supportive context of P-AT, inclusive of pre-

and after-care, known dosing, and medical support, is associated with a greater risk of adverse events (Bouso et al., 2022; Schlag et al., 2022)[25].

The second pathway, engaging an underground therapist, may reduce some safety risks around drug quality but introduces new concerns. The illegality of the practice means that it is inherently risky due to the lack of effective regulatory oversight: although there are undoubtedly some knowledgeable therapists who take seriously the practical and ethical challenges associated with P-AT (Brennan et al., 2021), it is not easy for anyone - let alone vulnerable or desperate patients - to discern skilled and professional practitioners from those who are well-intentioned but inadequately trained, or otherwise bad actors[26].

The third route, undertaken by Eleanor, involves international travel to take psilocybin legally within a retreat setting at a personal cost of thousands (Kamin, 2021), excluding travel costs. The psychedelic retreat industry is burgeoning, although, with the exception of 'supported adult use' legislation in Colorado and Oregon, it exists largely outside of regulatory oversight. Many retreats draw attention to the results of early phase clinical trials of P-AT, implicitly or explicitly extrapolating those results to what could be expected by prospective clients (Rucker & Young, 2021). With no effective regulation of these sites, their practices or practitioners, the 'psychedelic tourism' industry offers none of the safeguards afforded by a licensed clinical trial. Growing reports of sexual abuse by shamans and guides in retreat settings (Peluso et al., 2020) may not filter down to prospective clients, further aggravating the risk profile of such ventures.

The distribution of these risks falls disproportionately on already disadvantaged groups. While wealthy participants can access supervised sessions abroad, those with limited means face starker choices between accepting a return of debilitating symptoms or risking procurement through illegal channels. As in many areas of drug policy (Earp et al., 2021), racial disparities in enforcement mean that participants of colour face heightened legal risks should they attempt to secure psilocybin through illegal means. Even among those able to travel internationally, geographic distance from jurisdictions permitting psilocybin use creates additional barriers.

[25] Notably, the pharmacotherapy-psychotherapy hybrid model of P-AT, and the role of extrapharmacological factors on outcomes, provide ambiguity as to whether individual self-medication with psilocybin could be adequately described as PTA; I turn to the significance of these considerations in sections below.

[26] One survey of underground psychedelic practitioners working therapeutically found that a plurality had no credential related to counselling or therapy, while a substantial minority did not routinely screen prospective clients for physical or psychiatric contraindications (Glynos et al., 2024).

Unlike typical trials in which PTA depends solely on sponsor provision, P-AT trials create a situation where participants may face serious safety and legal risks in pursuing treatment they reasonably believe will be effective. The ethical implications of this scenario for researcher obligations are examined more thoroughly in §5.4.1 below.

5.3.2 Therapeutic process & integration

Standard frameworks for post-trial obligations focus on continued access to investigational drugs. However, the experiences of P-AT participants suggest that drug access alone may be insufficient in this context. A repeated theme across my conversations with participants was the use of privately funded psychological support to help integrate the trial psychedelic experience. Perhaps as a result of being able to capitalise on the increased psychological flexibility and new perspectives following his psilocybin experience, Aaron reported that the therapy he undertook in the six months following the trial was more valuable than nearly a decade of earlier psychotherapeutic work. In contrast, Helen, who was provided with a list of private integration therapists that she could not afford, was left feeling "ripped open, left with all the mess and having to deal with it on my own."

This striking difference in outcomes reflects a fundamental feature of psychedelic treatments: unlike typical pharmacotherapies, the effects of which cease with discontinuation, P-AT is a hybrid pharmacotherapy-psychotherapy intervention. By design, treatment catalyses psychological dynamics that persist long after the drug's metabolism and excretion. These processes, sometimes referred to as the 'unfolding process' (Gorman et al., 2021; Welwood, 1982), cannot simply be opted out of once initiated. In some instances, they can create ongoing therapeutic needs that extend beyond the question of drug access alone. As evident in Helen's case, powerful symbolic experiences —such as her vision of her own funeral— may demand ongoing therapeutic support to process meaningfully.

Although post-psychedelic integration —the process of making meaning from and incorporating insights from psychedelic experiences into daily life— remains conceptually undertheorised (Bathje et al., 2022; Thal et al., 2024), it is widely acknowledged to be crucial to therapeutic outcomes (Gorman et al., 2021; Watts and Luoma, 2020). It is also consistently recognised as beneficial by trial participants (Breeksema et al., 2020) and associated with improved clinical outcomes (Amada & Shane, 2022; St. Arnaud & Sharpe, 2023).

While the offered provision may be enough for some, perhaps most participants, Helen is not alone in finding the protocol-defined support insufficient (see, e.g., Watts et al., 2017, p.557; Anderson et al., 2020, p.8; Breeksema et al., 2022, *passim*; Breeksema et al., 2024). That some P-AT participants seek out further support after the trial is an acknowledged phenomenon (Noorani, 2019; Schwarz-Plaschg, 2022), but, as with rates of self-initiated psilocybin use, data on this support-seeking remains limited. In two trials of psilocybin P-AT for depressive disorders that report this data (Carhart-Harris et al., 2018; Gukasyan et al., 2022), participants self-initiated further psychotherapy at rates of 33% by 4 weeks, and 26% by 3 months after treatment, respectively.

The reality of this need among some trial participants is further evidenced by how psychedelic researcher-therapists have responded: a number have established low-cost integration groups independent from their trials, which regularly attract returning trial participants (Bird et al., 2024). However, even these support options may be inaccessible to some participants. In Helen's case, while such a group existed, the considerable distance and lack of affordable transport made attendance impractical.

The unpredictable nature of psychedelic experiences poses particular challenges for trial design. Unlike manual-based psychotherapeutic interventions where the therapist and participant have more control over the therapeutic process, the content of psychedelic experiences is largely unpredictable. Participants may encounter deeply challenging psychological material, transpersonal experiences, or previously unconscious content that requires substantial unpacking and processing. While the protocol-defined number of integration sessions may suffice for some participants, others require more extensive support to reach psychological stability. The case of Helen, though concerning, cannot speak to how much integration support a trial *should* provide (see §3.2.2). Typically, the amount provided is between two and six hours. The limited provision of integration therapy in trials is driven at least in part by its expense, which has health-economic implications for P-AT's cost and accessibility after licensing. In Noorani's words, "the time commonly allocated to integration in clinical trials is costly and, without a fuller account of when and how it is done well, is liable to be attenuated and/or automated in for-profit contexts" (2019, p.36).

Researcher-therapists have a clear duty of care during the acute vulnerability of drug sessions. But increased vulnerability following psychedelic use can, in some cases, extend much longer. *Prima facie*, there is a corresponding duty of support in these instances. While determining precise temporal boundaries for this duty presents challenges, I claim that trial teams ought at minimum to ensure that

psychological processes initiated during the trial reach an appropriate point of resolution. Such an obligation is best understood as a deriving from the duty of non-maleficence, which can be most clearly recognised in cases like Helen's. This creates an inherent tension between therapeutic needs and protocol constraints - between researchers' responsibilities to participants in their care and the standardisation that scientifically meaningful RCTs demand. This tension is particularly acute given that psychedelic integration remains conceptually undertheorised, making any definitive account of necessary integration support challenging. Individual differences in participant needs further complicate standardisation efforts. However, as Helen's case demonstrates, ending support prematurely can leave participants struggling with psychological material they cannot process alone. As I discuss in §5.5, these competing demands between therapeutic flexibility and scientific rigour need not be viewed as an either-or proposition, but can potentially be transcended through thoughtful trial design.

The typical P-AT practice of referring participants back to existing mental healthcare support following trial completion proves particularly inadequate in this context. In many healthcare systems, including the UK's NHS, demand for mental health services far outstrips supply (Cummins, 2018; Docherty & Thornicroft, 2015) . Moreover, the uncommonness and novelty of challenges that can arise following psychedelic experiences mean that even where mental health support is available, practitioners may lack the specialist knowledge needed to support integration effectively. As Helen's father noted regarding their attempts to secure help: "they did raise it with the person who was our contact. Didn't get much help back from them... I sort of felt [the trial team] were very sympathetic, but there wasn't any sort of help from them."

These features of P-AT —the initiation of ongoing psychological processes and the inadequacy of standard mental healthcare referrals for addressing them— reveal a certain myopia in conceptualising post-trial obligations in terms of extended drug access. The distinctive therapeutic needs of some P-AT participants, combined with the limited availability of qualified integration support outside the trial context, create specific obligations for research teams that extend beyond simple provision of the experimental intervention. While the precise boundaries of these obligations require careful consideration, at minimum, trial teams ought to ensure that psychological processes initiated during the trial reach an appropriate point of resolution.

5.3.3 Depth of therapeutic relationship

Although not raised by participants in the case studies presented above, a third distinctive feature of P-AT trials emerges from consideration of the unusual depth and power of the relationship between

researcher-therapists and participants (Jacobs, Murphy-Beiner, et al., 2024). As explored in Chapter 2, P-AT generates more intense transferential dynamics than typical psychotherapeutic relationships, with patients frequently feeling particularly emotionally connected to their therapists (Brennan et al., 2021; Palitsky et al., 2025). Patients often report feeling deeply bonded to their guides, describing shared experiences of unusual intensity and significance. These heightened dynamics shape moral obligations in ways that conventional research ethics frameworks may not fully capture.

The relational context of psychedelic administration, as a component of set and setting, is understood to be particularly significant (Nayak & Johnson, 2021; Brennan et al., 2021). Feelings of *communitas* - experiences of intense togetherness and shared humanity - during group psychedelic sessions are predictive of reductions in depressive and anxiety symptoms, as well as improvements in wellbeing (Kettner et al., 2021). As with other psychotherapies, the quality of the therapeutic relationship is predictive of clinical outcomes in P-AT (Levin et al., 2024; Murphy et al., 2022). The nature of this relationship has several distinctive characteristics. Significant attention must be paid to developing rapport and trust with participants during screening and preparation sessions, as the competent therapeutic handling and containment of potentially powerful and emotionally challenging experiences during acute drug effects is seen as critical to both psychological safety and therapeutic success (Johnson et al., 2008; Phelps, 2017; Phelps & Henry, 2021). Dosing sessions typically last eight hours, during which participants experience extremely vulnerable states. These sessions can be among the most meaningful experiences of participants' lives (Griffiths et al., 2006; 2016). Such conditions are liable to naturally generate bonds of unusual intensity between participants and therapists. A qualitative study of psilocybin for depression found that "after the dose, many reported feeling bonded to their guides, saying they had been through something substantial together" (Watts et al., 2017, p.557).

The depth of this relationship is not incidental to the research process but is actively cultivated as an essential component of the treatment. Researcher-therapists consciously seek out and cultivate these deep connections because the safe and effective administration of P-AT is understood to be dependent on rapport and therapeutic alliance. This instrumental fostering of meaningful emotional bonds as a prerequisite for treatment delivery has particular ethical implications when viewed through Richardson and Belsky's (2004) ‘partial-entrustment’ model. Their framework suggests that researcher obligations to provide ancillary care vary based on several key factors: the depth and intensity of researcher-participant relationships, the value of potential ancillary care to participants, and participants' dependence on researchers for that care (Richardson, 2013, ch.2).

By these criteria, P-AT trial participants present an especially strong case for ancillary care obligations. The deliberately cultivated depth of the therapeutic relationship, combined with the specialised nature of psychedelic integration support, creates what Richardson (2013) terms a distinctive "moral entanglement." For treatment-resistant participants who have found success with P-AT, additional drug-assisted sessions or integration support represent highly valuable care that is typically unavailable outside the research context. This combination of deep relational bonds - fostered as essential to the research process itself - and researchers' unique position to provide needed care, strengthens the fiduciary relationship between researcher-therapists and participants, generating particularly strong obligations for post-trial support.

The current practice of abruptly ending these carefully cultivated therapeutic relationships at trial completion, while referring participants back to standard mental healthcare that may be either unavailable or ill-equipped to handle psychedelic integration, appears difficult to justify. In response, researcher-therapists at some centres have responded by establishing independent, low-cost integration groups where trial participants can continue to receive support. While admirable, this ad hoc solution places the burden of meeting post-trial obligations primarily on researcher-therapists who are already engaged in emotionally demanding work. Given that these deep therapeutic relationships are necessary for proper trial implementation, the obligation to ensure adequate post-trial support should extend beyond individual researcher-therapists to encompass all stakeholders in the research process.

5.4 Objections and Responses

Having laid out the case for P-AT trials being a particularly strong candidate for PTA, I now address four challenges to this case, which speak both to the points I raise above, and more generalised reservations about PTA.

5.4.1 Researchers are not responsible for participants' post-trial choices

A reasonable response to the argument that the illicit and unsafe availability of psilocybin places demands on the research team runs as so: former trial participants who choose to undertake risky activities following their trial experience do so freely and voluntarily. There is no obligation for sponsors or researchers to protect participants from their autonomous choices outside of the trial context. As such, P-AT trial participants engaging in risky behaviour to procure further psychedelic treatment should not impose any additional obligations on trial sponsors or researchers. That some participants may choose risky behaviours, and that some may come to harm having done so, is not only

an inevitable part of honouring autonomy, but expecting researchers to intercede in this is an overreach of their duty of nonmaleficence: i.e., researchers should not harm participants, but they are not obligated to prevent harm befalling them.

Such a position flows naturally from the archetypal conception of the research participant as an autonomous, competent adult who, in agreeing to participate in research enters into a contractual (or quasi-contractual) agreement, on equal terms with the research team, which is "grounded on the obligation to fulfil the promises, express and implied, that researchers and participants freely and reciprocally assume" (Lawson, 1995, p.213). So framed, there can be no post-trial *obligations* on the part of researchers towards participants beyond what is expressly or implicitly agreed upon. As such, researchers are not obligated to provide PTA/C, because (i) participants voluntarily agreed to participate in the knowledge that support would not be provided, and (ii) as there was no agreement about provision of care outside of the trial context, it is not the responsibility of researchers to protect individuals from their own choices outside of the trial.

There are several shortcomings with this position. First, as discussions with Helen and her father make evident, there is reason to worry that at least some participants were not wholly clear about the support they might get from the trial team following participation. This raises doubt about the extent to which participation takes place from a position of informed consent, which is the principal legitimising process for agreements about participation in clinical trials.

Second, Lawson's conception of researcher-participant relations as defined wholly by voluntary, sterile and detached contract is contested. Medical researchers are widely recognised to have obligations around incidental findings significant to medical decision-making (Koplin et al., 2020), with professional bodies maintaining clear policies on managing these findings (Medical Research Council and Wellcome Trust, 2014; The Royal College of Radiologists, 2011). The partial-entrustment model (Richardson and Belsky, 2004), as well as other frameworks for considering PTA (Ashcroft, 2005; Lavery, 2008), acknowledge that the weight of obligation for providing additional support is influenced by contextual factors. It is telling, too, that some psychedelic research teams themselves will provide integration groups *pro-bono* (and unsupported by trial funders), suggesting that those closest to P-AT recognise that such provision of post-trial support is an appropriate component of undertaking this research.

Finally, researchers have a duty to minimise harms that participants are exposed to. While this duty is not limitless, the risks associated with post-trial psilocybin access warrant particular consideration. Trial

participants who smoke tobacco or choose not to wear seatbelts while under the aegis of the trial team are indeed taking on risks, but it is hard to motivate why researchers should override (sober) participants' autonomy in these regards. The key distinction is that attempts to secure more psilocybin treatment are causally related to trial participation in a way that these other risks are not.

The causal relationship between trial participation and subsequent treatment-seeking behaviour is more complex than cases of direct causation, such as when a trial drug creates physiological dependence that drives participants to seek illicit supplies. Trial participants who seek out psilocybin are not acting from addiction or compulsion - indeed, this is not analogous to cases like deep brain stimulation patients developing pathological gambling behaviours (Lu et al., 2006). Rather, as seen in Helen's careful weighing of illegal options, and Aaron's considered decision to self-medicate, these are the deliberate choices of competent adults.

Nonetheless, I contend that these autonomous choices are still relevant to researcher responsibilities. Through trial participation, individuals can gain definitive, personal knowledge that P-AT can provide meaningful relief from significant suffering. For treatment-resistant participants like Aaron, who had exhausted conventional options and by his own description "was getting desperate" before joining the trial, experiencing "full remission" from his depression for the first time in years, can reveal a new potential reality that cannot easily be ignored.

While the causal chain from trial participation to illicit treatment-seeking may be indirect, it is nonetheless foreseeable. Trial participation fundamentally transforms participants' knowledge about effective treatment options, creating a new epistemic context that can make pursuing risky alternatives rational from their perspective. Where no PTA is made available, but psilocybin is accessible elsewhere, at least some participants will predictably seek it out. [27]

This creates a particular form of moral hazard. By virtue of participating in a P-AT trial, participants can come to know that effective treatment is available to them, fundamentally altering their understanding of treatment options. This epistemic transformation, combined with the lack of legitimate

[27] Another way to think about this is to imagine yourself as a member of an IRB reviewer considering an application for a clinical study: what limited evidence is available suggests that participants in previous studies of a proposed intervention go on to engage in criminal or otherwise risky activity at a rate far higher than the relevant population, in a way that is at least indirectly caused by that intervention. It seems unlikely that such a study would be approved without appropriate accommodations to limit this risk. Extending this line of thought, if it were found that psilocybin administration *did* increase the prospect that a patient takes up smoking (*n.b.* in fact the opposite may be true, see Johnson et al., 2017), or to ride without seatbelts, these too would require taking seriously and accommodating: in these cases not via PTA but perhaps by psychoeducation, the provision of nicotine replacement therapies, or gentle reminders at close of session about the importance of seatbelts.

access pathways that researchers are aware of during trial planning and execution, creates conditions where pursuing risky alternatives becomes rational from participants' perspective. Executing a P-AT trial, and initiating this epistemic transformation in some participants, raises issues of exploitation: allowing researchers to benefit from participants' contributions while leaving participants in an invidious position, having to choose between returning to their previous condition or pursuing risky alternatives. So framed, the benefits of P-AT trial participation become more ambiguous, weakening the strength of the argument that PTA need not be provided because the benefits of trial participation suffice.

5.4.2 Proposing PTA on the basis of a single trial exceeds epistemic warrant of that trial

If the case for PTA in P-AT trials is framed as at least partially grounded by beneficence (roughly, trial teams are uniquely placed to provide the good of continued health to participants), it can be challenged by arguing from epistemic humility. In the case of treatment-resistant participants, the stakes of both action and inaction are high. But the *costs* of action are also high, and where a trial of, e.g., one psychedelic session supplemented by preparation and integration generates a substantial, if not enduring clinical response, this is not sufficient evidence to support further treatment. It is widely acknowledged that it is as yet uncertain what the best practice is following a self-contained P-AT intervention, and there is no systematic data on either the benefits or risks of repeated drug sessions in clinical contexts. As such, PTA should not be considered for P-AT trials until better long-term data is generated.

Granted, the data from a single trial - especially an early phase clinical trial - constitutes minimal evidence in comparison to the extensive testing required for drug licensing, which demands sufficiently positive signals regarding safety and efficacy from a substantial number of participants. Crucially, this objection overlooks an important distinction. The evidence threshold needed for establishing clinical practice standards differs significantly from what's required to determine an individual patient's medical interests. Rather than using trial data to justify broad provision of the intervention, the argument is for PTA specifically for those participants who have demonstrated a clear therapeutic response - a more limited claim that requires only evidence of individual benefit.

Where a licensed drug, when prescribed to a patient, elicits no therapeutic response in that patient, a clinician would not persevere in its continued prescription: the lack of therapeutic response in a given patient is more relevant for the ongoing treatment of that particular individual than the evidence from

phase 3 clinical trials that the average treatment effect across a large group of patients is positive. Clinicians make treatment responses on the basis of whether a treatment's benefits outweigh its disadvantages *as manifested in a particular patient*, and the positive effect of an investigational intervention on an otherwise unresponsive patient is a highly salient data point when considering their future care.

Moreover, while extensive trial data concerning risks of further psychedelic-drug administrations remains limited, emerging clinical evidence aligns with other sources in suggesting safety of repeated administration. The first controlled trial of repeated psilocybin dosing (n=29) found that additional sessions were associated with further symptom improvements without increasing adverse events (Rosenblat et al., 2024). This finding is consistent with broader epidemiological evidence: large-scale population surveys report no increase in adverse outcomes among psychedelic users who report multiple lifetime uses (P. S. Hendricks et al., 2015; Krebs & Johansen, 2013). Communities that engage in regular ritualistic consumption of psychedelics present with health abnormalities no higher than controls (Bouso et al., 2012; Halpern et al., 2008)[28]. Considering clinical populations, in jurisdictions that permit administration of psychedelics according to case-by-case licensing, repeated sessions of P-AT produce positive clinical effects without serious adverse events (Oehen & Gasser, 2022).

Objecting to PTA on the grounds of epistemic uncertainty is thus not convincing. While the evidence from a single trial may be insufficient to justify broad clinical implementation, it can be adequate to support continued provision to individual participants who have demonstrated clear benefit.

5.4.3 PTA inappropriately blurs research/healthcare distinction

A common objection to PTA rests on the well-established distinction between research and healthcare (Litton, 2006). *Per* Miller (2006, p.11), "Medical care has a personalized focus. It is directed to helping a particular person in need of expert medical attention. Clinical research essentially lacks this purpose of personalized help for particular individuals… The distinctive purpose of clinical research [is] to

[28] These findings about the consequences of repeated psychedelic use in non-clinical contexts is, however, indicative, and should not overshadow the specific vulnerabilities of trial participants, who by virtue of their participation are known to have serious mental health conditions. The structured support and medical oversight in these trials serves a protective function that is especially important for clinical populations (Johnson et al., 2008; Schlag et al., 2022). While some individuals may navigate unregulated access successfully, directing trial participants (especially those with treatment-resistant or otherwise clinically complex presentations) towards these channels is fraught with concerns.

develop generalizable knowledge." By requiring the provision of PTA/C to P-AT trial participants, it might thus be argued that I am making an inappropriate demand of researchers. At the sharp end of this objection is the reality that some major funders of clinical research, including the US National Institutes of Health, are not authorised to fund normal healthcare services if requested by grantees (Aldinger et al., 2017).

However, this objection from the research/healthcare distinction assumes an existing healthcare system capable of meeting participants' needs outside of the trial. But at present, neither post-trial access to psilocybin, nor the provision of post-trial care (i.e., psychedelic integration therapy), straightforwardly constitute 'normal healthcare' - they will be components of future psychedelic healthcare systems but are not yet available. The infrastructure and expertise needed to provide this care exists effectively only within psychedelic research centres.

This unique positioning of research centres as potential providers of specialised care is not coincidental: it reflects their direct role in initiating participants' need for ongoing support, where that need arises. When administering psychedelics in a clinical trial context, researchers knowingly catalyse psychological processes that can extend far beyond the drug's acute effects. These processes - including confronting previously unconscious material, processing challenging symbolic experiences, or reassessing fundamental aspects of one's life, cannot simply be switched off at trial completion. The principle of nonmaleficence takes on particular force here. Having deliberately initiated these potentially destabilising processes, researchers bear some responsibility for supporting trial participants in navigating them, preventing harms that may result from prematurely withdrawing support. While practical constraints may limit the extent of this responsibility, I suggest that, in meeting this responsibility, researchers may also uncover valuable opportunities that would be in their interest to pursue (see §5.5 below).

The partial-entrustment model introduced above provides a more nuanced framework for understanding researcher obligations that moves beyond the simple dichotomy between contractual research relationships and full clinical duties. According to this model, when participants entrust aspects of their health to researchers, this creates corresponding obligations proportional to a range of contextual factors[29]. The most salient of these factors when considering P-AT are the extent of the vulnerability

[29] In full, these include the scope of entrustment (determined by permissions granted during informed consent); participant vulnerability and dependency on researchers; the potential magnitude of benefit from care provision; the uniqueness of researchers' capacity to provide care; gratitude owed to participants for their contribution; practical resource constraints; and the evolution of entrustment relationships over time through ongoing interaction (Richardson, 2013).

participants must enter into, depth of the relationship between researchers and participants and participants' recourse to alternative healthcare providers. In P-AT trials, all these factors point towards significant obligations: participants entrust themselves to researchers in a state of extreme vulnerability, the therapeutic relationships are uncommonly deep, and participants have a lack of access to alternative qualified providers of specialised care.

Even under the partial entrustment model, which is more expansive in its view of post-trial obligations than when research is viewed as a contractual, transactional exchange, obligations remain bounded. They are neither unlimited nor equivalent to full clinical duties, but are rather contextual and proportional to features of P-AT. Although the model focuses on the contextual features of a given *trial*, its logic can be extended to considering weight of obligations at a per-participant level, according to individual circumstances. Treatment resistance affects the adequacy of referrals to standard care. Where participants neither receive benefits from P-AT, nor experience the kinds of psychological challenges as a result of participation like Helen did, have weaker claims to post-trial provisions.

5.4.4 PTA/C makes psychedelic research prohibitively expensive

The resource implications of my call for expanded post-trial support in P-AT trials is liable to be significant, and is deserving of some discussion. Later (§5.5), I speak to the practical dimensions of these costs. For now, I will attend to the ethical dimensions of the additional resource demands, which might fruitfully be framed as the conflict between the *specific* obligations of beneficence that researchers may have towards their participants, and the more *general* obligations of beneficence they have towards the wider patient population[30] In a context of resource scarcity, making trials more expensive by providing support to participants beyond that which is typically given, could potentially limit the number of trials that can be conducted, impeding scientific progress and limiting the number of people (both participants and the public) who can access a potentially beneficial intervention.

This objection has particular force in the context of P-AT, where: trials are already resource-intensive; the field is at a critical stage where generating evidence in more trials could unlock access to many; and the potential benefit to future patients is substantial given the treatment-resistant nature of conditions being studied.

[30] With thanks to Jonathan Pugh for suggesting this framing.

It is true that the addition of extra expenses to P-AT trials may slow the development and licensing of this treatment, with consequent losses for the wider patient population. But the scope of research ethics extends well beyond choosing the path that maximises aggregate benefit. Post-trial provisions are not the only costly element of trial design that incurs costs and impedes progress without directly contributing to scientific advance. All trials involve elements that reduce efficiency in order to safeguard or promote other moral values: welfare monitoring of participants, fair recruitment of participants (rather than recruiting by, say, vulnerability), and the institutional apparatus of IRBs all act as impediments to running clinical trials. We accept these 'inefficiencies' out of a recognition that other ethical obligations (e.g., justice and non-exploitation) to treat participants ethically provide independent moral reasons for action that exist separately from consequentialist calculations about optimal resource allocation.

The trade-off between the speed of scientific progress and the robustly ethical treatment of participants is not a problem that was definitively 'solved' by the established status quo safeguards. My argument in favour of introducing post-trial provisions is implicitly an argument that the current trade-off may not be the optimal one. While these case studies alone cannot definitively establish the need to fundamentally alter the balance between scientific progress and participant care, they raise important questions about whether the current status quo appropriately addresses the unique features of P-AT trials. The experiences of participants like Helen and Aaron suggest we should carefully examine our assumptions about what constitutes adequate post-trial support in this novel therapeutic context.

Sceptics of PTA/C are rightly worried that its establishment could lead to runaway costs. Of course, the responsibilities of sponsors and researchers cannot be absolute, and any feasible implementation of PTA/C must recognise limits to those responsibilities. Although principled limits to this provision specifically for P-AT should be established, for now I point to Zong (2008, p.190) whose suggested baseline criteria to delimit provision of PTA/C bear a striking resemblance to those that can be derived from the partial-entrustment model.

- Only those who make a positive response to the intervention during the trial should be considered
- After the research is over, discontinuation of the intervention may cause harm or losses for trial subjects
- Intervention is better than or at least equal to those that are available through local regular health system

- There are no alternative ways to access the beneficial experimental intervention beyond the study period
- Participants agree to receive the intervention after they fully understand potential long-term harm and benefits of it. For this purpose, an additional consent form is necessary

The most helpful question is not whether post-trial provisions will increase expenses - they will - but whether there exists an approach to PTA/C that allows the competing demands of scientific progress and the protection of participant interests to move beyond the zero-sum game that the above framing implies.

5.5 Developing Infrastructure for Psychedelic Healthcare

Rather than viewing PTA/C provision purely as an ethical burden that trades off against scientific progress, I propose reconceptualising it as an integral site of psychedelic research - one that can simultaneously meet obligations to participants while developing crucial knowledge and infrastructure for the field's development.

Helen's case, while atypical among my conversations, represents the starkest example of a participant being failed by the trial team. Considering the role of socioeconomic status in psychopathology (Freeman et al., 2016; Peverill et al., 2021), any P-AT research study that seeks results that are generalisable to the broader population will inevitably intake participants that do not have the means to privately fund needed integration support beyond a protocol-defined limit. Thus, the obligation to avoid exploitation, an ethical grounds to provide PTA/C more typically invoked for research in low and middle income countries, is salient here. At the minimum, this suggests that research teams have a responsibility to provide additional integration where indicated, whether directly, or indirectly by subsidising a private practitioner. This option however misses a substantial, if ambitious, prospect for benefit not only to individual trial participants, but to future patients as well, dissolving the tension between *specific* and *general* duties of beneficence (5.4.4).

The integration of P-AT into mainstream healthcare will begin with the licensing of the first psychedelic for clinical use, but this remains just one step in a larger journey. Wide-scale accessibility, either through public health care networks or via insurers, will also depend on the establishment of health economic data relating to pricing and cost-effectiveness (Marseille et al., 2023). But best practice guidelines, as regards both timing and frequency of drug sessions, and the implementation of integration support, will

also need to be established via an evidence base that will take years to develop. The technical and physical infrastructure needed for a well-functioning psychedelic healthcare system will require the growth of knowledge and practical systems in just the areas in which I advocate for the expansion of post-trial provision. Incorporating post-trial provision into current, pre-licensing trials will thereby meet the needs not only of former trial participants, but also the incipient psychedelic healthcare system's need to understand best practice for treatment and aftercare.

This can be done by conceiving of PTA/C not as an expensive burden to be carried by research sponsors, but as an integral site of psychedelic research, and an appropriate destination for research funding. By building these provisions into the clinical trial framework, including appropriate monitoring and reporting of practice and outcomes, understanding the longer-term sequelae and support needs of future patients can begin now. Data generated here will ultimately pay dividends to the sponsors of psychedelic research by providing meaningful first signals about how best to optimise the longevity of positive outcomes, and minimise the risks of negative outcomes. As the least understood component of P-AT (Cheung et al., 2024; Greń et al., 2024), research into integration is likely to yield the greatest benefits. Moreover, as a costly component of P-AT, investigation of ways to reduce the resource-intensiveness of integration - for example by determining how much of the process can be peer-led or co-facilitated - may well provide cost-effectiveness savings that makes P-AT more widely accessible.

Rather than maintaining rigid distinctions between research and healthcare delivery, the limited and carefully managed integration of these functions by expanding PTA/C in P-AT trials has potential to better serve the field's development during the transition to mainstream healthcare. In the larger part of this chapter I have made an ethical case for the provision of PTA/C, but it can also be a natural site for other crucial areas of infrastructure development: guidelines for spacing and sequencing of additional sessions beyond the trial protocol, models for sustainable care delivery, the establishment of quality metrics for psychedelic healthcare, and evidence-based standards of care.

The structure and funding of such post-trial research requires careful consideration. Some elements of post-trial care, such as flexible numbers of integration sessions or additional drug sessions after primary endpoints, more naturally fit within trial protocols. For instance, Rosenblat et al. (2024) demonstrate how protocols can incorporate additional drug sessions after primary endpoints, while maintaining scientific rigour. That study, which provided second and third psilocybin sessions if and when participants relapsed in the 20 weeks following trial initiation, allowed systematic study of repeated dosing while preserving the integrity of core trial outcomes.

However, broader questions about optimal care delivery may require dedicated implementation research. This distinction matters not just administratively but ethically. Trial sponsors' obligations to participants might reasonably include basic post-trial support, while the broader development of sustainable care models, investigation of peer-support systems, and the optimisation of integration approaches could draw on different funding streams, including healthcare delivery research grants or public health funding.

Nonetheless, this practical division should not obscure the underlying ethical imperative: the field as a whole must develop infrastructure to support participants through processes that its trials initiate. Whether through expanded trial protocols, post-trial access and care, or dedicated implementation research, systematic study of post-trial care serves both ethical and scientific goals.

5.6 Implementing PTA/C: Stakeholder Responsibilities and Practical Steps

The most recent iteration of the Declaration of Helsinki (World Medical Association, 2013) calls on research sponsors, host governments, and trial teams to "make provisions for post-trial access for all participants who still need an intervention identified as beneficial during the study." The Declaration itself is silent on how this responsibility should be allotted between stakeholders in practice, and a responsibility that is vague is thereby less likely to be discharged (Millum, 2011). While other frameworks agree on the need for post-trial provisions, they disagree over the strength and nature of the obligation, and which specific stakeholders are required to act (Council for International Organizations of Medical Science, 2016; Iunes et al., 2019; Sofaer et al., 2014). Rather than attempting a generalisable account for determining post-trial responsibilities across all clinical trials, I focus here on specific steps that key stakeholders can take in P-AT trials to minimise risks and optimise care.

5.6.1 Role of national governments

Although operating at a distance from the psychedelic research process, governments can play a significant facilitative role in improving post-trial experiences. In the UK, the Schedule 1, Class A status of psilocybin simultaneously introduces financial and bureaucratic burdens that impede post-trial access, discourages researcher-therapists from offering harm-reduction advice, and imposes criminal risks upon participants seeking what may be their only effective treatment option. While removing

criminal penalties for possession would reduce legal risks for former trial participants, it would not address safety risks associated with uncontrolled use. A more targeted approach would be revising psilocybin's schedule downwards to Schedule 2, or creating a bespoke schedule to permit research and post-trial access but not wider prescription. Such a move, which enjoys significant public support in the UK (Jacobs, 2021), would meaningfully reduce costs for trials and post-trial provisions while being achievable via statutory instrument, rather than requiring the significant legislative burden of typical law changes.

5.6.2 Role of researcher-therapists

Researcher-therapists, who develop direct connections with trial participants, face competing moral demands when trials end. These include balancing clinical judgment about participants' ongoing therapeutic needs against protocol constraints, managing trial endings that are premature for some participants, and navigating requests for further treatment. Perhaps most challenging is how to handle information-seeking about alternative treatment routes. Even when further drug treatment appears clinically indicated, legal and liability concerns can lead practitioners to discourage or shut down such conversations. However, this approach is structurally equivalent to abstinence-only sex education - we know some participants will seek treatment elsewhere regardless of researcher guidance.

These challenges can be addressed at two levels: direct participant support and structural protocol modifications.

For direct participant support, researcher-therapists could:

1. Develop standardised procedures for psychoeducation for participants who predictably will self-initiate further treatment about drug checking, dosage, set and setting, and safety priorities (Berkeley Center for the Science of Psychedelics, 2024; Palmer & Maynard, 2022). Pilecki et al. (2021) offer guidelines for providing preparation and integration information within a harm-reduction framework without being complicit in delivering P-AT outside of the legal context of the trial. While this doesn't resolve the risks associated with unregulated access, it reduces them relative to leaving participants to pursue this course of action completely independently.

At the protocol level, researcher-therapists could advocate for:

2. Incorporating additional psychedelic sessions where clinically indicated. While additional intervention could be deferred until after primary trial endpoints (typically symptom reduction

at 3-6 months), protocols can be designed to include optional additional sessions thereafter. This approach serves multiple purposes: it provides participants clarity about potential future treatment options, potentially reducing anxiety about post-trial access; it allows for systematic collection of valuable data about the effects of repeated dosing; and it maintains scientific integrity by clearly separating primary trial outcomes from longer-term treatment effects. This systematic approach to providing additional sessions, rather than leaving participants to seek treatment elsewhere, also creates opportunities to better understand optimal spacing between sessions and factors predicting positive outcomes from repeated treatment.

3. Building flexibility into protocols regarding integration session numbers. While P-AT trials understandably seek standardisation for licensing purposes, this can be counterproductive for individual therapeutic needs. Clinical trials for surgical interventions would not be undertaken with a time limit of six hours on the operating table, with surgeons downing scalpels at this point regardless of the stage of the surgical process. Just as surgery patients need to be stitched back up, the psychological operations undertaken during P-AT can leave open wounds which must be safely closed, and this process will not take the same time in each instance. This analogy is imperfect but used advisedly: Helen describes being left "ripped open… with all the mess and having to deal with it on my own." Non-psychedelic psychosocial and behavioural intervention trials, even for manualised treatments, often specify a therapy 'dose' range out of recognition that psychotherapeutic processes are inherently individual in nature.

5.6.3 Role of research sponsors

Research sponsors, upon whom much of the implementation costs will fall, have a unique opportunity to view post-trial care not merely as an ethical requirement but as a strategic investment in field development. By focusing beyond simply meeting clinical endpoints, providing post-trial care can support development of the infrastructure necessary for a sustainable psychedelic medicine ecosystem that sponsors will need to profit from their investments. Systematic monitoring of post-trial outcomes can increase understanding of the best, most cost-effective practices for repeated sessions, minimising relapse, and providing appropriate long-term support: factors that single-payer health systems and insurers will want to establish before supporting P-AT.

5.7 Conclusion

This chapter has argued that distinctive features of P-AT trials generate particularly strong obligations for post-trial provision. The availability of psychedelics through unregulated channels creates unique risks for participants who have experienced symptom relief. The unpredictable nature of psychedelic experiences and importance of integration support mean that standardised trial endpoints may not align with therapeutic needs. Perhaps most distinctively, the unusual depth of relationship between researcher-therapists and participants, deliberately cultivated as essential to treatment delivery, generates a distinctive 'moral entanglement' (Richardson, 2013) that can ground obligations for providing additional support (Jacobs, Murphy-Beiner et al., 2024).

These features demand reconceptualising post-trial provision beyond simple drug access to encompass broader therapeutic care. While this expansion faces practical challenges, particularly around resources, viewing post-trial care as an important site of research rather than merely an ethical burden reveals opportunities. Through systematic study of post-trial provision, the field can develop crucial infrastructure for sustainable psychedelic healthcare: evidence-based integration practices, optimal protocols for repeated sessions, and cost-effective delivery models.

The path forward requires coordinated action from multiple stakeholders. Research sponsors, on whom most of the additional burden will fall, can conceive of PTA/C as a strategic investment for the development of the field. Governments can reduce barriers through targeted policy changes. Researcher-therapists can develop standardised approaches to harm reduction and flexible trial designs that accommodate support beyond the fixed limits that define typical P-AT protocols. Research sponsors can view post-trial care as strategic investment in field development. While this represents a shift from current practice, the negative experiences of some trial participants invite us to consider that the status quo may need adjustment. By thoughtfully expanding post-trial provision, stakeholders can better serve both current participants and the future development of psychedelic medicine.

The proposal here is not for unlimited care obligations, but rather for carefully structured support that recognises both the unique features of psychedelic therapy and the practical constraints of research. In doing so, we move toward a model that better reflects the hybrid nature of psychedelic-assisted therapy itself - neither purely pharmacological nor purely psychotherapeutic, but rather an integration of both. By embracing the complexity of P-AT, we can work toward trial designs that better protect participant interests while advancing the development of the field.

The proposal outlined here represents a starting point rather than a definitive solution. Further refinement and development will be necessary as the field evolves, particularly regarding funding mechanisms, implementation protocols, and the appropriate scope of post-trial obligations. Some concrete proposals are already emerging: Evans et al. (2025) advocate for sponsors to explicitly commit 1% of funds toward safety initiatives, drawing parallels to the 3% commitment from the U.S. National Center for Human Genome Research for ethical, legal, and social implications research. Such approaches could provide sustainable resources for post-trial support without imposing prohibitive costs on research.

6. The Matrix: Social Contexts and the Protection-Inclusion Dilemma

6.1 Introduction

This chapter foregrounds the importance of the *matrix*, the social and environmental context from which patients come and to which they return, as a critical yet conspicuously absent factor in contemporary discussions of P-AT. While discussions of extrapharmacological influences typically focus on 'set and setting,' the concept of the matrix emerged in early psychedelic literature (Eisner, 1997)[31] as a third significant factor influencing outcomes following P-AT. Eisner describes the matrix as "that environment from which the subject comes, such as family and living situation; the environment the subject is living in while having sessions" (p.214) and "the environment to which a patient returns after successful therapy - the everyday living space" (p.215).

The importance of the matrix implicitly emerged as a recurring theme across participant experiences, with each case highlighting different aspects. Eleanor's supportive matrix enabled her resilience in the face of external challenges; Aaron's isolated environment created new sources of distress despite symptom improvement; and Helen's well-intentioned but underprepared support system contributed to her difficulties in sustaining therapeutic momentum. As in the other chapters, the three case studies are not offered as definitive empirical evidence for the matrix's importance. Rather, the matrix concept offers a valuable interpretive framework through which to understand participants' varied experiences following P-AT.

Our understanding of psychedelic-induced neural plasticity provides theoretical support for paying attention to the matrix in P-AT. During periods of enhanced plasticity, patients may be particularly sensitive to environmental influences, both positive and negative. This theoretical foundation is strengthened by empirical evidence: survey and interview studies, as well as qualitative reports following clinical P-AT trials, indicate that features of the matrix are often identified as contributing to both positive and negative outcomes. The presence of valued social support following psychedelic use

[31] Eisner's therapeutic practices and residential treatment communities have been subject to significant ethical criticisms and allegations of cult-like practices (Cult Vault, 2023; Davidson, 2017). This thesis engages with the matrix concept on its theoretical merits while acknowledging these serious concerns about its historical implementation.

can help navigate long-term challenges (Robinson et al., 2024), while its absence can lead to feelings of vulnerability, isolation and alienation (Lutkajtis & Evans, 2023; Watts et al., 2017).

As will be explored, taking the matrix seriously leads to cascading salient ethical tensions that require attention. The enhanced neuroplasticity following psychedelic administration creates heightened vulnerability to environmental influences - a vulnerability that researchers or clinicians initiate. This artificial induction of vulnerability might suggest special obligations to protect participants during this sensitive period. However, fulfilling such obligations appears complex: any interventions on a patient's life outside of the clinic must be balanced against respect for their autonomy. Minimising the risks from disadvantageous matrices on environmentally sensitised patients by screening out prospective patients in adverse environments may disproportionately exclude those from less advantageous socio-ecological contexts, raising serious equity concerns. This chapter seeks to resolve this 'protection-inclusion dilemma' (Friesen et al., 2023) by proposing approaches that can support more vulnerable participants while respecting both autonomy and equity considerations.

In this chapter, I draw on interviews with trial participants to examine how different matrices—the environments from which patients come and to which they return—influence post-trial trajectories. After establishing theoretical foundations for understanding matrix effects, I analyse three dimensions of the matrix in P-AT: how matrix quality shapes post-treatment experiences, the dynamic nature of the matrix, which can both shape and be shaped by post-psychedelic experiences, and the matrix's function as a resource for integration. The ethical salience of these dimensions is then made explicit, leading to an ethically informed approach that addresses practical challenges in implementing matrix-informed frameworks, before proposing concrete steps for supporting positive matrices in contemporary P-AT practice.

Before examining how the matrix influences outcomes in P-AT, it is necessary to establish the theoretical foundations that support my call to attend carefully to patients' broader socio-ecological environments.

6.2 Re-situating the Matrix within Contemporary Understanding

6.2.1 Theoretical foundations

The biopsychosocial model of psychopathology (Bolton, 2023; Engel, 1977, 1980) provides an initial frame through which to understand the relevance of matrix effects. This model emphasises that mental

health conditions emerge from and are maintained by the dynamic interaction between biological, psychological, and social factors. The matrix, in this context, encompasses those social and environmental aspects of a patient's life that interact with biological and psychological factors in the genesis, maintenance, and resolution of psychopathology. That social and environmental factors play at least *some* role in mental health is widely accepted, even among those who do not explicitly endorse the biopsychosocial model. This framework, however, with its emphasis on the interconnectedness of various factors involved in mental health supports the idea that the social environment that a P-AT patient comes from and returns to, is not just a backdrop for the intervention, but potentially an active component in the therapeutic process and life course of psychopathology.

Whatever clinical mental health intervention is under discussion, a patient's broader environmental context merits at least some attention: in many instances, after all, it is exactly *that* context within which psychopathology emerged. Accordingly, it can potentially provide information about the genesis and maintenance of pathology, as well as the prospect of salutogenesis. Additionally, typical psychotherapeutic interventions tend to take an hour of a patient's week. The highest intensity interventions may be as much as five hours a week. The impact of the other ~100 weekly waking hours of a patient's life is liable to have *some* effect on the progress of psychopathology. Indeed, the relationship between environment and mental health is well-established, with social support and access to supportive relationships repeatedly associated with better outcomes across a range of mental health conditions (Corrigan & Phelan, 2004; Hallgren et al., 2017; McGaffin et al., 2018).

In examining matrix effects in P-AT specifically, it is necessary to focus not only on Eisner's original articulation of the matrix, principally characterised by the potentialities it can offer following psychedelic use — "a good matrix, like a good group or a good marriage, is a place where the best interests of the separate individuals are served within the creative context of the larger relationship" (p.215). We must also consider, *per* sociologist Logan Neitzke-Spruill (2022), the structural constraints that features of the matrix can impose: "Phenomena such as discrimination, victimization, opportunity for gainful employment, family ties, and social networks all constitute situational vulnerabilities in an individual's matrix" (p.222). Importantly, a matrix need not be considered as uniformly ‘good’ or ‘bad’; a matrix may be a source of strong emotional support but limited material security, or offer stability but resist certain types of change.

The ecobiodevelopmental framework (Shonkoff et al., 2012) extends this understanding by articulating how the interaction of biology, personal experiences, and environmental factors shapes developmental trajectories and health outcomes across the lifespan. This framework identifies how childhood adversity

can disrupt healthy brain development and other physiological systems, creating long-term vulnerabilities to disease and maladaptive behaviour. Crucially for our purposes, it also highlights how protective relationships and supportive environments can buffer against these risks. The framework advocates for integrated approaches that address not only immediate health care needs but also systemic issues like social isolation and structural inequities, emphasising the importance of horizontal integration between health care, social services, and other support systems. This systems-level perspective reinforces the attitude that therapeutic interventions cannot be considered in isolation from the broader context in which they occur: the impact of *any* clinical intervention is necessarily mediated to some extent by the patient's ongoing engagement with their social and physical environment.

The direct evidence base for the relevance of the matrix on outcomes following P-AT is admittedly limited. As one recent rapid scoping review of extrapharmacological factors underlined, "generally, the studies above have suggested, assumed, or tried to assert that environmental sociocultural context can influence psychedelic experiences and outcomes. However, they did not provide empirical controls or rigorous testing of these hypotheses" (Golden et al., 2022). This absence of evidence, however, should not be taken for evidence of absence. Empirically controlling, rigorously testing, or indeed quantifying the influence of the complex, dynamic, and often subjective social and interpersonal dynamics of the matrix is inordinately harder than systematically assessing the influence of easily standardised and replicated factors such as dose and 'setting', the physical environment of the drug administration. Given that the regulatory (and therefore funding) landscape for psychedelic research does not prioritise the comparatively nebulous effects of the social and cultural, relative to the biological, rigorous testing of the matrix may be some time away[32].

While the biopsychosocial and ecobiodevelopmental frameworks offer support for the general importance of environmental factors in mental health, specific features of P-AT may make these factors especially salient.

6.2.2 Plasticity, beliefs, and environmental sensitivity

The relationship between plasticity and environmental sensitivity is central to understanding why matrix considerations are particularly salient for P-AT. Ample evidence from neuroscience demonstrates that psychedelics are plasticity-enhancing agents (Lukasiewicz et al., 2021; Ly et al., 2018, 2021). In the clinical context, the REBUS model proposes that psychedelics acutely shift brain functioning in such a

[32] Although I provide suggestions for beginning this research below, § 6.5.1.

way that confidence in high level priors (~beliefs) about the self and the world are relaxed (Carhart-Harris and Friston, 2019). Sub-acutely, the context of relaxed priors, coupled with enhanced plasticity confer a period of malleability in which maladaptive established patterns of thinking and behaviour become more modifiable by experience (Zeifman et al., 2025). This heightened plasticity can catalyse cognitive-behavioural changes, primarily through increased sensitivity to environmental inputs. During this period, typically strongly held beliefs become more responsive to feedback signals that indicate mismatches between beliefs and expectations about how the self and world are, and evidence from sensory experience in the world.

Although this increase in plasticity —of brain, mind, and behaviour—has been touted as one of the reasons for their therapeutic benefits (Calder & Hasler, 2023; Kočárová et al., 2021; Nardou et al., 2023), enhanced plasticity is not intrinsically a good thing. It is, after all, plasticity that supports the learning and reinforcement of maladaptive patterns of thought and behaviour, as in the development of some anxiety disorders, phobias and addictions. While psychedelics may create an *opportunity* for change, the nature of that change will be influenced by the heightened sensitivity to environmental signals in the post-psychedelic period. In as much as plasticity represents the capacity to be shaped by experience, its therapeutic value depends entirely on what experiences shape the plastic state. Just as enhanced plasticity is neither intrinsically good nor bad, outcomes following enhanced environmental sensitivity are likewise dependent on whether the environment is salutogenic or pathogenic. Exposure to psychotherapeutic support, or to a significant life stressor, in the wake of a plasticity-enhancing psychedelic experience, are liable to produce divergent outcomes (Castrén, 2005; Majić et al., 2015). Of particular note, Bremler and colleagues' (2023) case analysis of people experiencing long-term negative psychological responses to naturalistic psychedelic use (n=15) identified stressful life circumstances, and lack of social support during or after the experience, as risk factors for negative outcomes. By the same token, exposure to psychologically adverse environments leaves open the possibility of muting the therapeutic effect of P-AT, or risking iatrogenic harm.

This heightened plasticity appears particularly consequential when considering that psychedelic experiences frequently generate insights that may have implications for patients' relationships and social connections. Psychological insight has been repeatedly identified as a significant predictor of beneficial outcomes following psychedelic use (Agin-Liebes et al., 2021; Carhart-Harris et al., 2018; A. K. Davis, Barrett, et al., 2021; Peill et al., 2022), yet the content of these insights may be liable to extend beyond individual cognition to touch on aspects of life that can affect one's social matrix.

As illustrated in Tables 6.1 and 6.2, validated measures of psychological insight following psychedelic use capture aspects that may have significant implications for a patient's relationships. Insights like those described by the selected items below, while potentially therapeutic for the individual, may significantly affect—and potentially disturb—established patterns within their social matrix.

This creates a complex dynamic where therapeutic benefit may be partly mediated by insights that simultaneously create tension within the patient's matrix. When patients gain clarity about lifestyle changes they wish to make—whether directly relationship-focused or not—these changes may be unwelcome to family members or others in their social environment. This introduces a potential double vulnerability: patients are implementing insight-driven changes precisely when they are most sensitive to environmental responses to those changes. The matrix thus becomes both a potential source of support for positive transformation and a potential source of resistance that might undermine therapeutic momentum.

Gained resolution or clarity about past traumas or hurtful events.
Discovered clear similarities between my past and present interpersonal relationships. Discovered new feelings or perspectives about significant relationships in my life.
Realized certain actions I should take in regards to important relationships in my life

Table 6.1: Sample items from the Psychological Insight Questionnaire (PIQ, Davis et al., 2020)

I have become more conscious of aspects of my lifestyle that I used to ignore or not be fully aware of
I have had important new insights about how I would like to change aspects of myself or my lifestyle

Table 6.2: Sample items from the Psychological Insight Scale (PIS, Peill et al., 2022)

6.2.3 Matrix in psychedelic contexts

Early evidence from the comparatively small psychedelic literature also gives us reason to anticipate that matrix effects matter at least as much in P-AT as in other treatment modalities. The connections between social support and post-psychedelic experiences are suggested by the role of supportive

relationships in integration, the impact of adverse social environments on outcomes, and the heightened need for understanding from others following profound psychedelic experiences.

The Challenging Psychedelic Experiences Project, which has investigated extended negative experiences following naturalistic psychedelic use, highlights a range of successful coping strategies that involve the matrix. In an online questionnaire study of those who had experienced extended difficulties (n=608), ⅓ of respondents endorsed the value of peers and community support, with respondents "emphasis[ing] the importance of empathy and shared experience in the support process" (Robinson et al., 2024, p.9).[33] The most frequently endorsed features of helpful social support were "*talking and feeling heard* by others, followed by *Acceptance and validation* and *Shared similar experiences*" (p.4). Community support was not consistently helpful - one respondent wrote that "support from family and regular friends (non-psychedelic) was almost useless. I felt like I was existing in a totally different terrain than 'normal' people" (p.9).

These findings align with recent work by Palitsky et al. (2025), who found that both participants and therapists in P-AT trials expressed a desire for treatment teams to better understand before drug sessions patients' "ideographic conditions and medical histories," particularly as these might manifest during dosing sessions. This identified need for contextualised understanding reinforces the salience of matrix considerations, suggesting that patients themselves intuitively recognise how their personal histories and situations influence therapeutic outcomes.

Interview studies with ayahuasca and psilocybin truffle retreat attendees (Cowley-Court et al., 2023; Lutkajtis & Evans, 2023) also point to social challenges depending on the environment that they return to: "there was definitely a disconnect when coming back home. It is hard to relate to some people, especially those that have limited experience in altered states, especially from psychedelics..." (Cowley-Court et al., 2023, p.212); "it made me feel a little disconnected from others around me because … [it's like] you get on an elevator and you reach the top floor, and you see something that's really amazing. And then you go back down to the first floor, and you're unable to explain to others what you saw at the top floor. It can be quite isolating sometimes" (Lutkajtis & Evans, 2023, p.216).

The influence of matrix factors also appear to be salient in clinical contexts. Analysis of interviews with patients of P-AT for cancer-related anxiety found that 13 of 13 participants addressed the relational

[33] Noteworthy is the fact that this is nearly twice the rate at which people endorsed the value of 'professional therapeutic or coaching assistance.'

valence of their psilocybin experience without prompting, with half underscoring that sharing aspects of their experience with loved ones led to valued increases in connection with family (Belser et al., 2017, p.10). In contrast, patients in a P-AT trial for treatment resistant depression “who did not have strong support from family or friends described feeling vulnerable and alienated afterward” (Watts et al., 2017, p.548).

These findings align with observations in early psychedelic literature that "rapid change is very difficult to sustain if the living environment is the same as the one which caused difficulties in the first place" (Eisner, 1997, pp.215-6). Regardless of the problematic contexts in which this insight emerged (see n.31), contemporary frameworks of neuroplasticity and environmental influence provide independent theoretical support for this observation: if psychedelic experiences create periods of enhanced plasticity and belief updating, then the quality of the environment during this sensitive period becomes more relevant for supporting or undermining therapeutic change. The matrix thus appears to play a dual role - both as a source of support for processing and integrating profound experiences, and as an environment that can either reinforce or challenge the insights and changes that emerge during treatment.

The complex and subjective nature of the matrix, as well as the limitations of the case study method, prevent any strong causal claims about the influence of the matrix on my interlocutors’ post-trial journeys. Nonetheless, the different matrices that participants returned to following trial treatment can offer a coherent framing through which to understand their later experiences. In what follows, I draw on their accounts - of navigating complex social environments, managing periods of heightened sensitivity, and seeking understanding from those around them - not only exemplify these broader patterns but to add greater texture to ways that the matrix can shape post-psychedelic trajectories.

The theoretical frameworks and empirical evidence discussed above suggest that the matrix may be particularly relevant in P-AT for at least three reasons. First, psychedelics' enhancement of neuroplasticity appears to create a period of heightened sensitivity to experience, during which environmental influences may be especially impactful. Second, given that psychopathology often emerges and is maintained within specific social-environmental contexts, sustainable therapeutic change may well require attention to these contextual factors rather than treating them as mere background conditions.

Finally, as evidenced by both naturalistic and clinical studies, post-psychedelic experiences appear to be heavily influenced by the availability and quality of social support within the matrix. While the complex and subjective nature of the matrix prevents definitive causal claims about its influence, the experiences of Eleanor, Aaron, and Helen offer valuable insight into how these three dimensions

manifest in practice. In what follows, I examine how their different matrices shaped their post-trial trajectories, exploring how they navigated complex social environments, managed periods of heightened sensitivity, and sought understanding from those around them.

6.3 Three Important Matrix-related Considerations in P-AT

Drawing on the experiences of Eleanor, Aaron, and Helen, this section illustrates three dimensions of the matrix: its role in shaping post-treatment trajectories, its dynamic capacity to both influence and be influenced by post-psychedelic changes, and its function as a crucial resource for integrating psychedelic experiences

6.3.1 Matrix quality and post-treatment trajectories

The quality of a patient's matrix - supportive or adverse, resourced or impoverished, understanding or alienating - is posited to be particularly consequential during the sensitive period following psychedelic administration. My participants' accounts of their life after trial participation serve to demonstrate how this can play out.

Eleanor and Aaron both had to contend with significant external challenges swiftly following their trial participation due to the onset of COVID-19-related lockdowns and associated stressors including financial instability - in Eleanor's words, the "brutality" of "everything falling apart" after leaving the "cocoon of the trial" was "a disaster". Nonetheless, their experiences within their respective matrices highlight crucial differences. Eleanor's husband was a source of encouragement and stability, "unequivocally supportive" of her journey, able to reflect back to her his perceptions of her newfound happiness and 'sparklingness' when her resolve waivered. In contrast, Aaron entered the trial from a position of relative social isolation. With his partner sceptical of and resistant to his trial participation, he struggled to find someone to pick him up from the trial site: "I had to go through my whole contact list, and then it's like - who would I trust to take me home from this experience… That list rapidly shrunk. And then who of those that I call were actually willing? Yeah, almost everyone said 'no thanks… The one person that I would have called without hesitation was dead." The absence of immediate familial or social support forced Aaron to seek understanding and community online, leading to a complex emotional entanglement that predominated his sense-making following the trial. While both faced substantial external pressures, Eleanor's supportive matrix facilitated her resilience, while the lack of external support and understanding from Aaron's partner and sober community created significant emotional distress: "The isolation, or the separateness is intensified when I'm not around

people that can relate…I'm inside, and I've got no one to talk to about any of this." Reflecting on the anticipated licensing and rollout of P-AT, he offered "if the person that's going through it has an adverse family environment or an unsupportive or rejecting family environment, there has to be a team waiting on the other side…going forward, we need a much bigger landing pad."

Helen's matrix, in comparison, was typified by well-intentioned but inadequately prepared support. Her father, despite his willingness to support her, lacked the guidance and preparation necessary to provide effective assistance in navigating life after the trial. Despite experiencing initial positive shifts in motivation and outlook, she struggled to channel these changes without adequate guidance. Her father, though eager to help, "could just see me completely like so positive and wanting to do things that he didn't know what to do or how to channel that." This lack of knowledgeable support left her feeling overwhelmed by possibilities: "It was quite overwhelming the amount of things I wanted to do, and my brain was like 'wow, what could I do?' It was just too much." Without sufficient structure and support to help her navigate this sensitive period, Helen's initial therapeutic gains proved difficult to maintain.

So presented, the three cases illustrate how matrix quality can influence post-P-AT trajectories. Eleanor's supportive matrix facilitated resilience and continued growth, while Aaron's isolating environment necessitated potentially destabilising searches for understanding elsewhere. Helen's case highlights how insufficiently prepared or resourced, may not adequately sustain therapeutic momentum.

This suggests that attending to matrix quality is not merely about ensuring the presence of social support, but about consciously preparing and equipping that support system to help navigate periods of heightened sensitivity and potential change. Consider also that Aaron's case demonstrates that the impact of the matrix need not only influence *therapeutic outcomes*, understood as symptomatic change. Despite his distress in the time since his trial participation, he was clear that he had not returned to his previous *depression*. Rather, his case brings to mind what Noorani describes as the "new problems and riddles that emerge from participant experiences when these are unrelated to the clinical targets the trials were designed to treat." (Noorani, 2019, p.36)

6.3.2 Matrix as both source and site of change

Consider Eisner's assertion that 'rapid change is very difficult to sustain if the living environment is the same as the one which caused difficulties in the first place' (1997, pp.215-6)[34]. Ostensibly, such an

[34] For the psychoanalytically oriented Eisner, this was likely because the same environment would reactivate established defensive patterns and unconscious dynamics that, while ultimately limiting, served to protect against earlier emotional wounds or psychic conflicts.

assertion is hard to square with the results of contemporary psychedelic research, which record high levels of treatment efficacy even though participants typically return home after their acute drug experiences. That modern trials report positive outcomes without attending to the matrix is not, however, evidence for its superfluousness for two reasons. Firstly, despite their success, modern trials show considerable variation in individual outcomes, with some experiencing brief or no improvement at all. But as trials do not assess or track features of participants' matrices, they cannot determine whether they contribute to variance in outcomes.

More importantly for our present purposes, this overlooks a key feature of the matrix which is well-evidenced in my conversations with participants: people need not merely be passive recipients of their matrix. Indeed, *per* Eisner, "[w]hen a matrix is working properly, it also becomes a process: the setting is one in which individuals can change and mature, and as they grow, the matrix expands to contain the additional growth" (p.215).

Eleanor's experience most clearly exemplifies the dynamic nature of the matrix. Following her trial participation, she actively restructured her social relationships to make sure they were reciprocally nourishing. Prior to the trial, her life was "very mundane, operating on an existing kind of level, not really living," a pattern she attributes to prioritising external determinations over engaging with her own values: "I think my life prior to the trial was always very sort of externally determined, you know, 'what do your parents think? What [does] society think?'...do the 'right' thing." Through consciously reshaping her matrix after the trial, she developed an environment more personally fulfilling than before, supporting continued growth and, potentially, the solidifying of therapeutic effect.

But it should not be overlooked that Eleanor started from a position of relative advantage. A relatively well-resourced matrix, characterised by professional engagements, educational pursuits, friendships and strong family support is plausibly an environment more conducive to positive change than that of Helen: not only were Helen's mental health challenges longer-established and more complex, but her social life was more impoverished. With the intensity of her symptoms leaving her unable to maintain a job, Helen reflected that "I don't have that many relationships because of how isolating the eating disorder [is] and also probably the autism." While Eleanor could tap into a source of energy to pursue new and valued, but risky undertakings, "*do the thing* - irrespective of the outcome," Helen, who felt underequipped by the trial team to navigate life after the trial – "yeah, but now what do I do with this? What do I do now when I go home?" - was ultimately frustrated in her attempts to make changes in her

life. Despite her father's eagerness to support these attempts, as evidenced by their trip to the seaside, he too felt unclear about how to provide the ongoing support that Helen needed.

Aaron's case illustrates how pre-existing matrix dynamics can actively maintain patterns of distress, while also demonstrating the challenges that arise when the matrix lacks the dynamic responsiveness that Eisner suggested was crucial for growth and progress. His relationship with his partner, while supportive in maintaining sobriety, became a source of tension when insights from his psychedelic experience brought relationship difficulties into focus: "things that I'd been suppressing about our relationship were not suppressible anymore." Her unwillingness to engage with his trial experiences left him unable to process important insights: "there was this really dismissive attitude from them, of hoping that this was just a phase I'd be passing through." This rigidity in the relationship system - its inability to "expand to contain the additional growth" as Eisner put it - created its own form of distress[35]. Though he did not directly attribute his pre-trial depression to these relational difficulties, he suggested that they were a contributing factor, with the "issues in the relationship [becoming] a kind of status quo that had been dragging me under." His case demonstrates how families and intimate relationships function as dynamic systems - when one member experiences significant psychological change but other parts of the system remain rigid or resistant to accommodating this transformation, it can create new sources of tension and emotional burden.

Collectively, these cases demonstrate how the matrix functions not merely as a static backdrop, but as an active participant in the unfolding of post-psychedelic processes. Eleanor's ability to reshape her social world supported continued enrichment, while Helen's confined social environment and Aaron's complex relationship dynamics illustrate how features of the matrix can constrain, as well as enable, change. This suggests that sustainable therapeutic change requires attention not just to individual psychological processes, but to the dynamic social-relational contexts that patients both inhabit and help shape. When the matrix lacks the flexibility that Eisner identified as crucial for therapeutic progress, even successful symptom reduction may be accompanied by new forms of interpersonal challenge.

[35] Cf. Szapocznik & Prado (2007, p.474); who, reviewed three trials of psychosocial treatment which found negative effects on family functioning. "One possible hypothesis is that if an individual is changed by an intervention that is designed to change the individual and not to help the family to adjust to these changes… the family may be negatively affected. The family will attempt to achieve its state of homeostasis, but because the family will not be accustomed to the new behaviours of the individual, the family may have a difficult time adjusting."

6.3.3 Matrix as resource for integration

The period following psychedelic experiences presents unique challenges that highlight the critical role of the matrix as a resource for integration. While the acute drug effects may catalyse insights and emotional breakthroughs, as well as alerting patients to the very possibility of change, the work of integration - of making sense of these experiences and translating them into sustained behavioural change - may require ongoing engagement with supportive social networks. The Challenging Psychedelic Experiences Project identifies three key features of helpful social support during integration: "talking and feeling heard by others," "acceptance and validation," and "shared similar experiences" (Robinson et al., 2024, p.4). The cases of Eleanor, Aaron, and Helen illustrate how differential access to these features of support shaped their integration processes.

Eleanor's case exemplifies how a supportive matrix can facilitate positive outcomes. Her husband's consistent validation of her experience and changes - his ability to reflect back her "newfound happiness and 'sparklingness'" - provided exactly the kind of acceptance that supports integration. When overwhelming emotions, both positive and negative, led Eleanor to consider returning to SSRIs, "he's always unequivocally supportive of not doing that. He's like, no, keep going, just take one more step." This encouragement helped Eleanor maintain her therapeutic trajectory even through challenging periods.

In stark contrast, Aaron's experience demonstrates how a matrix that is experienced as isolating and unsupportive can complicate post-trial experiences and can complicate integration. His partner's unwillingness to engage with his trial experiences - "hoping that this was just a phase I'd be passing through" - left him without a crucial resource for processing his insights: especially influential given that his insights related to sources of dissatisfaction within their shared relationship. The absence of understanding within his immediate social circle led him to seek support elsewhere: "The isolation, or the separateness is intensified when I'm not around people that can relate...I'm inside, and I've got no one to talk to about any of this." While he eventually found connection within the broader psychedelic community, this came with its own complications. This pattern illustrates how inadequate support in the immediate matrix can create a cascade of challenges: forcing isolation during periods of heightened sensitivity, compelling patients to compartmentalise their experiences, and potentially driving them to make significant life decisions or form intense new connections from a position of vulnerability. The requirement to "pretend like it didn't happen" adds further emotional burden, creating new tensions in existing relationships while potentially limiting the process of integration.

Helen's situation illustrates a third possibility: a well-intentioned but inadequately prepared support system. Her father's eagerness to help - evidenced by their seaside trip together - was ultimately insufficient without proper guidance: "he could just see me completely like so positive and wanting to do things that he didn't know what to do or how to channel that." This case highlights that mere presence of support is not enough; the matrix must be equipped to provide appropriate guidance during integration. As Helen reflected, "I feel there was promise there, and hope - it just wasn't used. I didn't know what to do with it...I didn't feel I had enough help to try and tackle the behaviours and change." These cases demonstrate that the matrix serves not only as a context for integration but as an active resource that can facilitate or impede the translation of psychedelic experiences into sustained therapeutic change. The quality and character of social support available during integration appears particularly consequential, suggesting that preparation of the matrix - through psychoeducation and guidance for family members and other key supporters - may be nearly as important as preparation of the patient themselves.

The differential experiences of Eleanor, Aaron, and Helen reveal the matrix as a complex, responsive system - neither deterministic nor entirely malleable, but a nuanced interplay of individual agency and environmental influences which, when brought to focus, highlights both challenges and opportunities in the development of P-AT. This complexity demands careful consideration of whether, when, and how clinicians and researchers should engage patients' matrices, questions I now turn to from a bioethical perspective.

6.4 The Ethical Significance of the Matrix

The foregoing discussion of the matrix might appear to simply restate well-established insights from psychological treatments more broadly: namely, that psychological change occurs within, and is influenced by, the social environment of a patient. But standard adult psychotherapy[36] generally

[36] While systemic approaches to adult psychotherapy do exist and have demonstrated efficacy (Von Sydow et al., 2010), they remain less common in standard adult mental healthcare than in child and adolescent services. Psychotherapeutic interventions with children and adolescents are more liable to involve consideration of the broader social system, as in family and systemic therapies. In these scenarios, intervention outside of the presenting patient is generally seen as more acceptable because minors are more dependent on their 'matrix'. Indeed, as I have argued elsewhere (Insua-Summerhays & Jacobs, *unpublished*; Jacobs & Insua-Summerhays, 2025), the case for considering the matrix is *especially* heightened in the context of adolescent P-AT: not only are adolescents more *dependent* on their matrices than typical adults, they also have less autonomy to select, avoid, or upscale inputs from their environment that influence their mental health. While the content of the thesis focuses

respects clear boundaries around intervention with family or social systems except in cases where serious harm is likely (Bersoff, 2014; Klinka, 2009). These boundaries reflect both practical constraints and respect for patient autonomy.

But distinctive features of P-AT arguably justify the particular attention to the matrix that I advocate. Relative to the gradual unfolding of change in typical psychotherapy, the acute intensity and rapid onset of change in P-AT leaves comparably little time for relationships to adapt. Aaron's case illustrates the dramatic shifts that can come from a single session - previously manageable relationship tensions suddenly became 'insuppressible' following treatment. This compressed timeline of change may necessitate more active preparation of support systems. While all therapy patients remain embedded in their matrices, the enhanced neuroplasticity following psychedelic administration creates a window of particular vulnerability to environmental influences. Moreover, researchers and clinicians providing P-AT are knowingly initiating both rapid psychological change *and* a period of enhanced environmental sensitivity. This combination of effects - the potential for sudden disruption of social systems alongside heightened vulnerability to those systems - creates distinct risks that warrant expanded consideration of matrix effects.

Taking the matrix seriously in P-AT research and practice requires careful navigation of core bioethical principles (Beauchamp & Childress, 2001). From the perspective of non-maleficence, heightened environmental sensitivity increases the risk of harm from psychologically adverse environments[37]. These risks need to be acknowledged and attended to when a clinician or researcher knowing initiates this state of enhanced vulnerability.

The principle of beneficence likewise points towards clinical consideration of the matrix, given that optimising therapeutic outcomes may depend on a salutary social environment. But while the duty of beneficence may impose obligations on clinicians and researchers, the scope of that responsibility needs to be bounded, especially in the context of finite medical resources. This necessity for bounded responsibility stands in stark contrast to Eisner's therapeutic communes, where patients "were allowed

on adult P-AT, the established precedent for attending to the social environment in both child and adult systemic therapies helps illustrate how therapeutic obligations can legitimately extend beyond the presenting patient when warranted by specific vulnerabilities or treatment mechanisms.

[37] While the theoretical frameworks and case studies presented here provide *prima facie* reason to consider heightened environmental sensitivity as a source of potential harm, it is far from conclusive given the lack of empirical investigation. The assessment approaches outlined in §6.5.1 offer preliminary pathways for examining this relationship.

to stay as long as necessary" (p.215). Contemporary healthcare constraints require a more targeted approach.

Moreover, any engagement with the matrix must be balanced against respect for patient autonomy, particularly given that P-AT can lead to reassessment of existing relationships and life circumstances. Some relationships may be damaged or dissolved following treatment - we cannot assume, especially in advance, that this represents a negative outcome: insights gained during P-AT may legitimately prompt patients to reevaluate and sometimes withdraw from relationships they find unsupportive or harmful.

This balance between supporting matrix adjustment and respecting autonomy requires careful consideration of diverse values systems. The significance attached to maintaining family structures versus pursuing individual change varies considerably across cultures and between individuals. It should not be assumed that preserving existing relationship structures should be prioritised without explicit agreement from the patient that this constitutes a treatment goal. Cases like Aaron's highlight the complexity of navigating matrix effects when insights about relationships emerge during treatment—respecting patient autonomy means acknowledging their right to reassess social connections according to their own values, even when this creates tension within existing relational systems.

Moreover, the influence of the matrix on therapeutic outcomes is not straightforward, suggesting the need for appropriate humility about what aspects of a patient's social environment clinicians should seek to influence. Even with a developing understanding of matrix effects, we cannot precisely predict which environmental factors will prove most consequential for a particular patient's trajectory. This complexity warrants caution against overly prescriptive approaches to matrix intervention, while still acknowledging that some preparation and support of the broader social environment may be beneficial. The goal should be to provide informative guidance rather than directive instruction about how patients and their support networks navigate post-treatment changes.

There is a need, then, to balance the risks of the matrix with a respect for patient autonomy. One seemingly straightforward approach would be to screen prospective patients based on matrix quality, excluding those whose social-environmental contexts appear unfavourable. While this might satisfy the principles outlined above, an approach driven by screening raises serious justice concerns.

This tension exemplifies the 'protection-inclusion dilemma' (Friesen et al., 2022), an important challenge in which efforts to protect vulnerable individuals from potential harms simultaneously deny them access to important potential benefits. Credible candidate features for relevant aspects of the

matrix—those that have been shown to influence mental health outcomes outside of P-AT—including strong social support networks, stable housing, meaningful employment or purposeful activity, and access to nature, are not evenly distributed goods. Indeed, lack of these goods is strongly associated with social and economic marginalisation: excluding those without them from P-AT would make for a perverse system[38] that risks denying treatment to those who might need it most.

While acknowledging the heightened vulnerability that may accompany psychedelic administration in the context of less supportive matrices, I argue that the solution lies not in exclusion but in developing appropriate support mechanisms – there are, after all, other steps that can be taken to minimise risks of harm. As well as equity and justice-related concerns, a P-AT trial that excludes on the basis of suboptimal matrices to that extent compromises generalisability of trial findings and limits our understanding of how to help the diverse populations who will ultimately seek P-AT treatment. Excluding participants with challenging matrices as standard will limit our understanding of how P-AT functions in real world contexts.

Any research or clinical consideration of the matrix needs to accommodate and balance multiple competing imperatives: respect for patient autonomy; the need to limit risks of harm; a bounded duty to secure good outcomes for patients; and the avoidance of practice that cements or exacerbates health inequalities. The time-limited nature of heightened neuroplasticity following psychedelic administration suggests a possible resolution. While the exact duration of this period remains under investigated (though our best evidence suggests it is somewhere between two and six weeks, (Majić et al., 2015; Nardou et al., 2023; Skosnik et al., 2023), this temporal boundedness suggests that more intensive engagement with the matrix might be justified within this critical window, as the circumscribed extent of such intervention makes it more ethically defensible than indefinite oversight.

The time-limited nature of this window of environmental sensitivity also underscores the practical necessity of ensuring the matrix is adequately prepared before treatment begins. Without proper preparation, even well-intentioned support systems may struggle to help patients make the most of this critical period. The stakes are particularly high given that this window represents a unique opportunity: the confluence of psychological insights from the psychedelic experience with a period of enhanced

[38] On this, others may disagree. Drawing attention to conflicting imperatives embedded in the obligation for fair participant selection in clinical trials, (MacKay & Saylor, 2020) argue that deviations from fairness can be ethically justified where (i) research significantly advances a valuable purpose, (ii) there is no less unfair alternative available, and (iii) the value of the study outweighs its fairness. Such a position focalises a trade-off between risks of harm and fairness. With no systematic data on the influence of disadvantaged matrices available, balancing these concerns is challenging. Mitigating the harm from adverse matrices through other means, through additional support described below, may be one method of avoiding exclusion.

neuroplasticity may create conditions particularly conducive to positive change. However, this same period of heightened environmental sensitivity also creates vulnerability to adverse influences. The prospect that this time-bounded window of opportunity for supporting therapeutic change might be missed without adequate preparation provides motivation to make sure the matrix is prepared before treatment begins

Instead of screening out prospective patients with less favourable matrices, in the next section I propose a more equitable approach that involves, where indicated, the temporary provision of increased oversight and support for the whole system during the window of enhanced sensitivity. To borrow a phrase from Aaron, “going forward, we need a much bigger landing pad” - more intensive, albeit temporary support where indicated, rather than an indefinite intervention. In the following, I emphasise providing extended psychoeducation to family or other matrix-members and offering resources for navigation of change, rather than seeking to direct or prevent that change.

Moving from these ethical considerations to practical implementation requires first addressing a fundamental methodological challenge. Before we can develop systematic approaches to matrix support, we must establish more rigorous ways to assess and characterise the matrix itself

6.5 Operationalising Matrix Support

6.5.1 From folk concept to systematic assessment

The arguments and cases presented thus far, while suggesting the importance of the matrix in P-AT, are far from conclusive - they are 'vouchers', rather than 'clinchers' (Cartwright, 2007, 2018). While the foregoing evidence does not yet suffice to fundamentally reshape P-AT practice as it relates to the matrix, I submit that it offers a valuable insight that merits thoughtful consideration and warrants further empirical scrutiny.

However, at present, systematically investigating - let alone supporting - something we cannot yet systematically measure or define presents a challenge. As with other concepts more commonplace to P-AT (e.g., set, setting, integration), matrix has at best the character of a folk concept; one which is intuitively recognised and understood, but lacking in formal definition or rigorous scientific elaboration. While I hope that the case studies and theoretical frameworks discussed above provide compelling reasons to take the matrix seriously, translating this understanding into research and practice requires more systematic approaches to assessment and intervention.

Given the paucity of focused investigation on the matrix, however, such definition and elaboration should be delayed until a stronger empirical foundation is established. Given the complex and dynamic nature of the matrix—socioecological environment encompasses multiple layers of potential influence that may interact in hard-to-predict ways— the first steps to understand the influence of the matrix on P-AT outcomes should involve its most accessible, well-characterised dimensions that have been extensively studied in other contexts.

These might include the measurement and description of social climates and relationships within the family, as in the Multidimensional Scale of Perceived Social Support (MSPSS, Zimet et al., 1988); the Social Support Questionnaire (SSQ, Sarason et al., 1983), which measures both social support and satisfaction with that support; or the Interpersonal Support Evaluation List (ISEL, Cohen et al., 1985), which assesses the perceived availability of social support, including subscales for 'appraisal' and 'belonging'—thus attending to two of the features of social support found to be most helpful in post-psychedelic integration by Robinson et al. (2024).

One approach to acknowledging and accommodating the matrix within contemporary P-AT practice would be the routine inclusion of *systemic psychological formulation* at intake (Dallos & Stedmon, 2013; Jacobs & Insua-Summerhays, 2025; Insua-Summerhays and Jacobs, *unpublished*). In contrast to diagnosis, which involves categorising symptoms into predefined disorders based on standardised criteria, formulation offers a personalised understanding of an individual's psychological issues in the context of their life, history and relationships. Identifying a potentially adverse matrix through formulation may highlight patients who would benefit from additional preparation and support, given that they risk exposure to second-order iatrogenic harm by way of unregulated exposure to environmental stressors while in a state of enhanced plasticity and environmental sensitivity.

However, this presents a challenge to clinician-researchers designing and executing clinical trials of P-AT. Restricting the intake of prospective trial participants not only by virtue of their diagnostic status, but also their meeting some formulation requirement for having a matrix well-suited to P-AT, might unacceptably limit the generalisability of any safety and efficacy findings required for drug licensing. Moreover, selecting prospective trial participants on the basis of their socio-ecological environments may risk violating ethical norms for participant recruitment that require fair burden sharing and fair opportunity.

6.5.2 Matrix-informed preparation and support

Having established approaches to matrix assessment, we can now address the ethical tension introduced earlier between protecting vulnerable patients and ensuring equitable access. Rather than using matrix assessment to screen out patients, these tools can identify areas and patients for whom additional preparation and support may be needed. This approach satisfies both imperatives: it acknowledges and addresses matrix-related vulnerabilities while maintaining equitable access to treatment.

The case of Helen and her father exemplifies both the need for, and potential benefit of, matrix-informed preparation. Despite his eagerness to support his daughter, he felt under-equipped by the trial team: "It wasn't a huge amount. They gave us some literature to look at...It wasn't as much as I thought it would be... [I've now read] a lot - A LOT - of books since then, and articles and things I should have read before, really in more detail." His reflections suggest that comprehensive psychoeducation for family members (which some recent trials have begun to incorporate) could better prepare them to provide appropriate support during the sensitive post-treatment period.

Matrix-informed preparation need not be limited to immediate family. Aaron's experience of isolation from his sober community, and his partner's resistance to engaging with his trial participation, suggests value in broader psychoeducation that could help existing support networks better understand and accommodate the changes that can emerge following P-AT. Such preparation might include:

- Education about the nature of psychedelic experiences and their potential impacts on beliefs, behaviours, and relationships
- Guidance on supporting someone through periods of enhanced environmental sensitivity
- Resources for understanding and responding to existential or spiritual aspects of psychedelic experiences
- Clear pathways for accessing additional support if needed, and, crucially, the provision of funds for such support where indicated, if necessary on a means-tested basis.

Where existing matrices are identified as potentially challenging, rather than excluding patients from treatment, practitioners might consider:

- Developing temporary support structures through more intensive group integration sessions (Modlin et al., 2025)
- Connecting patients with peer support networks (Skiles et al., 2023)

- Providing guidance for identifying supportive social networks and building new supportive relationships (Boardman et al., 2023; Perry & Pescosolido, 2015)
- Incorporating social workers into the therapeutic team to help address systemic barriers

Eleanor's case demonstrates how patients can actively reshape their matrices when properly supported. Her ability to restructure social relationships and maintain therapeutic momentum was facilitated by having both adequate resources and supportive relationships. For patients with less advantaged starting positions, providing explicit guidance and support for matrix development could help level the playing field without resorting to exclusionary practices.

The goal of matrix-informed preparation is not to ensure perfect conditions—an impossible and potentially counterproductive aim—but rather to identify and strengthen those elements of support that could help sustain therapeutic momentum.

6.5.3 Implementation challenges and solutions

Historical approaches to creating supportive matrices for psychedelic therapy included residential arrangements where "patients would come from out of town for treatment and find lodging in one of [the] 'communes'...and were allowed to stay as long as necessary" (Eisner, 1997, p.215). Setting aside the ethical concerns with these specific historical implementations (Davidson, 2017; Cult Vault, 2023), such immersive residential models are also impractical for contemporary healthcare systems. The highly structured approach is incompatible with the lives of patients who have significant external responsibilities. Additionally, modern mental healthcare has shifted decisively toward outpatient and short-term care models, prioritising accessibility, cost-effectiveness, and immediate crisis intervention rather than extended residential treatment.

Nonetheless, contemporary healthcare systems offer multiple pathways for addressing matrix-related needs within existing structures. Social prescribing—connecting patients to community resources and non-clinical support—provides one approach for strengthening matrices, while social workers can offer complementary expertise in navigating complex social systems and facilitating access to services. Such an integration aligns with the horizontal integration advocated by the ecobiodevelopmental framework—connecting healthcare, social services, and community support systems to address not just immediate clinical needs, but also the broader systemic issues that can impact therapeutic outcomes. Such an approach acknowledges that sustainable therapeutic change requires attention to the full spectrum of a patient's social and environmental context, not just their acute clinical care.

As with the recommendations for expanded post-trial access and care in the previous chapter, the distribution of responsibility for matrix support across stakeholders must balance ideal practice against practical constraints. As the principal providers of P-AT with specific expertise, therapists and trial teams have primary responsibility for assessment and preparation, which could include:

- Conducting initial matrix assessments through systemic formulation
- Providing psychoeducation to identified support persons
- Developing individualised integration plans that account for matrix features
- Establishing clear pathways for additional support if needed

Integration specialists, whether within trial teams or in private practice, play a crucial role in supporting ongoing matrix development. Helen's experience, though, highlights an important equity consideration: "It kind of feels unfair that I would be expected to pay quite a lot of money to see a therapist, which I wasn't really warned I might need. This is not cheap. It could be a hundred pounds or something a session." This suggests that trial teams should either build extended integration support into their protocols or ensure that participants are fully informed about potential ongoing support needs and associated costs.

Family members and other support persons constitute a critical but often overlooked resource for therapeutic change. Eleanor's case demonstrates the beneficial impact that an informed and engaged support system can have on maintaining therapeutic momentum. Her husband's consistent validation of her experience and post-psychedelic changes provided exactly the kind of acceptance that supports integration. However, as evidenced by Helen's father's experience, supporting matrix members require adequate preparation to fulfill this role effectively.

But ‘taking the matrix seriously’, when taken to its logical conclusion, has more expansive (and expensive) implications. The broader health and social care infrastructure bears significantly on patients’ matrices. A full exploration of how to optimise these systems, which have impacts well beyond the limits of P-AT, is a complex policy conversation that extends well beyond the scope of this chapter, or indeed thesis. In lieu of doing so, here I gesture towards some practical steps within current constraints. These might include:

- Incorporating social prescribing, social work services, and community partnerships into P-AT delivery
- Establishing sliding scale fees for integration services
- Creating peer support networks

- Training healthcare staff in matrix-informed approaches

The challenge lies in balancing these responsibilities against resource constraints while maintaining quality of care. The roll-out of P-AT, with its attendant resource intensiveness and unorthodox model of delivery, will already require rethinking traditional models of mental health service delivery. As the field moves towards implementing P-AT in standard healthcare contexts, consideration of matrix effects may help inform decisions about how to optimise delivery within existing systems, even if broader structural changes remain beyond immediate reach.

6.6 Conclusion

In this chapter, I have argued for renewed attention to the *matrix*—the environment from which a psychedelic-assisted therapy patient comes, and to which they return—as a crucial factor in post-treatment outcomes. Drawing on Eisner's original articulation of the concept, contemporary frameworks for understanding psychopathology, emerging evidence from the psychedelic literature, and the three case studies, I have demonstrated how features of patients' socio-ecological environments can support or constrain change following P-AT.

The matrix appears particularly salient in P-AT for at least three reasons. First, psychedelics' enhancement of neuroplasticity creates a period of heightened environmental sensitivity, during which the quality of the matrix becomes especially consequential. Second, given that environmental factors play a role in maintaining both adaptive and maladaptive patterns of thought and behaviour, sustainable therapeutic change requires attention to these contextual influences. Given what we know about the influence of environmental factors on the trajectory of psychopathology in non-psychedelic contexts, it would be highly surprising if the same was not true in P-AT. Finally, the process of integrating intense, insightful, or otherwise personally meaningful psychedelic experiences appears to be influenced by the availability and quality of social support within the matrix.

The cases of Eleanor, Aaron, and Helen illustrate these dynamics, highlighting how the matrix is not merely a backdrop against which therapeutic change occurs, but an active component in both enabling and constraining change. However, their stories are vouchers, rather than clinchers - they suggest possibilities rather than establishing certainties. Before re-orienting research and practice in line with any of the suggestions made here, a first priority is the systematic assessment of the ways in which features of the matrix can influence post-psychedelic outcomes, and I have pointed towards validated instruments that might meaningfully serve to begin such investigations.

Looking further ahead to clinical practice, I have argued that, rather than screening out patients with challenging matrices —which may raise serious equity concerns— attention should focus on developing and testing ways to provide enhanced, temporary support during the critical window of post-psychedelic sensitivity. This approach, I have suggested, resolves the protection-inclusion dilemma by maintaining equitable access while still addressing heightened vulnerability. Rather than excluding patients on the basis of suboptimal matrices, a matrix-informed approach would provide temporary scaffolding, such as family psychoeducation to best prepare support systems, more intensive integration support where indicated, strategic integration of social services where needed, and connection to peer networks during the critical period of integration. Such a middle path can allow P-AT to simultaneously honour commitments to equity, autonomy and nonmaleficence.

By foregrounding the matrix in contemporary P-AT, this analysis offers an alternative to persisting narratives about psychedelic therapy as a quick fix or magic bullet for treating psychopathology. Instead, it suggests that sustainable therapeutic change requires careful attention to, and sometimes intervention in, the broader social-ecological systems within which patients are embedded. As we move toward wider implementation of P-AT, this understanding should inform both research protocols and clinical practice.

7. Considering Adverse Events

7.1 Introduction

When Aaron participated in a P-AT trial to treat his long-standing, treatment resistant depression, his acute response was striking: "in one single session - full remission." Yet in the weeks and months that followed, he found himself in a state of turmoil as he struggled to work through new insights related to his sexual and relational disposition. While his depression remained in remission, Aaron faced what he called an "intricate" struggle with "the level of raw intimacy it open[ed] up within." His psychedelic experience had brought previously suppressed relationship dissatisfactions "suddenly in [his] face," creating tensions with his partner who had been resistant to his trial participation. While the resultant emotional and relational challenges were highly distressing and painful, and came to dominate his emotional life, these aspects of his experience went completely unrecorded in the reported trial data. As well as demonstrating the value of qualitative research methods - this salient mismatch between patient experiences and trial reporting would not have been established without talking to Aaron - his case exemplifies how current approaches to assessing and reporting adverse events (AEs) in P-AT trials may miss consequential patient-relevant outcomes that fall outside standard reporting frameworks.

The choice of reporting measures for AEs used in P-AT trials are, in large part, born of the regulatory environment that the developers of psychedelic treatments are operating in. Given the status of psychedelics as unlicensed drugs, wider rollout will depend on the approval of health agencies including the FDA, MHRA, and EMA, a reality that will naturally shape the design and reporting of P-AT trials. But these agencies are geared towards, and have expertise in, assessing the safety and efficacy of drugs and medical devices, rather than psychotherapies. Their conception of AEs is grounded in the norms appropriate to pharmacological research, wherein AEs are understood as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related" (FDA, 2012). As I will examine below, this definition, while appropriate for conventional pharmaceutical trials, proves particularly unhelpful when considering psychotherapies and hybrid approaches such as P-AT.

In this chapter, I analyse how current approaches to identifying and reporting AEs in P-AT trials are both practically and ethically lacking. Not only does AE reporting not happen enough across the field, where it *is* done, it is often done partially and non-exhaustively. As a consequence, our understanding of the risks of P-AT, and thereby of its true risk:benefit profile, is markedly incomplete.

The reasons to address these shortcomings in AE reporting are numerous. Respecting the autonomy of prospective P-AT patients requires disclosing accurate risk information, such that they can make truly informed decisions about their treatment. In addition, establishing the risk:benefit profile of P-AT is needed in order to ensure compatibility with the principle of beneficence, i.e., making sure that the risks of a treatment are not disproportionate to its potential benefits. Finally, it is not an exaggeration to say that the field's future depends on improving AE reporting. Inadequate AE reporting in MDMA-assisted therapy trials for PTSD was cited by one member of the FDA's advisory committee as a reason to block regulatory approval despite strong efficacy data (Hardman, 2024).

After reviewing what is currently known about AEs from P-AT trials, including systematic gaps in reporting practice and structural limitations in trial designs, I situate these challenges by reference to other psychiatric interventions - Deep Brain Stimulation (DBS) and Ritalin (methylphenidate) to underline that systems and standards for measuring and recording outcomes are neither neutral nor inconsequential, but rather can shape thinking and practice around an intervention. I argue that AE reporting in P-AT faces a dual challenge: not only are trials often failing to meet existing standards for AE reporting, but those standards themselves, developed for conventional pharmaceutical interventions, are inadequate for capturing the full range of consequential, patient-salient outcomes, such as those experienced by Aaron. I review the distinctive challenges of adequately and accurately recording AEs in P-AT trials: the temporal and interpretive complexity of psychedelic experiences, the hybrid psychotherapy-pharmacotherapy modality of P-AT and its practical and regulatory implications, and the role of extrapharmacological factors. In identifying these challenges, I lay out the features that more appropriate frameworks of AE reporting in P-AT will need, critically assess two recent attempts to solve this problem, and propose concrete steps towards more comprehensive assessment and documentation of AEs, which captures both immediate safety concerns and the complex, meaning-laden nature of psychedelic experiences.

7.2. Current Landscape

7.2.1. Evidence of reporting gaps

While a number of reviews suggest low rates of AEs in P-AT (Romeo et al., 2024; Roscoe & Lozy, 2022; Schlag et al., 2022), these findings belie significant failures in reporting. Field-wide evidence suggests that AE reporting in P-AT research is markedly inadequate. A comprehensive systematic review and meta-analysis by Hinkle et al. (2024) found that 46.7% of P-AT trials reported no AE data whatsoever.

While this rate of reporting appears as good as, or perhaps better than, clinical trials of health interventions generally (Coates et al., 2018; Golder et al., 2016; Lodewyk et al., 2023), psychedelic science should aspire to *good* practice rather than being satisfied with poor practice because it is commonplace (Jacobs, Earp, et al., 2024).

This pattern of incomplete reporting is corroborated by other attempts to collate findings from the field. Breeksema et al. (2022) identified three contemporary pilot studies of classic psychedelics with no AE reporting at all, while noting that among studies that did report AEs, the reporting was often inconsistent and poorly defined. A meta-analysis of AEs in psilocybin P-AT RCTs by Yerubandi et al. (2024) had to exclude more trials than it included because they lacked sufficient AE data.

Hinkle et al. found that, even among the contemporary studies of P-AT that did report adverse events, approximately 70% were not systematic in their approach, recording only suspected 'adverse drug reactions' rather than adverse events properly understood (i.e., any undesirable event, regardless of causality assessment). Current approaches to AE reporting in P-AT trials are typically limited in several ways. Some rely solely on spontaneous patient reporting and open questions, which are unlikely to capture the full spectrum of adverse events (Allen et al., 2018). Even when AEs are recorded, crucial information about their severity and onset timing is frequently omitted, hampering adequate interpretation of the reported events (Breeksema et al., 2022).

7.2.2. Limitations in trial design

These reporting gaps are further compounded by familiar limitations in P-AT trial design that restrict our understanding of P-AT's true risk profile. Most likely due to the resource intensiveness of the intervention, clinical trials of P-AT are typically small (Van Elk & Fried, 2023). While small sample sizes are common in early-phase research, they threaten the validity of statistical conclusions. *Per* Breeksema et al. (2022), small sample sizes can mask AEs that occur at lower frequencies, making it difficult to extrapolate safety data to the population at large. This limitation is particularly pertinent for rare but potentially serious adverse events, which might not manifest in small cohorts but would become apparent when P-AT is applied to a broader base of patients. If some AE occurs in 2% of patients - a non-negligible, clinically relevant risk - there is a 36.4% chance that a trial of 50 participants would not detect this event at all. Additionally, follow-up periods tend to be brief (a median of 3 months, according to Hinkle et al., 2024), limiting our ability to assess long-term safety.

Another significant issue in current P-AT research is the unrepresentative nature of trial participants relative to the clinical population at large. As well as recruiting ethnically and socioeconomically

homogeneous study populations, a consideration I turn to later, many P-AT trials employ strict exclusion criteria, often barring individuals with co-morbidities or complex clinical presentations. While this approach is not uncommon in clinical research to minimise confounding variables, it can result in trial populations that poorly represent real-world patients. As Palk et al. (2020, p.164) observe in the context of inpatient psychiatric research, there is a risk that the "interests of [patients], in terms of their right to participate in research, may be subsumed by the pragmatic goals and interests of institutions." Such exclusions may lead to underestimation of AEs in real-world applications, as patients with more complex clinical profiles may experience different risk profiles. Laudable exceptions to this practice (e.g., (Aaronson et al., 2024; Rosenblat et al., 2024) are extremely rare in the field[39].

Finally, P-AT trials frequently include a high proportion of participants with prior psychedelic experience. While this may be seen as a positive factor in terms of securing patient comfort and informed consent (and was a requirement of some IRBs for early studies), it poses a challenge for accurately assessing the risk profile of P-AT in psychedelic-naive individuals. Some evidence (Aday et al., 2021; Haijen et al., 2018) suggests that individuals with prior psychedelic use tend to report less severe challenging experiences during subsequent psychedelic sessions, jeopardising the external validity of P-AT trials.

7.2.3. Lessons from historical parallels

The challenges in capturing AEs in P-AT reflect a deeper problem in clinical research and practice. Our measurement frameworks can systematically blind us to important therapeutic outcomes. When we uncritically apply standardised measures and procedures in novel frameworks, we risk missing not just benefits but also adverse consequences. Two other examples from psychiatry illustrate different aspects of this risk. DBS research shows how standard clinical measures can fail to capture what is salient to patients and those in their lives, while the evolution of the use of Ritalin in treating ADHD demonstrates how measurement frameworks can themselves reshape treatment approaches, potentially diminishing important therapeutic dimensions.

[39] This pattern reflects the 'protection-inclusion' dilemma discussed in Chapter 6, where legitimate safety concerns must be balanced against ethical imperatives for equitable access. This weighting of methodological purity (or, abundance of caution) over ethical inclusivity is particularly troubling given that the most clinically relevant populations (those with treatment-resistant conditions and complex needs) are paradoxically the least studied. Future research would benefit from risk-stratified inclusion models that maintain safety while improving representation. While there are sound methodological and safety reasons for initial caution with novel interventions like P-AT, a gradual, evidence-based expansion of inclusion criteria will be necessary to understand the treatment's true risk profile across different populations.

DBS research provides a relevant demonstration of how standardised measures can miss crucial outcomes. In a mixed-methods study of DBS patients and their caregivers, Lewis et al. (2015) found that the significant changes in personality discussed during semi-structured interviews went completely undetected by a battery of validated quantitative measures. These are not minor oversights, but fundamental failures to capture what Witt et al. (2013) described as the '"sometimes more poorly defined and perhaps more difficultly quantified changes experienced by...patients following the procedure." Notably, these personality changes following DBS sparked significant neuroethical debate about the intervention's permissibility (Boulicault & Emmanuel Brown, 2018; Gilbert et al., 2021; Maslen et al., 2018; Pugh, 2020), with scholars questioning, among other issues, tensions between potential therapeutic benefits and concerns about alterations to identity and autonomy. Particularly relevant for P-AT, Thomson et al. (2023) documented how post-DBS changes led to shifts in relationship dynamics that standard clinical measures missed entirely—precisely the kind of outcomes highlighted in Aaron's case.

Like the participants in the DBS study of Thomson et al., Aaron experienced significant shifts in his interpersonal dynamics following treatment that went entirely unrecorded in trial measures. While his depression symptoms dramatically remitted, the psychedelic experience catalysed insights about his relationship that brought previously suppressed dissatisfactions "suddenly in [his] face," creating tensions with his partner. These relationship challenges dominated his post-trial emotional life, yet remained invisible to standard outcome measurements. The historical evolution of the use of stimulant drugs to treat ADHD offers another instructive parallel (Singh, 2002; Whitaker, 2010). Initially positioned as adjuncts to help children become more receptive to psychotherapy, stimulants gradually shifted from facilitating a broader therapeutic process to becoming the primary intervention. As easily quantifiable measures like classroom behaviour and academic performance became the dominant metrics for assessing treatment success, more complex dimensions of children's experience, including emotional development and long-term wellbeing, were gradually sidelined (Rafalovich, 2004). Even potentially concerning changes, such as emotional blunting, increased anxiety, and shifts in self-concept, were often reframed not as adverse effects of medication, but as evidence that the underlying disorder needed continued pharmacological management.

This history highlights a broader pattern in psychiatric treatment: measurement frameworks do not simply record outcomes, but can actively reshape how conditions are conceptualised and treated (J. E. Davis, 2020). The challenges in capturing AEs in P-AT reflect this deeper issue of implicit normativity—how unstated value judgments shape research. What we measure as 'adverse' embodies assumptions about which outcomes matter. Complementing this is what might be termed 'technical closure'—an overreliance on narrow metrics that obscures broader impacts. Aaron's case exemplifies this problem: his relational

difficulties dominated his emotional life yet went unrecorded—not because they were unimportant, but because they fell outside the technical frame of what counts as an 'adverse event'.

As such, decisions about how AEs are defined and recorded are not just technical choices, but have the potential to influence how the field develops. The current, pharmacological focus on measurable adverse drug reactions is silent about salient and consequential dimensions of the patient experience, which risks misrepresenting both the risks of P-AT and the relevance of psychological processes to its potential.

7.3 Ethical Considerations

The inadequacies in current approaches to managing AE in P-AT have bioethical importance that extends beyond concerns about regulatory compliance or methodological rigour. At its core, comprehensive and accurate AE assessment in P-AT serves three fundamental ethical functions: supporting beneficence and nonmaleficence through informed risk-benefit analysis, protecting patient autonomy by enabling genuine informed consent, and promoting equitable access to treatment.

7.3.1 Supporting beneficence and non-maleficence through accurate risk assessment

Both seeking to benefit patients, and taking reasonable steps to prevent harm, require a thorough understanding of the risk:benefit profile of a medical intervention. As such, our current inability to adequately capture and assess adverse consequences in P-AT compromises efforts to fulfil these basic ethical imperatives. As the review and meta-analysis by Hinkle et al. (2024) suggests, the field is some way away from comprehensive documentation of potential harms, accurate assessment of their frequency and severity, and an understanding of contributing factors that can support harm mitigation measures. For adverse consequences outside of the scope of standard pharmacological AE reporting, such as Aaron's relational difficulties, our current practices fail on all counts - these difficulties weren't documented, their frequency across trials is unknown, and because of their invisibility to reporting measures, we lack understanding of risk factors that might predict such outcomes.

Without comprehensive AE data, we cannot properly evaluate whether offering P-AT in a specific context upholds our duty to benefit while avoiding harm. At the granular level of individual patient care, clinicians must be equipped with accurate information to make informed decisions about whether P-AT is appropriate for specific prospective patients. At the policy and practice level, as P-AT moves closer to

regulatory approval, policymakers and clinical guideline developers need accurate risk:benefit information to determine its appropriate place in treatment algorithms. Whether P-AT should be considered as a first-line treatment for Major Depressive Disorder, for example, or reserved for treatment-resistant or difficult-to-treat cases, hinges largely on understanding its risk:benefit profile relative to other clinical options.

7.3.2 Enabling genuine informed consent

Clinicians and policymakers are not the only stakeholders who are dependent on accurate information on the risks, as well as the benefits, of P-AT. Respecting the autonomy of prospective patients themselves requires that they can make informed decisions about their medical care based on accurate information about their treatment choices. Current limitations in AE assessment and reporting therefore not only compromise beneficence and nonmaleficence obligations, but also threaten our ability to secure genuinely informed consent from prospective patients.

Consider Aaron's experience: his pronounced relational difficulties and challenges to his sense of self. The limitations of the case study approach mean we cannot definitively attribute these difficulties to his P-AT experience, nor estimate how common such outcomes might be. And current trial AE recording practices do not incorporate their detection. The field's current position effectively makes a default judgment that these outcomes are not salient enough to warrant systematic documentation and disclosure. But this judgment should, at least partially, belong to prospective patients, rather than simply trial designers and regulators: it does not stretch the imagination to consider that some prospective patients, shown experiences like Aaron's, could consider their consent inadequately informed if such possibilities had been withheld. That Aaron's post-trial challenges fall outside of conventional definitions of AEs is an irrelevant distinction from the perspective of patient autonomy. What matters for informed consent is not whether an outcome meets regulatory criteria for an AE, but whether knowledge of its possibility would materially affect patient decision-making[40].

However, the relationship between AE reporting and informed consent takes on particular complexity in P-AT due to the suggestibility-enhancing properties of psychedelics (see §2.2.1.1; Carhart-Harris et al., 2015; Duerler et al., 2020; Devenot et al., 2022a). Devenot and colleagues demonstrated that material

[40] This much remains true regardless of how definitive the causal relationship is between P-AT and outcomes like Aaron's relationship difficulties. If there is evidence of an association between P-AT and certain psychosocial outcomes, and a plausible mechanism exists by which the intervention might contribute to these outcomes, this constitutes material information that should be disclosed to support autonomous decision-making, even if the causal relationship cannot be definitively proven.

introduced to participants before their P-AT psychedelic experience can impact both the content of the acute experience itself, and longer-term outcomes. In psychedelic research, this is intuitively graspable through the concept of 'set', the conglomeration of beliefs, attitudes, expectations and intentions at the time of psychedelic administration. But the influence of mindset on negative outcomes is also well-documented in non-psychedelic interventions as the nocebo effect (Colloca & Miller, 2011), wherein patient expectations, including those shaped by the informed consent progress, can manifest adverse consequences even where a patient is given an inert intervention (Faasse & Petrie, 2013).

7.3.3 Promoting health equity

The imperative to promote health equity is likewise made more difficult by the current state of our understanding of AEs in P-AT. As established in the previous chapter, a patient's matrix has the potential to shape their therapeutic trajectory, including by providing a buffer and social support to navigate challenges during and after treatment. But social and economic disadvantage typically affects both the availability and quality of support systems (Turney & Harknett, 2010), potentially creating a compound vulnerability in which some patients are simultaneously more at risk of AEs and less equipped to manage them when they occur.

Evidence from population-level studies suggests that benefits of naturalistic psychedelic use may be attenuated in minority groups (Jones, 2023; Jones & Nock, 2022b; Viña & Stephens, 2023). While we must be cautious about extrapolating from naturalistic to clinical contexts, these findings raise pressing questions about differential risk profiles across populations. However, current trial practices severely limit our ability to assess any such differences. The marked lack of ethnic and socioeconomic diversity in P-AT trials (P. Hendricks, 2024; M. E. Hughes & Garcia-Romeu, 2024; Michaels et al., 2018) means that even if adverse events are comprehensively recorded, the resulting data may not reflect the risk profile for underrepresented populations.

Understanding whether and how risks vary across populations is crucial for ensuring equitable access to safe and effective treatment. With current trials too small for meaningful subgroup analyses, and samples largely homogeneous, we remain largely in the dark about differences that could inform strategies to promote equitable access while maintaining appropriate safety standards. Having established the ethical implications of inadequate AE reporting, I now turn to examine three distinctive challenges that make the assessment of AEs in P-AT particularly complex compared to conventional psychiatric interventions. These challenges —the subjective interpretation and temporal complexity of psychedelic experiences, the hybrid nature of P-AT as both a pharmacological and psychotherapeutic intervention, and the crucial

role of extrapharmacological factors— encourage us to reconsider how adverse events are conceptualised, measured, and reported.

7.4 Three Distinctive Challenges in P-AT AE Assessment

7.4.1 Subjective interpretation of experiences and temporal complexity

The assessment of adverse events in P-AT faces two distinct but related challenges: the inherent ambiguity and subjectivity of many psychedelic-related experiences, and the way their interpretation can shift over time as psychological processes unfold. Unlike conventional pharmacological side effects such as headaches or nausea, which are consistently experienced as unwanted, psychedelic experiences and their aftermath often defy simple categorisation as either adverse or beneficial. Standard frameworks, developed for conventional pharmaceuticals, assume a relatively straightforward relationship between adverse events and harm, but psychedelic experiences challenge this framework: experiences that are acutely distressing may be retrospectively valued as therapeutic.

This interpretative complexity is not unique to psychedelic therapy. In the treatment of anorexia nervosa (AN), weight restoration—a central therapeutic goal—is often experienced as profoundly distressing by patients, despite being a necessary health outcome (Vitousek et al., 1998). While clinicians may see weight gain as an unambiguous marker of progress, many patients initially perceive it as a loss of control, an attack on their identity, or even a harm rather than a benefit (Serpell et al., 1999). Similarly, in P-AT, certain experiences—such as Eleanor's heightened emotional sensitivity or Helen's distressing insights—may initially be framed as aversive, only to later be reinterpreted as part of a meaningful therapeutic process, or vice versa.

This ambivalence is easy to find in the psychedelic literature. In their investigation of side-effects reported one day after LSD administration, Calder & Hasler (2024) found that "many potentially uncomfortable side-effects received positive average ratings, such as anxiety and crying" (p. 262). More broadly, challenging experiences or 'bad trips' during acute drug effects can be "ambiguous, subjective, context dependent, and subject to interpretation" (Breeksema et al., 2022, p.1112). Paradoxically, these ostensibly negative experiences are frequently - though far from universally (Simonsson et al., 2023) - seen retrospectively as therapeutic or ultimately beneficial by participants (Barrett et al., 2016; Carbonaro et al., 2016; Johnstad, 2021). In Carbonaro et al.'s (2016) study of challenging psilocybin experiences, for example, 84% of 1993 respondents reported benefiting from their difficult experiences,

even when these ranked among the most challenging of their lives. In the Global Ayahuasca Survey (n=10,836), while 56% of respondents reported experiencing adverse mental health effects in the weeks and months after ceremonies, 87% viewed such effects as "part of a positive process of growth or integration" (Bouso et al., 2022). And yet, in many clinical P-AT trials such experiences are reported as AEs - agitation; despair, distress or fear; tearfulness; or panic (Hinkle et al., 2024). The self-same AE during acute drug effects might be seen as negative in the acute or sub-acute phase, but as positive when they have been psychologically processed (Gashi et al., 2021). This raises not only a temporal complication, but also a question about the possible function of challenging experiences within therapeutic trajectories, a matter I return to below (§7.4.2).

Eleanor's experience of increased emotional sensitivity following her trial participation illustrates this ambivalence. While this heightened sensitivity allowed her to better discern which relationships were energising versus draining, and to develop a more authentic way of being in the world, it was simultaneously overwhelming, requiring ongoing navigation: "Sometimes I think I just need to go back on the [SSRIs] to mute some of this, because it's just intense - you know, it can be quite overwhelming at times...sometimes it just feels like I'm feeling too much." The same experiential outcome - increased emotional sensitivity - resists classification as either adverse or beneficial, instead existing as both simultaneously.

This ambivalence highlights a fundamental tension between the need for systematic measurement and the reality that consequential outcomes for patients may resist quantification. As one P-AT trial participant articulated when asked if the treatment 'worked': "...when my depression reemerged—and it did—it wasn't that it had gotten any smaller, but rather, that the space around it had grown much bigger" (R. Peterson, 2020). Such nuanced changes in *relationship* to symptoms, rather than symptoms *per se*, may be particularly significant while remaining invisible to standard metrics.

Although her vision of her own funeral was distressing, Helen positively evaluated her second psilocybin experience: a vividly felt sense of how high the stakes were in relation to her disordered eating behaviours became, for her, a welcome source of motivation for change. When that motivation later proved insufficient to sustain behavioural changes, the same insight became a source of heightened internal conflict - "it's almost made it more painful because I've got both thoughts stronger." At the time of our interview, she occasionally felt that "I wish I'd never done it. It was just not worth it."

These complexities challenge conventional risk-benefit analysis, and current reporting frameworks fail to capture the ambivalent nature of certain post-trial changes . An intervention's effects may not be fully apparent until months after treatment, as participants work to integrate insights and navigate changes in

their lives. Standard approaches to AE reporting, typically focused on acute and short-term effects, may miss important longer-term outcomes that emerge through this process of integration and meaning-making.

7.4.2 Hybrid nature: regulatory and practical implications

The inadequacy of current approaches to reporting AEs in P-AT stems in part from its hybrid nature as both a pharmacological and psychotherapeutic intervention. Integration of the distinct norms governing AE assessment within each domain is a nontrivial task, reflective not only of a 'merely' practical challenge, but also a conceptual tension about what constitutes an AE in P-AT.

While the regulatory landscape necessarily shapes trial design and reporting (as noted in §7.1), its impact on AE assessment goes beyond procedural requirements. The conceptual frameworks used by regulatory bodies like the FDA, developed for conventional pharmaceutical trials, struggle to accommodate interventions that intentionally engage with challenging psychological material as part of their therapeutic mechanism. These agencies' expertise in evaluating discrete pharmacological interventions has created assessment paradigms that, while appropriate for conventional drugs, risk mischaracterising or overlooking crucial aspects of hybrid interventions like P-AT. For instance, in a trial of psilocybin-assisted therapy for major depressive disorder, Raison et al. (2023) define an AE as such: "any untoward medical occurrence in a research participant, whether or not considered drug related, which occurs during the conduct of a clinical trial. Any change in clinical status, ECGs, routine labs, x-rays, physical examinations, etc., that is considered clinically significant by the PI is considered an AE" (supplementary materials). Such a definition proves particularly unhelpful when considering psychotherapies. Negative outcomes following psychotherapy can and do extend beyond the *medical* (consider Aaron's experience), and it is less straightforward to characterise an event as *untoward* (as outlined in the previous section). Moreover, even if we strike the term 'medical' from the pharmacological understanding of AEs, and record all untoward occurrences during psychotherapy as AEs, we risk drawing a false equivalence between physical or biological interventions and those that have a psychosocial character.

Unlike physical interventions such as surgery, where the patient is a passive recipient of treatment, psychotherapy requires active engagement with challenging emotional material. The distress that can emerge in therapy is not merely a side-effect to be catalogued, but often carries deep personal meaning that must be processed as part of therapeutic growth. Ratings of psychological distress as a course of psychotherapy progresses may be sanitised in clinimetric scores, but distress is almost always

experienced as 'thick' rather than 'thin' - embedded with personal significance rather than merely symptomatic[41].

This process is clearly seen in exposure therapy for PTSD, where engaging with distressing memories or material is not an unfortunate side-effect but a necessary component of treatment, with greater emotional engagement with memories associated with improved outcomes (Rauch et al., 2012). In this way, psychotherapy is more akin to physical therapy than massage - some discomfort may be integral to the healing process.

Something similar may be at work for P-AT, where challenging experiences during acute drug effects are frequently reframed as beneficial in retrospect (Carbonaro et al., 2016; Barrett et al., 2016). While this doesn't mean that every difficult experience serves a therapeutic purpose (Simonsson et al., 2023), it suggests that frameworks for identifying and reporting adverse events must be sensitive to the complex relationship between challenging experiences and therapeutic change. As Breeksema et al. (2022) observe, "framing 'anxiety' as adversity may prompt patients to try and avoid difficult feelings and thoughts rather than engaging with them as part of a therapeutic process" (p.1112).

The regulatory landscape has contributed to an emphasis on pharmacologically-oriented AE reporting in P-AT trials, with some actors even attempting to minimise or deny the psychotherapeutic component entirely (Goodwin et al., 2024; Kupferschmidt, 2024). The FDA has characterised psychotherapy within P-AT as an "additional variable [that] both complicates the assessment of effectiveness and presents a challenge for any future product labelling" while noting that the "contribution of the psychotherapy component to any efficacy observed with psychedelic treatment has not been characterized" (U.S. Food and Drug Administration, 2023). This regulatory stance reinforces the emphasis on pharmacological effects, potentially marginalising the psychotherapeutic dimensions that may be essential to both benefits and risks.

However, as evidenced by the experiences of Aaron, Eleanor, and Helen, this narrow focus risks missing crucial dimensions of the P-AT experience that can significantly impact participants' lives. A more nuanced framework is needed—one that can accommodate both the pharmacological and psychotherapeutic aspects of P-AT while remaining sensitive to the distinct ways in which interpretations of experiences can shift as psychological processes unfold (See §7.5).

[41] A psychodynamic frame can further highlight this. Consider psychological *defences*: Many forms of psychopathology can be understood as the result of maladaptive patterns developed to protect against emotional pain. If you want to address the difficulties that come from these patterns, some exposure to the very pain they guard against may be necessary.

As explored in Chapter 2, competing models of health suggest different criteria for evaluating adverse events. While the medical model prioritises symptom reduction and physiological markers, holistic and social models would encompass impacts on meaning, purpose, and relationships—precisely the dimensions where Eleanor and Aaron experienced challenges. Current AE frameworks implicitly privilege the medical model, rendering invisible outcomes that would be central from alternative perspectives. This conceptual misalignment, not merely inadequate implementation, underlies many of the field's current shortcomings in capturing the full spectrum of consequential outcomes.

The crux of overcoming this challenge will be establishing how to systematically document adverse events while remaining sensitive to the potentially therapeutic role of challenging experiences. A well-established principle in AE reporting - to document all untoward events first, and establish causal relationship to treatment later (A. L. Peterson et al., 2013) - can serve some function here. This approach has proven valuable for regulatory oversight, with the cardiovascular risks of COX-II inhibitors, for instance, was only identified by systematic documentation of events across multiple trials (A. L. Peterson et al., 2013). Such systemic thinking would be particularly useful in P-AT where trials are too small.

However, the comparative complexity of P-AT as a hybrid modality suggests the need for a layered approach to documentation that can serve both regulatory and therapeutic needs. The first layer involves the systematic recording required by regulators; i.e., the comprehensive documentation of all potential AEs. This creates the empirical foundation needed for safety and regulatory review, and for multiple layers of subsequent analysis: assessment of causality, evaluation of therapeutic value, and examination of how interpretations evolve over time. Doing so will help avoid the premature exclusion of important outcomes based on their therapeutic value.

7.4.3 Role of extrapharmacological factors

Just as extrapharmacological factors (e.g., set and setting, therapeutic alliance) can impact positive outcomes following psychedelic administration (Carhart-Harris et al., 2018; Levin et al., 2024; Murphy et al., 2022), there is growing evidence that contextual factors influence adverse outcomes. Bremler et al.'s (2023) case analysis of people experiencing long-term negative psychological responses to psychedelics (n=15) identified contributory factors including stressful life circumstances and lack of social support during or after the experience.

These contextual influences, considered more fully in the previous chapter, are evident in the experiences of my interviewees. Eleanor's supportive husband played a crucial role in helping her navigate periods of intense emotional sensitivity, encouraging her to persist rather than return to SSRIs when challenged. In contrast, Aaron's isolating environment and complex relationship dynamics served as additional sources of distress. As he reflected, 'if she had…just been there and believed [in] me, it would be a completely different world right now." Helen's case particularly highlights how inadequately prepared support systems, despite good intentions, may fail to sustain therapeutic momentum or help process challenging material.

This introduces an additional layer of complexity to establishing the AE profile of P-AT. While extrapharmacological factors are widely acknowledged as important mediators of patient experience and outcomes (Pronovost-Morgan et al., 2024), their systematic documentation in trial publications remains inconsistent and often superficial (Brennan et al., 2023). This gap between theoretical recognition and methodological practice creates a significant blind spot: the field accepts that these factors matter, but lacks the granular detail needed to understand precisely their influence on adverse outcomes. This is not a trivial point: with developers trying to make P-AT interventions less resource intensive (principally by reducing therapist time, see §1.5.1), there is a real risk that future, more streamlined therapy packages with reduced extrapharmacological support will lead to increased AE rates.

To mitigate this, it is essential to establish the 'minimum viable context' necessary for safe and effective treatment during the acute intervention phase and the 'minimum viable matrix' that buffers against adversity post-acutely. *Per* the previous chapter, key features of participants' socio-relational 'matrices' are not systematically tracked, limiting our ability to assess their influence on outcomes or to identify individuals for whom certain lifestyle factors may contraindicate treatment. Addressing this gap will require targeted qualitative research, specifically recruiting participants who have experienced negative outcomes, to better understand the conditions under which adverse events arise and how they can be minimised without rendering the treatment prohibitively resource-intensive.

The challenges of AE reporting in P-AT are driven by conceptual and practical tensions that standard pharmacological frameworks fail to adequately address. Any comprehensive approach must solve three interconnected problems:

First, the subjective and temporally complex interpretations require multiple assessment timepoints that can track how outcomes evolve and are reinterpreted over time, moving beyond a simple classification

to capture experiences that may be simultaneously challenging and beneficial, or shift from therapeutic to adverse (or vice versa) during integration.

Second, as an investigational drug intervention, P-AT requires systematic documentation of medical adverse events, from cardiovascular changes to psychiatric symptoms, to establish its basic safety profile. However, this pharmacological lens must be complemented by frameworks that can capture the broader psychosocial impacts that emerge through treatment. P-AT needs assessment tools that can distinguish between different categories of challenge: untoward medical occurrences, expected therapeutic difficulties that may ultimately serve a salutogenic function, and broader psychosocial impacts that can significantly affect patients' lives but which fall outside of conventional medical frameworks. This distinction is critical - while some challenging experiences may serve therapeutic functions when properly supported, others may represent genuine adverse outcomes requiring intervention. The field needs clear criteria, grounded in both empirical evidence and therapeutic theory, to distinguish between these categories and identify when ostensibly therapeutic challenges have become harmful[42]. Like Aaron's relationship difficulties or Eleanor's sometimes overwhelming emotional sensitivity, these latter challenges may prove highly consequential for participants while remaining invisible to standard reporting measures.

Finally, the acknowledged role of extrapharmacological factors in P-AT outcomes needs to be matched by systematic assessment and recording of these factors as standard to establish their influence on consequential, negatively valenced sequelae.

7.5 Towards Better Practice

7.5.1. New models of assessment

Historical precedents demonstrate how dominant therapeutic models have been successfully challenged. The disability rights movement contested how medicine conceptualises 'normal functioning', highlighting how medical models obscure the role of social factors in creating impairment (Barnes et al., 2020). Similarly, the palliative care movement established that quality of life

[42] An important potential implication to carry over from Chapter 6, is that the assessment of adverse events cannot be separated from the matrix in which they emerge. The same experience, like Eleanor's heightened emotional sensitivity or Aaron's relationship insights, may be therapeutic in supportive matrices but harmful in those lacking adequate resources. Eleanor's husband provided crucial support that helped her navigate overwhelming emotions productively, while Aaron faced destabilisation when his insights emerged in a relationship context where such conversations were threatening or taboo.

considerations were as important as survival metrics, substantially reshaping end-of-life care (Saunders, 2001). These precedents suggest that questioning conventional metrics of therapeutic success and harm can lead to more patient-centred clinical practice. The inadequacies in AE reporting are not merely technical problems awaiting technical solutions but reflect deeper questions about what we value in mental healthcare and how we conceptualise both healing and harm.

Given the distinctive outcomes that can follow P-AT treatment relative to standard psychopharmacological interventions, as well the challenges outlined above, better understanding the rate and nature of AEs will be supported by the development of intervention-specific instruments for AE recording - cf. the *Ketamine Side Effect Tool* (Short et al., 2020). Two candidate approaches proposed in 2024 - the *Psychedelic Assisted Therapy Adverse Events assessment protocol* (PATAE, Palitsky et al., 2024), and the *Swiss Psychedelic Side Effect Inventory* (SPSI, Calder & Hasler, 2024). While neither fully resolves the tensions identified above, both incorporate psychedelic-specific outcomes, and each makes valuable progress in different domains.

Palitsky et al. (2024) offer the PATAE as a *framework* for exploring adverse events, rather than a refined tool, and it has yet to be validated in a patient population. Largely excluding physiological, as well as physical and mental health outcomes (presumably because these can be tracked with extant tools), the PATAE focuses on sociocultural, psychospiritual, interpersonal, behavioural, psychotherapy-related, affective, cognitive, and metacognitive, and perceptual AEs (p.694). Concerned with the power dynamics at play within P-AT, and the risk of patients failing to declare side-effects ("patients may not independently consider an even worth reporting, or may not want to report negative experiences…out of concern for speaking ill of the treatment or treatment team", p. 693), Palitsky et al. reject both open-ended questions and spontaneous patient reports which, when used alone, have failed to capture the full range of AEs. Sensitive to both the complicated the temporal complexity of P-AT AEs, and the subjectivity of interpretation, the PATAE advocates for regular and repeated assessments over at least six months, as well as prioritising patient appraisals and narratives about challenging or negative experiences, noting that "a clinician's determinations as to whether the patient's distressing experience subserves a therapeutic gain…is a separate question" (p.693). As such, it frames items in terms of subjective distress, e.g., "*My beliefs about the world and my place in it have changed in a way I find upsetting*" (Palitsky et al., 2024; supplementary materials).

The SPSI, by contrast, is a validated and interdisciplinary expert-assessed instrument which amalgamates items principally related to psychedelic-specific medical and psychiatric AEs, with a limited number of the broader challenges reported in the literature ("Feeling lonely, isolated, or

alienated from others", "Distress related to your understanding of reality or the meaning of life"; Calder and Hasler, 2024; supplemental materials). The SPSI would not, for instance, register the challenges faced by Aaron or Eleanor, although these may be highly relevant for judging outcomes from treatment. Although it asks a limited number of questions about the broader impacts of P-AT, which may be negative, it concludes with an open-ended item asking for self-report of any other side-effects. Importantly, each item is accompanied by scores for severity, patient-perceived likelihood of a causal connection to treatment[43], and the impact (negative, beneficial, neither, or both) of the outcome on their lives.

Evaluating these tools against the challenges identified above reveals complementary strengths and limitations. Both make progress towards capturing the complexity of patient experiences of, and after, P-AT, as seen through examining the three levels of assessment needs flagged in the previous section: pharmacological safety, psychotherapeutic process, and psychosocial impact.

At the pharmacological level, the SPSI's validated items provide essential coverage of medical and psychiatric AEs needed for basic safety monitoring. However, the PATAE's deliberate exclusion of these outcomes, while understandable given existing tools, means it cannot serve as a standalone solution for safety monitoring in an investigational drug intervention.

At the psychotherapeutic level, both tools acknowledge the temporal and subjective complexity of P-AT experiences, though in different ways. The PATAE's requirement for repeated assessments over six months allows for the tracking of how experiences and interpretations evolve during integration - crucial for cases like Helen's, where insights deemed initially beneficial become sources of heightened adversity over time. The SPSI's emphasis on tracking the valence of outcomes, allowing experiences to be rated simultaneously as both beneficial and adverse, helps capture experiences like Eleanor's increased emotional sensitivity - therapeutically valuable, but sometimes overwhelming enough to make her consider returning to SSRIs.

[43] Some might question whether patients can accurately assess causal relationships between their experiences and the treatment. While patients clearly lack insight into neurobiological mechanisms playing out in their own body, the P-AT context differs from standard pharmacotherapy in important ways. The intensely meaningful, personally-relevant nature of psychedelic experiences often provides patients with unique perspective on how specific experiences during sessions connect to subsequent changes in their symptoms, relationships, or worldview. This doesn't constitute privileged causal knowledge in a strict philosophical sense, but rather represents valuable phenomenological data that complements clinical assessments. Patient attributions of causality should therefore be understood as important subjective reports rather than definitive causal claims—useful precisely because P-AT's therapeutic mechanisms appear to involve subjective meaning-making processes (Watts et al., 2017; Noorani et al., 2018)

The SPSI remains relatively, but not completely insensitive to changes in broader psychosocial and relational functioning. The single item in the SPSI for 'loneliness or isolation' reduces acknowledged social and interpersonal outcomes that are covered by seven items in the PATAE[44], potentially leaving out important texture needed to properly map out the spectrum of post-intervention experiences. While the PATAE's expansive coverage of this dimension represents important progress, there may be value in casting an even wider net: Having found negative effects on family functioning when one family member undertakes an individual psychosocial treatment, Szapocznik and Prado (2007) argue that these outcomes should be tracked as standard. An analogy to medicine is offered elsewhere (Feaster & Szapocznik, 2002) to justify this suggestion: evaluating biological interventions (i.e., pharmaceutical drugs) for safety typically involves testing for deleterious impacts on a panel of critical organ systems that are essential to wellbeing. Analogously, sociobehavioural interventions should be tested for deleterious impacts on social systems, such as the family, that are essential to wellbeing. Relative to both the SPSI and the PATAE, such a framework would better capture highly consequential challenging outcomes that do not fit conventional understandings of AEs, like Aaron's experience of relational tensions with both his spouse and his sober community. While these are well outside the pharmacological definitions of AE outlined above, they remain important for improving the field's, and prospective patients', understanding of the modality.

While these tools make valuable progress toward capturing P-AT's complexity, improved AE tools require direct input from patients who have experienced negative outcomes to ensure frameworks capture what matters most to those undergoing treatment. This process must avoid inadvertently privileging researcher perspectives over patient-relevant outcomes. Even well-intentioned measurement development can embed assumptions about which outcomes deserve attention, potentially perpetuating the very blind spots the field is trying to address.

7.6.2. Implementation

While improved assessment tools are crucial, their value depends on integration with appropriate trial methodology and response protocols. Several adaptations to standard trial design can support more comprehensive understanding of, and response to, adverse events in P-AT.

There is much room for improvement on recording and reporting practices, but the direction of that needed improvement is relatively clear: AE monitoring must be more frequent and systematic, and

[44] Namely, community strain, social disconnection, reduced social support, marital or romantic relationship strain, global relationship strain, dependence on others, and disruption in healthcare relationships.

extend to a longer follow-up time to accommodate the temporal complexity identified above. This monitoring should extend beyond the standard clinical measures necessary for regulatory compliance, to incorporate a broader range of domains of potential change, *per* Paltisky et al. (2024), as prespecified secondary endpoints. Ideally, this would be in the form of a standardised procedure across the field, although the adoption of a tool like PATAE will depend on its validation. There is a trade-off between more comprehensive assessment, and the constraints imposed by resource requirements and assessment burden: multiple comprehensive assessments over six months or more, while valuable, may be liable to create significant participant burden and increase drop-out risk, as well as straining trial budgets. A tiered assessment approach, where briefer screening tools trigger more comprehensive evaluation when warranted, combined with digital platforms for longitudinal follow-up, could be one avenue to reduce burden without overly compromising data quality. The strategic use of more qualitative assessment at key timepoints, rather than continuously detailed monitoring, may also help, providing phenomenological data about how adverse experiences and their interpretation evolve.

Some of the well-established calls to improve methodology in psychedelic science, including larger and more diverse samples that draw more from psychedelic-naive patients (Aday et al., 2022; Van Elk & Fried, 2023), will naturally improve our understanding of AEs. Where funding for larger trials may be limited, one alternative approach may be a more liberal approach to subgroup analyses, even in the absence of significant treatment x subgroup interactions. The utility of the convention to perform such analyses only when interactions are significant needs to be balanced against the potential value of identifying harm signals (Dimidjian & Hollon, 2010). This strategy is endorsed in relation to tracking psychotherapy AEs by Kazdin, (2007): “Rather than looking for main effects of an intervention and a uniform mechanism of change, we may need to identify and characterise subgroups, very much in the way that genetic researchers often profit from looking at special groups and individual outliers” (p.22). This may be particular germane for P-AT trials, which (i) may well be underpowered to detect all AEs, and (ii) are anticipated to have multiple mechanisms of action (Aftab & Stein, 2022; Van Elk & Yaden, 2022). By examining potential moderators of AEs, we may uncover important risk factors that could inform patient selection and care.

Trials should be designed with clear protocols for responding to identified adverse events in advance. Drawing on my reflections in Chapter 5, these may include guidelines for determining when additional integration support is warranted, criteria for referral to outside care, and processes for documenting resolution attempts. As evidenced by Helen's case, leaving participants to navigate post-trial challenges alone can compound initial difficulties.

Equally important is the development of guidelines for communicating potential AEs to prospective patients. Such guidelines are likely needed to strike the balance between providing comprehensive information to allow properly informed consent and thereby protect autonomy; and minimising nocebo effects, given the heightened suggestibility associated with psychedelic administration, in order to respect the principle of nonmaleficence. More carefully attending to the 'framing' of AE discussions ("you have a 90% chance of *not* experiencing x"; rather than "you have a 10% chance of experiencing x") may be one route forward here (Faasse et al., 2019). However, this approach intersects with ongoing philosophical debates about informed consent. Some argue that such framing effects fundamentally undermine valid consent, as patients may consent under one description, but dissent under a logically equivalent alternative (Hanna, 2011). Others maintain that consent remains valid despite framing effects, provided the informational content remains equivalent (Director, 2024). Further conceptual work is needed within the context of P-AT, which has several features that complicate the ethical calculus of balancing disclosure obligations against nocebo risks: the suggestibility-enhancing quality of psychedelics that may amplify framing effects (§2.2.1.1), the meaning-laden nature of psychedelic experiences means that patient expectations might shape core therapeutic processes (Devenot et al., 2022a), and the reality that, unlike conventional pharmacotherapy for which effects typically subside after discontinuation, patients cannot opt out of potentially challenging psychological processes once initiated by P-AT (§5.3.2).

Finally, trial teams should incorporate systematic tracking of extrapharmacological factors that may influence AE risk. This includes documentation of preparation time, therapeutic alliance measures, and assessment of participants' social support systems. Understanding how these contextual elements influence outcomes is crucial for identifying 'minimum viable contexts' for safe treatment delivery without making the entire package prohibitively resource intensive. This data can help establish evidence-based guidelines for the necessary support structures while maintaining cost-effectiveness.

7.7 Conclusion

Our ability to fully understand - and thereby, maximally mitigate - the risks associated with P-AT is currently hindered by two distinct but related problems. Although they may fare no worse from other areas of biomedical research, P-AT trials frequently fail to systematically record AEs even by conventional standards. While this failure of scientific rigour must be addressed, even a perfect adherence to current frameworks would be insufficient, as the frameworks themselves prove inadequate for capturing the full range of consequential outcomes that can follow P-AT. In the absence of a more

thoroughgoing understanding of the risk:benefit profile, our ability to uphold obligations of beneficence and non-maleficence is challenged, and prospective patients are hampered from being adequately informed before providing consent for treatment. Just as DBS research discovered that standard measures systematically missed changes that patients and their families considered highly significant, P-AT research needs frameworks capable of capturing outcomes that matter deeply to participants but fall outside conventional medical metrics. This gap between conventional reporting and participant-relevant outcomes was made clear by the case descriptions. While Aaron's depression immediately went into 'full remission', the pharmacologically-oriented AE framework meant that the relational turmoil he experienced, despite being a significant aspect of his post-P-AT journey, went unreported by the associated trial publication.

The shortcomings of using a pharmacologically-oriented framework for AE assessment stem from three challenges. First, the temporal and interpretive complexity of psychedelic experiences demands an assessment approach that can capture how outcomes evolve and are reinterpreted through time: Eleanor's heightened emotional sensitivity and Helen's shifting relationship to her insights demonstrate how experiences can be simultaneously beneficial and adverse, or transform in perception from potentially therapeutic to adverse, as the integration process continues. Such complexity requires moving beyond simple classifications of outcomes as adverse or beneficial.

P-AT's hybrid nature as both pharmacological intervention and psychotherapeutic modality creates tensions between regulatory requirements and therapeutic realities. While systematic documentation of medical adverse events remains essential for establishing basic safety, this pharmacological lens must be complemented by frameworks that can capture the broader psychosocial impacts that emerge through treatment. A narrow focus on adverse drug reactions risks missing crucial dimensions of the P-AT experience that can significantly impact participants' lives.

Lastly, while extrapharmacological factors are acknowledged as important mediators of the patient experience, their systematic documentation in trial publications remains inconsistent and often superficial. This creates a significant blind spot: the field accepts that these factors matter but lacks the granular detail needed to understand their influence on adverse outcomes.

These challenges demand an approach to AE assessment that can both accommodate the regulatory requirements of drug development, and track the complex unfolding of psychological processes in the wake of psychedelic administration. Recent tools like the PATAE and SPSI represent an

acknowledgment within the field that AE assessment for P-AT needs to become more sophisticated. But truly comprehensive assessment will require broader theoretical work to establish how we should conceive of adverse events in interventions that intentionally engage with challenging psychological material as part of their therapeutic mechanism. By developing standardised, psychedelic-specific AE reporting tools, that permit a more nuanced understanding of how individuals integrate and interpret their experiences over time, the field can build an accurate understanding of P-AT's risk profile - an understanding for ethical clinical practice and responsible expansion of access.

8. Conclusion

8.1. From Patient Experiences to Ethical Insights

The research project that culminated in this thesis aimed to identify features of the patient experience of P-AT that might lead us to rethink how P-AT is currently conceptualised and delivered, particularly regarding harms, support needs, and emerging challenges. Through in-depth interviews with former trial participants and subsequent ethical analysis, I sought to uncover dimensions of the patient experience that might be overlooked in current research and practice frameworks yet are crucial for the ethical implementation of this novel therapeutic approach.

The case-based methodology employed throughout the thesis allowed for a deep examination of how ethical challenges emerge from the interaction between therapeutic mechanisms, trial practices, and lived experiences. Rather than imposing a unified theoretical framework, this approach created a 'case book' in the ethics of P-AT, allowing multiple dimensions of ethical significance to emerge organically from patient narratives. This methodological choice proved particularly valuable for examining a treatment modality that is well-recognised to be unusually sensitive to extrapharmacological factors.

The case study approach, while offering rich phenomenological insights, has acknowledged limitations. As I have emphasised throughout, the experiential insights offered by Eleanor, Helen and Aaron serve as ‘vouchers’ rather than ‘clinchers’ (Cartwright, 2007, 2018), offering valuable perspectives that merit attention without claiming definitive authority. The generalisability of findings from case studies is necessarily limited, and the route between the arguments developed here and wider implementation should proceed through more systematic empirical validation. Nevertheless, this approach enabled me to explore dimensions of P-AT that quantitative methods are liable to overlook – the temporal unfolding of patient experiences, the influence of the matrix, and the interplay between psychological processes and therapeutic structures.

In the absence of a unified theoretical framework, in this chapter I present the key findings of the thesis through a temporal lens that attends to both the ‘before’ and ‘after’ of P-AT treatment. It is striking that, for a modality that is acknowledged to be unusually context-sensitive, current frameworks often treat the intervention as temporally isolated – a discrete event bounded by protocol-defined endpoints, rather than a dynamic process embedded within patients’ ongoing lives. By examining how pre-existing matrices shape treatment trajectories, and how psychological processes initiated by P-AT continue to unfold beyond the formal end of treatment, I aim to highlight the limitations of this time-bounded

conception of P-AT. The chapter then explores broader implications of these findings, including their ethical significance, and specific recommendations for different stakeholders involved in P-AT research and implementation. Finally, I identify priorities for future research that could address critical gaps in our understanding while advancing ethically robust approaches to P-AT delivery.

This contribution, I hope, comes at an opportune time as the field moves ever closer to licensing and implementation. Although the US FDA rejected a licensing application for MDMA-AT last summer, other psychedelic drug developers paid close attention to this decision and have been amending their pipelines and approaches to avoid a similar fate. With Australia having licensed psilocybin-assisted therapy, Canada significantly expanding special access routes, and an ever-increasing number of US state-level initiatives to legalise P-AT (or P-AT-like services) that bypass FDA approval processes, we find ourselves at a crucial inflection point where decisions about implementation are liable to have lasting consequences for the field. The thesis' examination of patient experiences revealed important dimensions of P-AT that risk being overlooked in the rush to implementation, while offering concrete recommendations for protecting these elements within real-world healthcare constraints.

8.2. The Extended Temporal Landscape of P-AT: Key Findings

8.2.1. Before: matrices and pre-existing contexts

The analysis of participants' matrices demonstrated how pre-existing socio-ecological contexts have the potential to shape treatment trajectories in ways that current frameworks fail to capture. This influence manifests not merely as a background condition, but as an active determinant of therapeutic potential.

That social and environmental factors play a role in mental health is widely accepted - indeed, the biopsychosocial model emphasises that psychopathology emerges from and is maintained by the dynamic interaction of biological, psychological, and social factors. However, the matrix takes on particular salience in P-AT. The enhanced neuroplasticity following psychedelic administration creates a state of heightened environmental sensitivity — a vulnerability that researchers knowingly initiate. Moreover, if psychopathology emerged within a specific social-environmental context, returning to that context after treatment while in a state of enhanced plasticity creates distinct risks that warrant attention.

These considerations are particularly significant given typical practice in P-AT research. While P-AT trials employ strict exclusion criteria around medical and psychiatric conditions, they do not assess or

track features of participants' matrices. Many trials exclude prospective participants based on the psychiatric histories of first-degree relatives — a defensible precaution given the known genetic component of conditions like psychotic disorders that are liable to be precipitated or exacerbated by classic psychedelics. But the influence of family on mental health outcomes is not limited to genetic inheritance. Family life is typically a key contributor to environment, and in Chapter 6 I made the case that environmental factors can significantly impact someone's ability to benefit from P-AT. More broadly, there is growing evidence that the benefits of naturalistic psychedelic use may be attenuated in socially disadvantaged groups (Jones et al., 2024; Jones & Nock, 2022b; Viña & Stephens, 2023), raising pressing questions about differential risk profiles that the field has so far made only very limited in-roads to addressing.

While social support and access to supportive relationships are repeatedly associated with better outcomes across a range of mental health conditions, the matrix in P-AT encompasses more than just available support. Structural constraints that features of the matrix can impose —including discrimination, victimisation, and opportunities for gainful employment— are minimally assessed in P-AT trials, limiting our understanding of how pre-existing socio-ecological conditions might influence treatment outcomes.

8.2.2. After: extended integration and evolving meaning

The most striking evidence for P-AT's temporal complexity emerges in how therapeutic processes extend far beyond protocol-defined endpoints. Current trial frameworks, focusing primarily on acute drug effects and short-term clinimetric outcomes, give insufficient attention to the extended nature of psychological change following P-AT. The analytic chapters identified two ways in which this temporal myopia manifests.

Firstly, the interpretation and therapeutic impact of experiences during drug sessions can evolve significantly through time. Helen's vision of her own funeral best demonstrates this dynamic: initially experienced as difficult but potentially therapeutic, underlining the stakes of recovery from anorexia and providing motivation for change. Later, however, memories of this vision became a source of heightened internal conflict when that motivation proved insufficient to sustain change. This evolution challenges conventional approaches to outcome reporting, which typically assess outcomes as either beneficial or adverse at fixed timepoints.

The ambivalence of post-psychedelic changes further complicates the temporal landscape. Eleanor's heightened emotional sensitivity, for instance, represented both therapeutic opportunity and potential challenge, an ambiguity that could not be neatly categorised as either beneficial or adverse but rather required ongoing interpretation and navigation. Aaron's evolving insights about his relationship similarly defied simple categorisation, revealing how the meaning and implications of psychedelic experiences continue to unfold through time. Such experiences are neither static nor unidirectional but dynamic and contextually influenced.

Second, the psychological processes that are catalysed during P-AT can give rise to ongoing therapeutic needs that extend beyond trial endpoints. Unlike typical pharmacotherapies, with which treatment effects cease with discontinuation, P-AT intentionally initiates psychological processes that cannot be simply opted out of once begun just because a trial has reached its predefined endpoint. Helen's experience of feeling 'ripped open, left with all the mess and having to deal with it on my own' demonstrates how premature withdrawal of therapeutic support can leave participants struggling to process challenging material.

The significance of these extended processes as described by my participants is also evidenced by how frequently participants in other studies seek additional support following trial participation. In two trials of P-AT for depressive disorders that report this data, participants self-initiated further psychotherapy at rates of 26-33% within the first few months (Gukasyan et al., 2022; Carhart-Harris et al., 2018). Some researchers have responded by establishing independent, low-cost integration groups that regularly attract returning trial participants, tacitly acknowledging these ongoing needs. Encouragingly, in February 2025, Johns Hopkins announced the launch of a new clinic with a focus on treating those experiencing extended difficulties following psychedelic use (L. Smith, 2025), which will contribute to better understanding how to support those in need of longer-term support.

Finally, I made the case that a P-AT patient's matrix can continue to shape these extended psychological processes in important ways. Eleanor's supportive environment enabled her to navigate periods of heightened emotional sensitivity productively, while Aaron's isolating context and complex relationship dynamics created new sources of tension as he attempted to process insights about himself and his relationship. This ongoing influence of matrix factors underscores the inadequacy of viewing P-AT as a discrete intervention separable from patients' broader life contexts.

An expanded temporal outlook helps illuminate important patterns across seemingly disparate phenomena. The influence of pre-treatment matrices on outcomes, the evolving interpretation of acute experiences, and the extended nature of integration processes all point to the limitations of viewing P-AT in isolation from the broader context of a patient's life. Moreover, this temporal lens reveals how current approaches to trial design, adverse event monitoring, and post-trial support may systematically overlook crucial determinants of therapeutic outcomes.

8.2.3. Limitations of temporally myopic frameworks

While the acute drug experience undoubtedly represents a crucial component of P-AT's therapeutic action, and has understandably been the focus of considerable research attention, this thesis reveals that focusing on this phase to the detriment of others provides an incomplete picture. The temporal myopia of current frameworks persists partly due to regulatory requirements designed for conventional pharmaceuticals and partly due to methodological inertia within the field itself.

These limitations echo challenges faced during the first wave of psychedelic research, where attempts to fit psychedelic treatment into standard trial frameworks —exemplified by a study that strapped participants to gurneys and left them alone to maintain experimental control— ultimately proved inadequate. Such approaches fundamentally mischaracterise the intervention being studied by failing to recognise the distinctive features that make P-AT unlike conventional pharmacotherapies. This insensitivity to P-AT's distinctive characteristics not only compromises scientific understanding but also imposes costs borne by the participants themselves.

However, a crucial difference distinguishes then and now. Unlike early researchers who lacked broader theoretical frameworks to justify adapting trial designs, today's researchers have multiple lines of evidence supporting such adaptation, including research on psychedelics' enhancement of neuroplasticity and developments in biopsychosocial models of mental health. These theoretical developments support the position that adapting trial frameworks to better capture P-AT's complexity is not merely desirable but can be scientifically justified. Rather than compromising methodological rigour, such adaptation may be necessary for accurately assessing treatment effectiveness.

By acknowledging the extended temporal landscape within which P-AT operates, we can develop more sophisticated approaches to trial design, outcome assessment, and therapeutic support. This expanded temporal understanding raises significant ethical implications across multiple dimensions: it challenges

current conceptions of beneficence and non-maleficence by revealing previously overlooked risks and benefits; it questions whether current informed consent processes adequately communicate the full range of potential outcomes; and it raises justice concerns regarding who can access appropriate integration support. The following section explores these ethical dimensions in greater depth.

8.3. Ethical Significance of Key Findings

The analyses presented throughout this thesis have articulated several important ethical dimensions of P-AT research and implementation that are as yet underexplored by the literature. By recognising P-AT's distinctive features: its temporal extension, context-sensitivity, and the complexity of its outcomes, we can better understand the ethical landscape of P-AT, and the issues that need to be attended to as the modality develops.

8.3.1. Autonomy and informed decision-making

The complex and evolving nature of P-AT outcomes significantly impacts what genuine informed consent requires. Current limitations in AE reporting, as revealed in Chapter 7, compromise informed consent by failing to capture the full range of consequential outcomes that might influence participation decisions. Not only do current trials frequently fall short of systematic AE reporting (Hinkle et al., 2024), but when significant experiential dimensions like Aaron's relationship difficulties go unrecorded by standard measures despite dominating his post-trial emotional life, prospective participants lack critical information needed for autonomous decision-making.

I argue that what matters for informed consent is not whether some outcome meets regulatory criteria for an adverse event, but whether knowledge of its possibility would materially affect patient decision-making. The temporal complexity of psychedelic experiences, interpretations of which can shift significantly over time, further complicates this process, requiring more nuanced approaches to consent that acknowledge how experiences initially perceived as adverse may later be reinterpreted as therapeutic (or vice versa).

The availability of psychedelics through unregulated channels creates a particular ethical hazard I identified in Chapter 5. By demonstrating efficacy to participants with treatment-resistant conditions, researchers fundamentally alter the epistemic context in which participants make health decisions,

potentially creating conditions where pursuing risky alternatives becomes rational for those seeking continued symptom relief. Indeed, both Eleanor and Aaron elected to continue using psilocybin, and Helen was sorely tempted to, though she was ultimately dissuaded by the risks. This epistemic transformation, combined with the lack of legitimate access pathways, creates a form of moral hazard I argue generates special obligations for post-trial provision.

The matrix analysis in Chapter 6 revealed another autonomy-related tension: while enhanced neuroplasticity following psychedelics creates a period of heightened environmental sensitivity that may warrant matrix intervention, such intervention sits uneasily with respect for the autonomy of other matrix members. When clinicians knowingly induce this plastic state, they create a condition where environmental influences, both positive and negative, can have amplified effects on patients, potentially increasing the risk of negative outcomes from psychologically adverse environments. Clinicians' causal role in heightening environmental vulnerability confers a degree of responsibility for subsequent outcomes, yet attempts to reshape or buffer a patient's socio-ecological environment, even temporarily, risk overreaching professional boundaries and infringing upon matrix members' self-determination. Simply put, Chapter 6 makes the case that behaviours, including action and inaction, of a P-AT patient's matrix members can influence treatment outcomes, though shaping the behaviours of patients' family members lies outside of medical authority. This tension becomes particularly acute when we recognise that matrix interventions require clinicians to make complex judgments about which aspects of a patient's life context merit attention or modification, judgments that extend well beyond traditional therapeutic parameters. Rather than resolving this tension definitively, I argue for a time-limited, supportive approach that acknowledges the special obligations created by induced vulnerability while respecting both the patient's autonomy to seek matrix support, and the autonomy of matrix members to decline such involvement.

8.3.2. Beneficence, non-maleficence, and the challenge of unpredictable outcomes

The extended nature of integration processes suggests that premature withdrawal of therapeutic support in trial contexts may not merely represent a missed opportunity for benefit but could actively cause harm, should participants be left "ripped open, with all the mess and having to deal with it on my own" as Helen described. Unlike conventional pharmacotherapies, P-AT intentionally initiates psychological processes that continue to unfold beyond formal treatment endpoints. This reconfigures the ethical

landscape, as researchers who knowingly initiate potentially destabilising processes bear responsibility for supporting participants through them.

The standardisation of therapeutic protocols in current trial designs presents another ethical challenge. Treating preparation and integration sessions as fixed ‘doses’ of therapeutic support conflicts with the unpredictability of psychedelic therapeutic processes. During P-AT, patients may encounter deeply challenging psychological material, confront previously unconscious content, or undergo transpersonal experiences; the processing and integration of such experiences cannot always be hurried to fit within predetermined time constraints. The analogy to surgery invoked in Chapter 5 is imperfect but instructive—no surgical clinical trial would impose a rigid time limit on procedures, requiring surgeons to down tools mid-operation regardless of the stage reached. Just as patients must be properly sutured before leaving the operating theatre, psychological material surfaced during P-AT requires adequate integration and containment.

I argue in Chapter 5 that this reconfigures ethical obligations: when research teams knowingly initiate potentially destabilising psychological processes, they incur obligations to support participants through them to an appropriate resolution. This obligation is best understood as deriving from the duty of non-maleficence and is heightened by two additional distinctive features of P-AT: the deliberately cultivated depth of therapeutic relationship during treatment, which creates what Richardson terms distinctive "moral entanglements," and the availability of psychedelics through unregulated channels, which creates unique risk profiles for participants.

Moreover, as demonstrated in Chapter 7, the field's current inability to adequately capture and assess adverse consequences compromises efforts to fulfil basic ethical imperatives around beneficence and non-maleficence. Without comprehensive data capturing the evolving interpretation of outcomes, we cannot properly evaluate whether offering P-AT in specific contexts upholds our duty to benefit while avoiding harm. These limitations in capturing adverse events not only compromise ethical duties of beneficence and non-maleficence but also raise significant concerns about justice and equity, particularly for vulnerable populations with fewer resources to mitigate potential harms.

8.3.3. Justice, equity and access

The lack of diversity in many P-AT trials compounds these concerns, as current adverse event data may not reflect risk profiles for underrepresented populations. Evidence from population-level studies

suggests that benefits of naturalistic psychedelic use may be attenuated in minority groups, raising pressing questions about differential risk profiles across populations that remain largely unexplored due to homogeneous trial samples.

The post-trial access analysis highlighted how risks of trial participation fall disproportionately on already disadvantaged groups. When formal support ends, wealthy participants can access supervised sessions abroad or private integration therapy should they need it, while those with limited means face starker choices between accepting a return of debilitating symptoms or risking procurement through illegal channels. This disparity is further exacerbated by racial inequities in drug law enforcement, meaning that the risks associated with trial participation are not evenly distributed across participants. The matrix analysis in Chapter 6 made the case that patients' broader socio-ecological contexts —their support systems, relationships, and living situations— can significantly influence post-trial trajectories. *Screening* patients based on matrix quality would raise serious equity concerns, as features of 'good' matrices —including strong social support networks, stable housing, meaningful employment— are not evenly distributed goods. Such exclusionary approaches would create a perverse system denying treatment to those who might need it most.

Instead of screening out prospective patients with less favourable matrices, I argue for a more equitable approach that provides enhanced, temporary support during the critical window of post-psychedelic sensitivity. This resolution to the protection-inclusion dilemma maintains equitable access while addressing the heightened vulnerability that P-AT creates. The time-limited nature of enhanced neuroplasticity following psychedelic administration (somewhere between two and six weeks) suggests that more intensive engagement with the matrix might be justified within this critical window.

8.3.4. Scientific rigour and therapeutic responsibility

Across the analytic chapters of the thesis, I have argued that P-AT is characterised by temporal extension, contextual sensitivity, and outcome complexity: features that exist in tension with the scientific imperative for standardisation and methodological control. Each dimension of 'messiness' that we acknowledge —whether the extended integration needs revealed in Helen's case, the matrix influences evident in Eleanor and Aaron's divergent trajectories, or the evolving interpretation of experiences over time— challenges conventional trial designs with their fixed endpoints and predetermined support structures. Yet acknowledging this complexity need not mean abandoning scientific rigour.

Current trial frameworks operate with an implicit model of P-AT as a temporally bounded, context-independent intervention with clearly categorisable outcomes. This model, while methodologically convenient, fails to capture the lived reality of P-AT evident in participant experiences. The challenge is not whether to acknowledge these complexities, as this thesis has built a case that they are a feature of P-AT whether we attend to them or not, but rather how to accommodate them within scientifically robust research designs that can still produce generalisable knowledge.

When research teams knowingly initiate potentially destabilising psychological processes, they incur obligations to see those processes through to an appropriate resolution. The ongoing nature of these processes means participants cannot simply "opt out" when trials end - Helen, for example, was still dealing with the psychological fall-out of her psilocybin experiences more than a year afterwards . This responsibility is heightened by the depth of therapeutic relationship deliberately cultivated during treatment, which creates what Richardson (2012) terms ‘moral entanglements’ that further justify providing continued care. While this support may come through formal post-trial access and care, other approaches exist: many psychosocial intervention trials specify therapy 'dose' ranges rather than fixed quantities, recognising that therapeutic processes inherently vary in duration and intensity across individuals.

Yet the standard approach to trial termination, i.e., referring participants back to conventional mental healthcare systems, is inadequate, at least for those trials of treatment-resistant conditions, recruitment into which is predicated on the inadequacy of conventional care. Healthcare systems are also ill-equipped to handle the specific challenges of post-psychedelic integration, and privately funded integration support may be entirely unavailable to some participants due to resource constraints.

In Chapter 5, I proposed reconceptualising post-trial care not merely as an ethical burden but as an integral site of psychedelic research that can simultaneously meet obligations to participants while developing crucial knowledge and infrastructure for the field's development. By systematically studying post-trial provision, the field can develop evidence-based integration practices, optimal protocols for repeated sessions, and cost-effective delivery models that are essential for sustainable psychedelic healthcare.

It's worth noting in this context that Dr. Rosalind Watts, former clinical lead at the UK's foremost psychedelic research centre, has turned her attention away from clinical trials to focus on developing

longer-term community containers for continued integration and support after psychedelic experiences, noting that "[t]he focus on the drug itself means that we neglect all the other aspects of what makes a psychedelic session healing. We isolate this one element, and ignore the rest" (Watts, 2022). This shift in focus from the acute drug experience to the extended integration process aligns with the findings revealed by participant experiences in this thesis.

Similarly, I argue in Chapter 7 that improved adverse event reporting frameworks can serve both scientific and therapeutic aims by capturing the full spectrum of consequential outcomes across multiple domains and timeframes. This approach would not only improve informed consent but also advance understanding of the complex mechanisms through which P-AT operates.

8.4. Implications for Key Stakeholders

Both the key findings and ethical arguments that have emerged from this thesis have significant implications for multiple stakeholders involved in research, regulation, and healthcare delivery. Drawing from the analyses presented in previous chapters, this section offers targeted recommendations for different groups while acknowledging the real-world constraints within which implementation must occur.

8.4.1 For researchers designing P-AT trials

The most significant implications for researchers emerge from the post-trial access and care analysis (Chapter 5), which argues for a substantial expansion of post-trial provision in P-AT research. Where providing comprehensive post-trial access and care is not feasible, researchers should consider designing protocols with flexible integration support. Adaptive trial designs that incorporate predetermined decision points for adjusting support based on participant needs could effectively balance standardisation with therapeutic responsiveness. Even with no such adaptations to trials, researchers might still take steps to minimise potential harms. As Pilecki et al. (2021) suggest, providing harm reduction information to participants intent on pursuing further psychedelic experiences for clinical relief can reduce risks associated with uncontrolled use without being complicit in controlled drug use outside the trial context. While this approach falls short of the full obligations outlined in Chapter 5, it represents a pragmatic step toward reducing risks within current constraints.

From the matrix analysis (Chapter 6), researchers should incorporate validated measures of social support and environmental quality. If, as I have argued, matrix quality significantly influences treatment outcomes, systematically tracking these factors through validated and widely used instruments could provide valuable data on their causal role while helping identify protective and risk factors.

The analysis of adverse events (Chapter 7) points toward the need for more comprehensive assessment frameworks that capture the full spectrum of patient-relevant outcomes. While the recent development of tools like the PATAE and SPSI represents promising progress, researchers should collaborate to establish field-wide standards for outcome assessment that move beyond conventional pharmacological measures while maintaining scientific rigour.

8.4.2 For regulatory bodies

Regulatory bodies face particular challenges in evaluating P-AT, as standard assessment frameworks developed for conventional pharmaceuticals prove inadequate for capturing its hybrid nature.

From the post-trial access and care analysis, regulators could consider post-trial provision requirements for P-AT research. The European Medicines Agency's guidelines already emphasise that sponsors must ensure participants are not left without necessary medical oversight, especially for trials involving high-risk interventions. The Declaration of Helsinki, adopted into EU regulations, similarly states that participants should have access to post-trial care when necessary for their health. These existing frameworks provide a foundation for more specific guidance regarding P-AT, where the ongoing nature of psychological processes initiated during treatment may create particular obligations for continued support.

From the adverse events analysis, regulators should expand AE frameworks to better capture P-AT's complexity. While regulatory agencies can consider certain patient-reported outcomes (PROs) in their assessments, as evidenced by the FDA's consideration of depression-specific PROs in the approval of esketamine (Spravato) for treatment-resistant depression, these measures must meet high standards of validity and reliability.

The FDA's draft guidance for industry on psychedelic trials (FDA, 2023) demonstrates scepticism toward the psychotherapeutic component of P-AT, focusing primarily on addressing potential expectancy and performance biases rather than acknowledging the inherently hybrid nature of the

intervention. The guidance also remains firmly anchored to a narrow conception of adverse events as "untoward medical effects," showing little sensitivity to the broader range of challenging outcomes patients may experience.

The PATAE and SPSI represent important first steps toward more comprehensive assessment, but they are unlikely to meet regulatory standards for validation in the immediate future. Nevertheless, both the EMA's Benefit-Risk Assessment Model, which explicitly includes PROs as part of the clinical evidence package in licensing decisions, and the MHRA's signalled greater flexibility in accepting PROs for neurology and mental health conditions, suggest potential pathways for integrating broader outcome measures into regulatory assessments. Without overestimating the pace of this evolution, researchers and regulators should work together to develop and validate measures that can capture the full spectrum of P-AT outcomes while meeting necessary standards of scientific rigour.

This work is particularly urgent given the emerging patchwork of regulatory approaches internationally, with Australia already licensing psilocybin-assisted therapy, Canada expanding special access routes, and various U.S. states creating P-AT-like services outside FDA oversight. Without coordinated effort toward harmonised standards for outcome assessment across jurisdictions, the field risks fragmentation that could compromise both scientific progress and patient safety. A comprehensive framework for evaluating not just safety and efficacy, but broader patient-relevant outcomes, could provide a common foundation for diverse regulatory pathways while acknowledging legitimate differences in national approaches to risk management.

8.4.3. For healthcare systems planning implementation

Healthcare systems will play a crucial role in determining whether and how P-AT is integrated into existing structures, with decisions about resource allocation, delivery models, and monitoring systems shaping access and outcomes.

While post-trial access and care obligations fall on research teams rather than healthcare systems, there are valuable opportunities for collaboration that could benefit the broader development of the field. Healthcare systems that fund healthcare delivery research (e.g., the NIHR in the UK) could partner with P-AT research teams on implementation studies that simultaneously address the needs of research participants while simultaneously generating knowledge about optimal support models.

From the matrix analysis, healthcare systems should consider how social determinants of mental health interact with P-AT outcomes. The integration of social work services into P-AT delivery models could help address systemic barriers to therapeutic change, while leveraging existing community resources to strengthen patients' matrices. This approach aligns with the horizontal integration advocated by the ecobiodevelopmental framework (Shonkoff et al., 2012), connecting healthcare, social services, and other support systems to address not just immediate clinical needs but also the broader social and environmental factors that shape health outcomes.

As we look toward the future implementation of P-AT within healthcare systems, several critical research directions emerge that build upon the temporal understanding developed throughout this thesis, addressing both the 'before' and 'after' dimensions of the psychedelic therapeutic process.

8.5. Future Directions

While my case-based approach does not offer definitive evidence, it highlights important aspects of patient experience that could inform future research priorities. These future directions span empirical investigation, conceptual development, and infrastructure needs that will be important for the ethically robust and therapeutically effective implementation of P-AT.

8.5.1 Key areas needing attention

Three domains emerge as priorities for future investigation: the development of sustainable models for extended therapeutic support, the systematic investigation of family influences, and the refinement of adverse event assessment.

Establishing sustainable models for extended therapeutic support remains a pressing challenge. P-AT is a highly resource-intensive modality, and identifying economies that preserve therapeutic effectiveness will be crucial for wider implementation. The findings from the Challenging Psychedelic Experiences Project highlighted the value of "empathy and shared experience in the support process" (Robinson et al., 2024, p.9), suggesting that peer-based approaches may offer particular promise. Integration—the component of P-AT that appears least theorised and most variable in delivery—presents a prime opportunity for exploring more efficient delivery models. Research comparing professional integration, peer-led groups, and co-facilitated approaches could identify cost-effective

models that maintain therapeutic quality while expanding accessibility. This aligns with existing trends in the field, where some research centres have already established peer-supported integration groups that draw former trial participants.

While Chapter 6 suggests that a patient's broader socio-ecological matrix may significantly influence treatment trajectories, establishing causal relationships requires systematic investigation. The matrix encompasses numerous elements, from interpersonal relationships to socioeconomic factors, making comprehensive assessment challenging in early research. A strategic approach would begin with family systems, where there are both established assessment instruments and precedent in other psychological interventions. Future research could incorporate validated measures of family functioning and environment into trial protocols as standard practice. An established psychotherapeutic literature confirms that family dynamics are mediators of treatment outcomes, making this focus an ideal testbed before initiating matrix research of a wider scope. Larger trials with sufficient power for subgroup analyses could help identify whether and how family support moderates treatment outcomes, potentially informing more targeted approaches to preparation and support.

The ambivalence and temporal complexity of P-AT outcomes demand more sophisticated frameworks for conceptualising adverse events. While Chapter 7 identified the limitations of current approaches to AE assessment, it did not resolve the conceptual challenge of distinguishing between therapeutically valuable challenging experiences and genuine adverse outcomes. This represents a significant gap not only in my thesis but in the field more broadly. Future work conceptual work should develop clear criteria for this distinction. This conceptual refinement is necessary not only for accurate risk assessment but also for ethical communication with prospective patients about what they might experience.

8.5.2 Research priorities

Three specific research directions emerge as priorities based on this thesis's findings:

1. **Optimal Support Models**: As healthcare systems prepare for potential implementation of P-AT, research comparing different models of integration support will be crucial for informing resource allocation. Studies examining the efficacy of peer support models, (blended) group integration formats, and professional individual therapy must balance considerations of both effectiveness and cost-effectiveness. No healthcare system operates with unlimited resources, making the identification of efficient yet therapeutically robust approaches a priority. This research should focus on identifying which components of support are most crucial for different

types of patients and challenges, and which can be delivered through less resource-intensive formats without compromising outcomes. The existence of peer support communities and integration groups suggests feasible alternatives to traditional one-on-one professional support for at least some aspects of the integration process.

2. **Family Assessment and Preparation**: Building on Chapter 6's analysis, researchers should prioritise the systematic documentation of family environment and functioning, and their influence on outcomes. Beyond merely tracking these factors, interventional studies might examine whether targeted preparation of family systems—through structured psychoeducation for family members—improves outcomes or reduces AEs. This aligns with established practice in other mental health interventions where family psychoeducation has proven valuable in supporting patient mental health and functioning outcomes, as well as family carer well-being (Brady et al., 2017; Katsuki et al., 2022; Shimazu et al., 2011). While the specific content and purpose of family psychoeducation in P-AT would differ from these precedents, they provide proof of concept for the approach. Such research could help establish whether and how family preparation might serve as a protective or salutogenic factor.

3. **Comprehensive Adverse Event Assessment**: Chapter 7 highlighted significant gaps in our understanding of adverse events in P-AT, with nearly half of all trials failing to report any AE data whatsoever. The most pressing requirement is for P-AT trials to consistently and systematically record adverse events as understood in the conventional, narrow sense. Without this basic foundation of safety data, more nuanced understanding remains impossible. As well as improving reporting practices, future research must address both empirical and conceptual dimensions of adverse event assessment. Empirically, more comprehensive assessment frameworks are needed that can capture the full spectrum of challenging outcomes across multiple domains. Conceptually, the field needs clearer frameworks for distinguishing between experiences that are therapeutically challenging but ultimately valuable versus those that represent genuine adverse outcomes requiring intervention. Mixed-methods approaches that combine quantitative tracking with qualitative investigation of how experiences evolve and are interpreted through time could help establish these distinctions. Such work is crucial for accurately communicating risks to prospective patients while avoiding the pathologisation of potentially therapeutic challenges.

These are research priorities for a field that must move beyond simply establishing efficacy toward understanding how P-AT can be optimally delivered and supported within real-world healthcare constraints. By addressing these questions systematically, researchers can help ensure that implementation decisions are grounded in evidence rather than expediency or financial considerations alone.

8.6. Concluding Reflection

The findings from these case analyses revealed patterns that deserve attention as the field develops. The temporal complexity of P-AT extends well beyond protocol-defined endpoints, with therapeutic processes unfolding over months and seemingly shaped considerably by contextual factors. Current norms and frameworks used by the field, whether about trial design, outcome assessment, or researcher obligations, don't adequately attend to important aspects of P-AT, not least its hybrid nature as both pharmacological and psychotherapeutic intervention. Finally, addressing these limitations requires developing sustainable infrastructure that accommodates P-AT's distinctive features while remaining feasible within healthcare constraints.

Given its substantial resource demands, P-AT faces understandable pressure to streamline delivery models for wider implementation. However, this creates tension between efficiency and the preservation of elements central to patient experience and therapeutic outcomes. No recommendations for change will be implemented if they are based on the assumption of limitless resources, and while acknowledging the potentially expansive implications of the recommendations offered throughout this thesis, I have sought to acknowledge the constraints of healthcare systems.

As P-AT transitions from experimental intervention to clinical practice, maintaining a patient-centred perspective becomes increasingly important. The participants who shared their stories for this research remind us that beneath the statistical analyses and regulatory considerations are individual human experiences—sometimes transformative, sometimes challenging, always complex. Their accounts reveal that P-AT cannot be fully understood without due sensitivity to its distinctive temporal, contextual, and experiential dimensions.

The rich, multi-dimensional experiences of Eleanor, Aaron, and Helen—and the many others whose complex journeys shape this emerging field—remind us that behind every trial endpoint and regulatory decision lie real, lived human stories deserving our careful consideration. Their experiences reveal how P-AT can simultaneously catalyse remarkable clinical benefit while generating new challenges that current frameworks fail to adequately address. In attending closely to these accounts, this thesis has illuminated gaps in current P-AT practice while pointing toward approaches that could more ethically serve the interests of patients. The "encounters with experience" presented in the thesis serve not merely as data points, but as a vital reminder that bioethics at its best emerges from the complex interplay between principled reasoning and attentive engagement with lived human experience.

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Appendix 1. Positionality Statement[45]

Personal and Professional Positioning

My approach to this research is shaped by my position as both an 'insider' and 'outsider' to psychedelic experiences and research. Since 2017, I have participated in ayahuasca ceremonies as part of my spiritual practice, and since 2018, I have occasionally used psilocybin to support my mental health alongside other approaches, including psychodynamic psychotherapy. In both spiritual practice and mental health regulation, psychedelics represent a substantive but non-dominant dimension of my life and practice.

I am an 'outsider' in that I am based at a university with no active clinical psychedelic research program and have no affiliation with the clinical trials my intended interviewees have experienced. This positioning provides me with enough distance to examine trial experiences critically while having sufficient understanding of psychedelic states to engage meaningfully with participants' accounts.

Professionally, I have engaged with psychedelics for approximately four years as a researcher and consultant. This has positioned me within multiple networks in the psychedelic community, exposing me to diverse perspectives on research, clinical practice, and regulatory approaches. My academic training bridges empirical social science methods and philosophical ethics, creating a particular lens through which I approach questions of normative significance in psychedelic research.

Following Chavez's (2015) conceptualisation of researcher positioning as existing along a spectrum rather than a binary insider/outsider division, I recognise that my dual status grants me certain insights while potentially creating blind spots. My familiarity with psychedelic experiences may help me understand participants' accounts in ways that might elude researchers without such experience, but it may also lead me to over-identify with certain narratives or interpretations that resonate with my own experiences.

Research Motivation and Topic Selection

My research interest was shaped by anticipating changes similar to those I had witnessed firsthand in myself and others. I am particularly attuned to less-discussed phenomena in the literature such as

[45] Drafted in March 2022 and edited for clarity in January 2025.

increased comfort with ambiguity and the recognition that one's perception of reality is just 'a way of seeing the world' rather than reality itself. This isn't simply an attempt to 'find the others,' as Timothy Leary once exhorted, but to better understand how different individuals attend to and interpret these changes across varied contexts and experiences.

As Magnusson & Marecek (2012, ch.5) note, knowledge is ‘interested’: there is always a reason why particular questions become interesting to researchers. A key motivation for this research was my recognition that although psychedelics are (or might be) medicines, that is not all they are. There exist a range of other uses of psychedelics and valued outcomes beyond symptom reduction[46]. This perspective informed my initial interest in 'non-clinical changes' as potentially valuable dimensions of psychedelic experiences that might be overlooked in strictly medical frameworks.

Epistemological and Methodological Stance

My research is grounded in a constructivist orientation that acknowledges the co-created nature of knowledge in research contexts. I recognise that participants' accounts of their post-trial experiences are not simply ‘collected’ but rather generated through our interactions. The interview process itself may shape how participants frame and articulate their experiences, though interviews will begin and end with broad-ranging questions to uncover the aspects that participants find most salient, or are otherwise hoping that I ask.

My familiarity with established ethical structures governing clinical research and practice may limit my sensitivity to how 'normal people', without systematised frameworks about how things are or should be done, experience participation in psychedelic research.

Assumptions and Potential Biases

I begin this research with certain assumptions that warrant acknowledgment. I hypothesise that non-clinical changes will be relatively commonplace and salient to participants, an expectation shaped by both literature and my own observations. To mitigate potential biases, I plan to explicitly encourage participants to be completely honest, not just ‘even if’ my questions don't resonate with their experiences, but ‘especially if’ they don't resonate. This approach is designed to create space for narratives that diverge from my expectations.

[46] A case I have since made elsewhere (Jacobs et al. 2023; Jacobs et al., 2024).

Regarding practice and regulation, I believe in the therapeutic potential of psychedelics while maintaining scepticism toward 'psychedelic exceptionalism'. Acknowledging and accommodating the distinctive properties of psychedelics doesn't necessitate special pleading or exemption from scientific scrutiny[47]. This position reflects my attempt to balance enthusiasm with critical distance.

My embeddedness in psychedelic research networks has exposed me to various competing narratives about proper clinical, research, and regulatory approaches. While this provides valuable context, it may also influence how I evaluate certain practices or policies. I will attempt to mitigate this through ongoing critical reflection on how these influences might shape my interpretation of participant accounts. Hopefully, the diversity of voices and perspectives that I engage with in the psychedelic community will help mitigate any blind spots in my own thinking and analysis.

Research Relationships and Power Dynamics

My relationship to clinical trial sites has evolved since the conception of the research project. Despite initial agreements with trial sites to facilitate recruitment, changes over time, including key personnel changes and new restrictions associated with government funding, have meant I could not make use of these connections as planned. This required alternative recruitment strategies and potentially affected the composition of my participant sample.

I present myself as a junior researcher, and am younger than the typical participant in P-AT clinical trials, which may somewhat mitigate traditional researcher-participant power imbalances. This positioning, alongside my non-affiliation with clinical research sites, may influence what and how participants share, potentially facilitating more candid accounts of their trial experiences than might be shared with researchers directly associated with those trials.

Throughout the research process, I've remained mindful that my suggestions for implementation are expensive and/or effortful to implement, which wouldn't be popular among all relevant stakeholders. I have responded to this by attempting to be constrained by practical realities while still advocating for what I believe would best serve patient welfare.

[47] I make this case more fully in Jacobs (2025).

Appendix 2.1: Ethics Approval Confirmation

MEDICAL SCIENCES INTERDIVISIONAL RESEARCH ETHICS COMMITTEE
Research Services, Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB
Tel: +44(0)1865 616575
ethics@medsci.ox.ac.uk

CONFIDENTIAL

Professor Ilina Singh & Edward Jacobs
Department of Psychiatry
University of Oxford
Warneford Hospital
Oxford

23 September 2022

Dear Professor Singh and Edward,

Research Ethics Approval - CUREC 1

Ethics Approval Reference: R68871/RE001

Study title: Changing Minds: Bioethical dimensions of psychedelic-assisted psychotherapy

Short title: Changing Minds: Experiences following psychedelic therapy

The above application has been considered on behalf of the Medical Sciences Interdivisional Research Ethics Committee (MS IDREC) in accordance with the University's procedures for ethical approval of all research involving human participants.

I am pleased to inform you that, on the basis of the information provided to the IDREC, the proposed research has been judged as meeting appropriate ethical standards, and approval has been granted for a period of **18 months**, commencing on **23rd September 2022.**

Amendments

Should there be any subsequent changes to the study, you should submit details to the MS IDREC for consideration and approval. Details of changes must be listed on an amendment form.

Yours Sincerely

DocuSigned by:
Leah Butts
9F14689D2BC549A...

Mrs Leah Butts
Research Ethics Administrator

for
Dr Helen Barnby-Porritt
Research Ethics Manager

Appendix 2.2: Invitation Letter (trial participants)

DEPARTMENT OF PSYCHIATRY
UNIVERSITY OF OXFORD
WARNEFORD HOSPITAL
OXFORD, OX3 7JX
Eddie Jacobs
Email: edward.jacobs@psych.ox.ac.uk

Changing Minds: Experiences Following Psychedelic Therapy
Ethics Approval Reference: R68871/RE001

VOLUNTEERS NEEDED FOR INTERVIEWS ABOUT LIFE AFTER PSYCHEDELIC THERAPY

We are looking for volunteers who have previously participated in clinical trials of psilocybin-assisted therapy, aged 18 and above, to take part in an interview study to talk about their experiences after the trial. You would meet a member of the research team at your home, a quiet public place, or online over software like Microsoft Teams, for up to two interview sessions.

The study aims to build a picture of the experiences people go through in the months and years after receiving psychedelic-assisted psychotherapy as a mental health treatment. Some people report changes to how they see themselves, their relationships, or the wider world, while for others life continues much as it always had. We want to talk to people who have participated in trials using psilocybin about what has stayed the same, what has changed, and how they have managed what comes next, following the trial.

Each session would take no more than 90 minutes of your time, and we can arrange the sessions at a time that suits you, around any work, caring, or other commitments you have. You would be asked to talk about how your life has been after your trial experience and your return to 'everyday life' – including aspects that are better, worse, or just different to life before the trial. To thank you for taking part, you will be reimbursed for your time.

If you are interested and would like more information please contact Eddie Jacobs at the Department of Psychiatry, University of Oxford on +44 (0)1865 613162, or psychedelic.experiences@psych.ox.ac.uk. There is no obligation to take part.

Thank you!

Appendix 2.3: Participant Information Sheet text

Changing Minds: Experiences Following Psychedelic Therapy

PARTICIPANT INFORMATION SHEET

Ethics Approval Reference: R68871/RE002

As part of my PhD research, I am inviting people to take part in interviews about their experiences following clinical trials with psychedelic drugs. My name is Eddie Jacobs, and I am undertaking a research project called 'Changing Minds: Bioethical Dimensions of Psychedelic-assisted Psychotherapy' (or just 'Changing Minds') at the University of Oxford.

Before you decide if you would like to participate, it's important to understand what the study is about, why I'm doing it and what it would involve for you. Please read and think about this leaflet carefully. Please feel free to talk to your family, friends, or me about it if you want. If anything isn't clear or you have more questions you can e-mail me, and I'll be happy to discuss it with you.

Why am I doing this research?

This study investigates the experiences people go through in the days, weeks, months and years after receiving psychedelic-assisted psychotherapy as a mental health treatment. While there has been some study of what people experience while under the effects of psilocybin, we want to better understand how these experiences can impact people in the long-term after they have left a clinical trial. We'd like to know about what happens next for people after they have had psychedelic-assisted therapy and gone back to 'everyday life'. This includes how people change their outlooks on life and themselves, including aspects that are better, worse, or just different to life before the trial. By participating in the research, you will be contributing to a project that will deepen our understanding of how patients, and those close to them, can be best supported before choosing, and after receiving, psychedelic-assisted psychotherapy.

Why have I been invited to take part?

You are being invited to take part because you have previously taken part in a registered clinical trial involving psilocybin. We are recruiting about 30 former trial participants, and we are hoping to speak to as wide a range of people as possible – the only requirement is that you have completed a clinical trial like this.

Do I have to take part?

No – it is up to you. If you would like to participate, you can contact me for more information, and I can send you a consent form to fill in to confirm that you agree to take part. You are free to stop taking part at any time during the research without giving a reason, by telling me. If you decide to stop, I won't use the information I have already collected from you unless you agree that I can.

What will happen to me if I take part?

You will meet me one or two times for an interview session. These can take place at your home, in a quiet public place, at the University of Oxford or over online software like Microsoft Teams. The first session will take about 90 minutes, and the second session around 60 minutes. The sessions will take place at a time and place that suits you, to accommodate any work, caring, or other commitments you may have.

Across the sessions, I will invite you to talk about your experiences after your psilocybin session, and especially after you finished the trial and returned to your day-to-day life. I am interested in all aspects of how life can change following psilocybin treatment, and would like to understand your experiences, both good and bad. The conversation will be recorded using a Dictaphone or similar equipment online. Any recordings will be held securely in password-protected files on an internal server at the University of Oxford.

If you feel uncomfortable during the interview processes, you can say you won't answer specific questions that make you uncomfortable. If you choose to stop participating in the research project, you will be able to withdraw no questions asked, and without any impact on your current or future care.

What happens to the results of the study?

Results may be published as part of my doctoral thesis, a report or journal article, in a book, blog or other media, or presented at academic events. The findings of the study may be used to improve practice, policy, and research involving psychedelic-assisted psychotherapy. You can keep up to date with the project and our findings by accessing www.psychedelicethics.com or contacting us directly (please find contact information below).

The study procedure has been carefully checked to ensure it meets high ethical standards. We will keep all information from the interview completely confidential. Data will be analysed and pseudonymised by the lead researcher who will interview you, Eddie Jacobs. While this processed data may be shared with collaborating researchers at Imperial College London or Johns Hopkins University, it will not reach the 'outside world', for example in publications, social media, or online repositories, in its 'raw' state.

We will also assure your anonymity, which means we will not use your real name or identifiable details about you during or after the research, or in any publications, social media, and so forth.

What about my personal information?

I would like you to feel completely comfortable sharing your story, and will do everything we can to protect your privacy. At the first opportunity when your interviews are transcribed, your name and other identifying information will be changed in order to preserve your anonymity. Only I will have access to any data that could link your identity to your answers. I may wish to use direct quotations from our interviews in publications. Quotes that could directly identify you will not be used, but you may withhold consent from *any* direct quotations being used. All data will be securely stored on a server at the University of Oxford until data collection is completed.

I might send anonymous data via email, using a secure server, to other researchers to study, or to an online data repository. This makes it possible for data to be more widely used, which is a good thing. The anonymous data will be stored for at least 10 years, in case I or other researchers want to look again at the data, in light of new developments in psychedelic research.

What are the advantages / disadvantages of taking part?

By participating in the research, you will be contributing to a project that will deepen our understanding of the long-term effects, good and bad, of psychedelic-assisted therapy. You may also enjoy talking at length about how things have gone for you since your trial participation, with someone who is interested and non-judgmental. In recognition of you giving up your time to support my research, I am also able to offer reimbursement of £30/hr. There are no serious risks to you in taking part in this study. However, if you wish to stop, you can do so at any point. If you become distressed,

you will be able to pause and take a break for as long as you need. I will point you to additional support if you need it.

Will anyone else know I'm doing this?

I won't tell anyone else, unless we think that there is an immediate risk of serious harm to yourself or to others. If this happens, we would first discuss with you who should be informed to make sure you stay safe. For example, this could be a family member, your doctor, or the clinical lead of the psychedelic trial you participated in.

What if I don't want to take part in the research anymore?

You are under no obligation to continue with the research once you've started – you are always free to stop. If you decide to stop, I will not use the information you have already provided unless you agree to it. On 30/6/2024 I will delete the password-protected list that links your pseudonymised responses to your real identity. As such, up until that point, I can remove your data in its entirety.

Who is organising and funding the research?

The research is organised by Eddie Jacobs, a doctoral student in the Neuroscience, Ethics and Society Group at the University of Oxford. The study is supported by the Wellcome Trust.

Who has reviewed the study?

Before any research involving people can start, it has to be checked by a Research Ethics Committee to make sure that it is OK for the research to go ahead. This study has been approved by a subcommittee of the University of Oxford Central University Research Ethics Committee, ethics reference number R68871/RE001.

What if there is a problem or something goes wrong?

Please reach out if you are worried about any part of this study, by contacting me (edward.jacobs@psych.ox.ac.uk) or, if you prefer, my supervisor Prof Ilina Singh (ilina.singh@psych.ox.ac.uk). If you are still unhappy or wish to make a complaint, you can contact the chair of the Research Ethics Committee at the University of Oxford (Chair Medical Sciences; Inter-Divisional Research Ethics Committee; Email: ethics@medsci.ox.ac.uk; Address: Research Services, University of Oxford, Wellington Square, Oxford OX1 2JD).

Data Protection

The University of Oxford is the data controller with respect to your personal data, and as such will determine how your personal data is used in the study. The University will process your personal data for the purpose of the research outlined above. Research is a task that we perform in the public interest.

Further information about your rights with respect to your personal data is available from https://compliance.admin.ox.ac.uk/individual-rights.

Contact details

If you would like to discuss the research beforehand (or if you have questions afterwards), please contact:

Eddie Jacobs
Department of Psychiatry
Warneford Hospital, Oxford, OX3 7JX
Email: edward.jacobs@psych.ox.ac.uk

Thank you for reading this – please ask any questions if you need to.

Appendix 2.4: Participant Information Sheet text (family members)

Changing Minds: Experiences Following Psychedelic Therapy

PARTICIPANT INFORMATION SHEET

Ethics Approval Reference: R68871/RE001

My name is Eddie Jacobs, and I am undertaking a research project called 'Changing Minds: Bioethical Dimensions of Psychedelic-assisted Psychotherapy' (or just 'Changing Minds') at the University of Oxford. As part of my PhD research, I am inviting people to take part in interviews about people's experiences after they have participated in a psychedelic trial. I am interested both in the perspectives of the trial participants themselves, but also their friends and families.

Before you decide if you would like to participate, it's important to understand what the study is about, why I'm doing it and what it would involve for you. Please read and think about this leaflet carefully. Please feel free to talk to your family, friends, or me about it if you want. If anything isn't clear or you have more questions you can e-mail me, and I'll be happy to discuss it with you.

Why am I doing this research?

This study investigates the experiences people go through in the days, weeks, months and years after receiving psychedelic-assisted psychotherapy as a mental health treatment. While there has been some study of what people experience while under the effects of psilocybin, we want to better understand how these experiences can impact people in the long-term after they have left a clinical trial. We'd like to know about what happens next for people after they have had psychedelic-assisted therapy and gone back to 'everyday life'. This includes how people change their outlooks on life, their illness, and themselves, including aspects that are better, worse, or just different to life before the trial. Some data suggests that these changes can have impacts not only the person who took psychedelics, but also those who are close to them. By participating in the research, you will be contributing to a project that will deepen our understanding of how patients, and those close to them, can be best supported before choosing, and after receiving, psychedelic-assisted psychotherapy.

Why have I been invited to take part?

You are being invited to take part because someone you know, who has participated in a registered clinical trial involving psilocybin, has suggested you may be willing to talk to us. We are recruiting about five friends and family members of former trial participants – the only requirement is that you are close to someone who has completed a clinical trial like this.

Do I have to take part?

No – it is up to you. If you would like to participate, you can contact me for more information, and I can send you a consent form to fill in to confirm that you agree to take part. You are free to stop taking part at any time during the research without giving a reason, by telling me. If you decide to stop, I won't use the information I have already collected from you unless you agree that I can.

What will happen to me if I take part?

We will meet for a recorded interview session. These can take place at your home, in a quiet public place, at the University of Oxford or over online software like Microsoft Teams. The session will take about one hour, and can take place at a time and place that suits you, to accommodate any work, caring, or other commitments you may have.

Across the sessions, I will invite you to reflect on your friend or family member who has participated in a psilocybin trial, especially after they finished the trial and returned to their day-to-day life. I am interested in all aspects of how life can change following psilocybin treatment, and would like to understand your perspectives, both good and bad. The conversation will be recorded using a Dictaphone or similar equipment online. Any recordings will be held securely in password-protected files on an internal server at the University of Oxford.

If you feel uncomfortable during the interview processes, you can say you won't answer specific questions that make you uncomfortable. If you choose to stop participating in the research project, you will be able to withdraw no questions asked.

What happens to the results of the study?

Results may be published as part of my doctoral thesis, a report or journal article, in a book, blog or other media, or presented at academic events. The findings of the study may be used to improve practice, policy, and research involving psychedelic-assisted psychotherapy. You can keep up to date with the project and our findings by accessing www.psychedelicethics.com or contacting us directly (please find contact information below).

The study procedure has been carefully checked to ensure it meets high ethical standards. We will keep all information from the interview completely confidential. Data will be analysed and pseudonymised by the lead researcher who will interview you. While this processed data may be shared with collaborating researchers at Imperial College London or Johns Hopkins University, it will not reach the 'outside world', for example in publications, social media, or online repositories, in its 'raw' state.

We will also assure your anonymity, which means we will not use your real name or any details that could identify you during or after the research, or in any publications, social media, and so forth.

What about my personal information?

I would like you to feel completely comfortable sharing your story, and will take a high level of care to protect your privacy. At the first opportunity when your interviews are transcribed, your name and other identifying information will be changed in order to preserve your anonymity. Only I will have access to any data that could link your identity to your answers. I may wish to use direct quotations from our interviews in publications. Quotes that could directly identify you will not be used, but you may withhold consent from *any* direct quotations being used. All data will be securely stored on a server at the University of Oxford until data collection is completed.

While the person close to you who has participated in the trial suggested you might be interested in talking with us, I am aware that you might feel uncomfortable talking about them, or your relationship with them, to someone else. I will not share anything that you tell me with that person, and published materials will not include any details that allow you to be identified.

I might send anonymous data via email, using a secure server, to other researchers to study, or to an online data repository. This makes it possible for data to be more widely used, which is a good thing. The anonymous data will be stored for at least 10 years, in case I or other researchers want to look again at the data, in light of new developments in psychedelic research.

What are the advantages / disadvantages of taking part?

By participating in the research, you will be contributing to a project that will deepen our understanding of the long-term effects, good and bad, of psychedelic-assisted therapy. You may also enjoy talking at length about how things have gone for you since your friend or family member participated in the trial, with someone who is interested and non-judgmental. In recognition of you giving up your time to support my research, I am also able to offer reimbursement of £30/hr. There are no serious risks to you in taking part in this study. However, if you wish to stop, you can do so at any point. If you become distressed, you will be able to pause and take a break for as long as you need. I will point you to additional support if you need it.

Will anyone else know I'm doing this?

I won't tell anyone else, unless we think that there is an immediate risk of serious harm to yourself or to others.

What if I don't want to take part in the research anymore?

You are under no obligation to continue with the research once you've started – you are always free to stop. If you decide to stop, I will not use the information you have already provided unless you agree to it. On 26/04/2024 I will delete the password-protected list that links your pseudonymised responses to your real identity. As such, up until that point, I can remove your data in its entirety.

Who is organising and funding the research?

The research is organised by Eddie Jacobs, a doctoral student in the Neuroscience, Ethics and Society Group at the University of Oxford. The study is supported by the Wellcome Trust.

Who has reviewed the study?

Before any research involving people can start, it has to be checked by a Research Ethics Committee to make sure that it is OK for the research to go ahead. This study has been approved by a subcommittee of the University of Oxford Central University Research Ethics Committee, ethics reference number R68871/RE001.

What if there is a problem or something goes wrong?

Please reach out if you are worried about any part of this study, by contacting me (edward.jacobs@psych.ox.ac.uk) or, if you prefer, my supervisor Prof Ilina Singh (ilina.singh@psych.ox.ac.uk). If you are still unhappy or wish to make a complaint, you can contact the chair of the Research Ethics Committee at the University of Oxford (Chair Medical Sciences; Inter-Divisional Research Ethics Committee; Email: ethics@medsci.ox.ac.uk; Address: Research Services, University of Oxford, Wellington Square, Oxford OX1 2JD).

Data Protection

The University of Oxford is the data controller with respect to your personal data, and as such will determine how your personal data is used in the study. The University will process your personal data for the purpose of the research outlined above. Research is a task that we perform in the public interest.
Further information about your rights with respect to your personal data is available from https://compliance.admin.ox.ac.uk/individual-rights.

Contact details
If you would like to discuss the research beforehand (or if you have questions afterwards), please contact:

Eddie Jacobs
Department of Psychiatry
Warneford Hospital, Oxford, OX3 7JX
Email: edward.jacobs@psych.ox.ac.uk

Thank you for reading this – please ask any questions if you need to.

Appendix 2.5: Participant Consent Form

PARTICIPANT CONSENT FORM

CUREC Approval Reference: R68871/RE001

Changing Minds: Experiences Following Psychedelic Therapy

[Former Trial Participant] Study Summary: *The study will involve two interview sessions, each no longer than 90 minutes long, to talk with a member of the research team about your experiences following your participation in a trial involving psilocybin. Since psychedelic experiences are often such powerful and significant events for people, many people report undergoing subtle and dramatic changes to their outlooks, temperaments, and preferences following treatment. We'll ask you about what has happened since you left the trial and went back to 'everyday life', including aspects that are better, worse, or just different to life before the trial.*

[Friends and Family] Study Summary: *The study will involve one interview session, lasting no longer than 90 minutes, to talk with a member of the research team about your individual and shared experiences following a loved one's participation in a trial involving psilocybin. Since psychedelic experiences are often such powerful and significant events for people, many report undergoing subtle and dramatic changes to their outlooks, temperaments, and preferences following treatment. We'll ask to you to reflect on how, if at all, your loved one changed in the weeks, months, and years following treatment, as well as how their trial participation has affected you.*

	Please initial each box
I confirm that I have read and understand the information sheet version_____dated _____ for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
I understand that my participation is voluntary: I can decline to answer any questions, and I am free to withdraw at any time, without giving any reason, and without penalty.	
I understand that I am free to withdraw consent for the use of my data up until 26/04/2024, without giving any reason, and without penalty.	

I understand that research data collected during the study may be looked at by designated individuals from the University of Oxford where it is relevant to my taking part in this study. I give permission for these individuals to have access to this data.	
I understand who will have access to personal data provided, how the data will be stored and what will happen to the data at the end of the project.	
I understand that all information will be kept strictly confidential except in rare circumstances in which it is judged that I am, or someone else is, at immediate risk of serious harm.	
I understand that this project has been reviewed by, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee.	
I understand how to raise a concern or make a complaint.	
I consent to being audio recorded.	
I understand how audio recordings will be used in research outputs.	
Use of direct quotations: Please indicate your preference (select *one* option):	
a) I agree to the use of quotations in research outputs if I am not identifiable ***or***	
b) I do not wish to be quoted	
I agree to take part in the above study.	
Optional:	
I agree for my contact details to be kept in a secure database for the purpose of contacting me about future studies.	

_____	dd / mm / yyyy	_____
Name of Volunteer	Date	Signature
_____	dd / mm / yyyy	_____
Name of person taking consent	Date	Signature