

# The Promise of Therapeutic Psilocybin: An Evaluation of the 134 Clinical Trials, 54 Potential Indications, and 0 Marketing Approvals on ClinicalTrials.gov

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**Introduction:** Psilocybin, a tryptamine psychedelic, has been touted in the media both historically and recently as a potential game-changing mental health therapeutic. ClinicalTrials.gov has over one hundred and thirty psilocybin clinical trials listed covering the last twenty years. The single most important aspect of any therapeutic is to gain approval for marketing and thus enter the real-world phase of development. A typical new chemical entity progresses from inception to US Food and Drug Administration (FDA) approval in approximately 12 years and seeks approval for a single indication.

**Methods:** An observational study was conducted with the available information on the ClinicalTrials.gov site to observe the extent of progress made demonstrating the clinical utility of psilocybin.

**Results:** The results showed 134 psilocybin trials typically unblinded studies of 10–20 participants, recruited over years at a single site. Additionally, there have been only three advanced trials (1 Phase 2/3 and 2 Phase 3) submitted, and only in the last two years.

**Discussion:** The hundreds of psilocybin clinical trials initiated over the past twenty years comprising a myriad of potential indications may actually be slowing this potential game-changing mental health therapeutic agent's approval and is costing excessive amounts of capital. To fully evaluate the actual potential of psilocybin, purposeful clinical trials need to be designed well, executed efficiently, and analyzed utilizing sequential and statistically valid processes for each potential indication. This will require a change from the current exploratory forays to defined, well-funded, sequential pharmaceutical development practices, including adequate and appropriate blinding of studies, statistical design to determine the number of participants and more importantly, professional expertise in conducting multicenter trials. Unfortunately, these results demonstrate little real progress towards FDA approval of psilocybin and a field with no clear direction forward.

**Keywords:** psilocin, psychedelic, FDA approval, mental health

## Introduction

Psilocybin, a naturally occurring tryptamine psychedelic found in numerous genera of mushrooms, has been the subject of intense media and popular culture discussion.<sup>1</sup> Hallucinogenic mushrooms have been consumed for millennia around the globe, historically in religious or healing ceremonies. More recently, from the late 1890s through the 1960s, a plethora of hallucinogens isolated and/or chemically synthesized including psilocybin have been described, and human studies were conducted with these hallucinogens for potential treatment of depression and schizophrenia. Psilocybin was evaluated by Sandoz Pharmaceutical company as a psycho-therapeutic drug.<sup>2–4</sup> The Federal Comprehensive Drug Abuse Prevention and Control Act of 1970, more commonly known as the Controlled Substances Act, was enacted to address the registration and distribution of controlled substances in the United States secondary to fear of widespread public utilization of psychedelic substances. As a result of this legislation, psychedelics, then referred to as hallucinogens, were placed under US Drug

Enforcement Agency (DEA) Schedule 1, defined as drugs with no currently accepted medical use and a high potential for abuse, and manufacture and use of these psychedelics was severely limited.<sup>5</sup> These newly introduced limitations upon psychedelics resulted in a virtual pause in any research for decades, until a small research resurgence began in the 1990s, and subsequent push towards clinical trial evaluation of these potentially useful compounds.

One analysis report describes the psychedelic drugs market size as projected to reach \$10.75 Billion by 2027, while growing at a Compound Annual Growth Rate (CAGR) of 12.36% during 2021–2027.<sup>6</sup> To help understand the scope of this clinical research and begin to explore the progress made towards understanding the clinical utility of psilocybin within the confines of regulatorily required data submitted to ClinicalTrials.gov, this retrospective study of clinical trial information listed on ClinicalTrials.gov involving psilocybin was conducted.

## Materials and Methods

### Data Collection

US National Library of Medicine's ClinicalTrials.gov is a website and online database of clinical research studies and information about their results. The purpose of ClinicalTrials.gov is to provide information about clinical research studies to the public, researchers, and health care professionals. The US has laws, regulations, and policies requiring sponsors and investigators to submit certain types of clinical trials to ClinicalTrials.gov.<sup>7</sup> An observational study was conducted with the publicly available information posted on the ClinicalTrials.gov registry as accessed 12/12/2023. The search term, psilocybin, was utilized and provided a list of 147 trials which was then exported as a single file for analysis.

The downloaded information consisted of up to 30 unique fields for each study, although not every field had information entered for every study. The initial list of 147 trials was parsed to focus specifically on those studies specifying psilocybin(e) as an intervention, resulting in 134 trials subsequently analyzed. The 13 trials not included in the final analysis were excluded as they did not specify psilocybin as an intervention. As this study utilized public, non-human subject data not constituting human participant research, does not require Institutional Review Board (IRB) or ethics committee approval, it was therefore not submitted for review, nor did it receive an approval by any IRB.

The components of the available information included in this study were: NCT Number, Study Title, Study URL, Acronym, Study Status, Brief Summary, Study Results, Conditions, Interventions, Primary Outcome Measures, Secondary Outcome Measures, Other Outcome Measures, Sponsor, Collaborators, Sex, Age, Phases, Enrollment, Funder Type, Study Type, Study Design, Other IDs, Start Date, Primary Completion Date, Completion Date, First Posted, Results First Posted, Last Update Posted, Locations, and Study Documents.

Trial records are required to be updated any time there is a change, and ClinicalTrials.gov requires updates to unfinished trials within 30 days to 6 months depending on the type of update or even with no changes to the record. Additionally, any trial completed on or after 1/18/2017 is required to submit results, when subject to Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801), within 1 year of the primary completion date.<sup>7</sup>

### Statistical Treatment

The data were analyzed by GraphPad Prism, version 10.1.2 (GraphPad Software, San Diego, California US). Continuous variables with normal distribution were presented as a count, percentage, or mean and 95% Confidence Interval (CI).

## Results

The earliest recorded start date for any trial listing psilocybin utilization was 4/1/2004. **Figure 1** shows every trial by proposed start year and phase showcasing a continued increase in psilocybin trials, both in sheer number and Phase number escalation. The last 5 years, including the proposed 2024 start year, have amassed 102 trials, and include at least 1 trial in every Phase, except Phase 4 as psilocybin has not been approved by the FDA.<sup>8</sup> However, prior to year 2022, no trial listed as Phase 2/3 or Phase 3 had been submitted to ClinicalTrials.gov.

To date, of the 134 psilocybin trials included in the evaluation, see **Table 1**, 28 (20.9%) have been deemed complete, and of those completions, only 9 (32.1% of the 28 deemed complete trials) have posted results to date. The average number of days reported to complete a trial was 1,217 ±345 (~3.3 years), with the shortest, an Interventional Basic

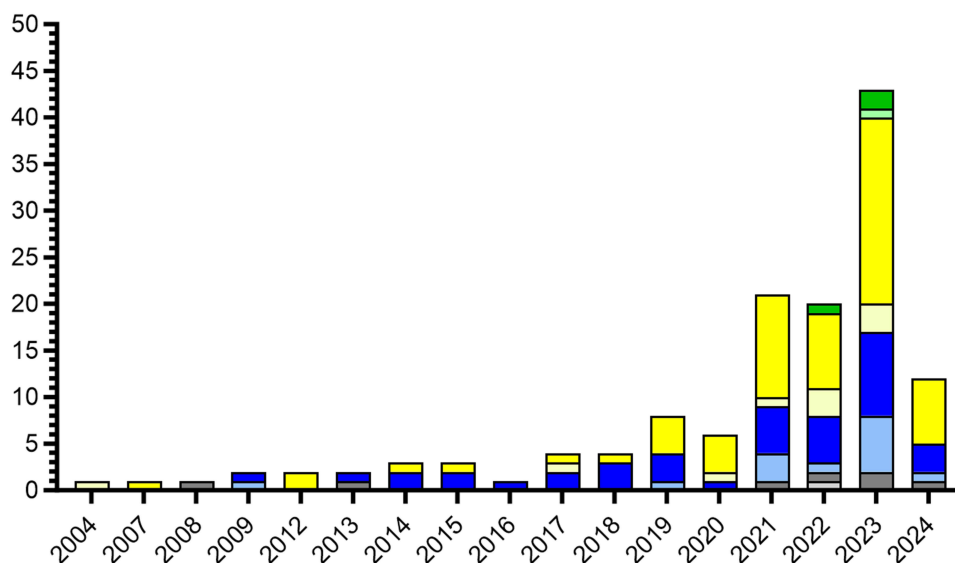


Figure 1 Trials by Phase and Proposed Start Year.

- Blank
- Not Applicable
- Early Phase 1
- Phase 1
- Phase 1/2
- Phase 2
- Phase 2/3
- Phase 3

Science trial (34 participants), lasting 254 days, and the longest, a Phase 2 trial (56 participants), was not completed until 3,532 days (9.7 years) had lapsed.

Of the 134 psilocybin trials evaluated, 32 had no evidence of having been updated on the website for at least 366 days. The largest group, 18 of the 32, are reported as completed trials and may not require additional updates. However, of those 18 completed trials, 13 show primary completion dates after 1/18/2017, yet only 5 have posted results as required. The other 8 trials average 839 ±266 days past the last recorded update. The remaining 11 unfinished trials, with

Table 1 Number of Trials by Phase and Status

Status	Phase									Total
	Early 1	1	1   2	2	2   3	3	4	N/A	Blank	
Completed	2	10	2	12	0	0	0	2	0	28
Active, Not Recruiting	2	6	1	10	0	1	0	1	0	21
Recruiting	4	12	4	20	1	2	0	1	1	45
Enrolling by Invitation	1	2	0	0	0	0	0	2	0	5
Not Yet Recruiting	3	5	2	14	0	0	0	1	0	25
Terminated	0	2	1	0	0	0	0	0	0	3
Withdrawn	1	1	0	3	0	0	0	0	0	5
Unknown	0	0	0	2	0	0	0	0	0	2

Abbreviation: N/A, Not Applicable.

more than a year since the last update and in a status potentially involving participants are 4 Active, Not Recruiting, 3 Recruiting, 2 Not Yet Recruiting, and 2 Unknown Status. Two trials were terminated, and one trial was withdrawn.

There are 54 conditions currently targeted in the psilocybin trials with the most frequently described “condition” being trials (27) done with healthy participants only. The FDA has awarded breakthrough therapy designation for psilocybin in 2018 for treatment-resistant depression (TRD) and in 2019 for major depressive disorder (MDD).<sup>9–11</sup> The analysis revealed TRD (16 trials) and MDD (17 trials) to be the next most common indications. However, if all indications comprising “depression” categories are combined, the total number rises to 39. The next most frequent indications cover substance use concerns including alcohol, tobacco, and opioids at 23 trials (1 trial is a combination of MDD and alcohol use disorder). The remaining 45 trials cover an extensive range of clinical indications.

One hundred and thirty-one psilocybin trials include both male and female participants. Two trials targeting female participants exclusively were focused upon anorexia nervosa and fibromyalgia as their clinical indications. The single male only participant trial involves alcohol use disorder.

The psilocybin trials evaluated have a wide variation in the age range of targeted participant recruitment. The low end of the age range targeted for enrollment ranged from 18 to 60 years of age, and the high end of the age range targeted was 35–100 years of age (or older). The simplest to describe and understand from a potential participant range for inclusion, participants 18 years of age and older, has been used in only 18 trials. The narrowest participant age range described, 60 to 75 years of age, was utilized in 1 trial. There were no documented psilocybin trials planned or conducted in individuals under the age of 18 years identified in this evaluation.

The 134 psilocybin trials evaluated demonstrated a large variation in the number of participants either recruited or planned for recruitment. Table 2 shows the trials broken down by phase and targeted enrollments of <20, 20–100, and >100 participants. 42 trials described a targeted enrollment of less than 20 participants, 80 trials had a targeted enrollment in the 20–100 participant range, and 12 trials with a >100 targeted enrollment. The average targeted enrollment number for a Phase 1 trial was 34 ±13, 49 ±11 for a Phase 2 trial, and 284 ±672 for a Phase 3 trial. For the Phase 2 trials evaluated, there are 19 trials with a targeted enrollment of 20 or less participants, albeit 3 of the trials have a targeted enrollment of zero as their status has been changed to withdrawn. The average when not including those 19 trials bumps the Phase 2 participant number up to 66 ±13.

There are 62 open-label psilocybin trials listed with 53 reporting an estimated start date within the last 5 years. Of those 53 open-label trials, 27 are designated as Phase 2 trials with a targeted average enrollment of only 16 ±3 participants.

**Table 2** Number of Trials by Phase and Targeted Enrollment

Phase	Targeted Enrollment Groups		
	< 20	20 – 100	> 100
Early I	3	10	0
I	16	20	2
I   2	4	6	0
2	19	36	6
2   3	0	0	1
3	0	1	2
4	0	0	0
N/A	0	6	1
Blank	0	1	0
Total	42	80	12

**Abbreviation:** N/A - Not Applicable.

There are 100 unique groups of sponsor/collaborator for the 134 psilocybin trials. Johns Hopkins University is listed as a sponsor/collaborator for 20 clinical trials, the first in early 2007 and with two scheduled to initiate in 2024. The next most active sponsor/collaborator are Compass Pathways and Heffter Research Institute that are each sponsoring/collaborating 13 trials. The next 3 sponsor/collaborator spots are held by Usona Institute (10), Yale University (8), and University of Wisconsin, Madison (7).

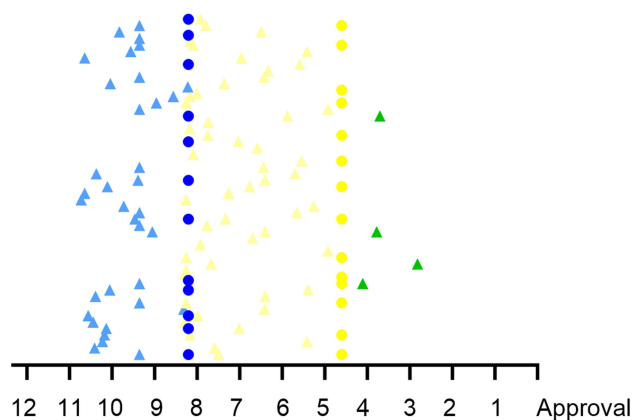
## Discussion

This review evaluates a total of 134 interventional psilocybin clinical trials over a span of more than 20 years as listed on the ClinicalTrials.gov website, and as of this publication, there have been no FDA approvals to date. It is important to remember that those numbers do not include the many decades of research and human work done prior to this century which predated the requirement to be listed upon or even the creation of ClinicalTrials.gov. The process to bring a drug to market from inception to FDA approval is arduous and is reported to average around 12 years.<sup>12</sup> Given the work done with this compound prior to 2004, as well as the 20 years since (eight years beyond the average for a new chemical entity (NCE)), there would appear to be significant roadblocks to approval.<sup>13</sup>

To date, 20.9% of the psilocybin trials listed have been reported as complete. If trials with a proposed start date listed in 2023 or later are removed from the calculation, then the completed trial percentage rises to 35.4%. The remaining 64.6% of trials are in a potential holding pattern to completion, especially the 20 trials in the status Active, Not Recruiting that typically would imply completion sooner than any another status. Possible complications can stem from governmental holds (up to and including pandemic-related movement restrictions), lack of approvals from regulatory authorities including both the FDA (necessary for all drug trials) and the DEA (necessary because of the Schedule 1 designation), insufficient funding, difficulty with participant recruitment, and a lack of drug to study. However, the relative contributions of each potential complication cannot be determined solely from the information available upon ClinicalTrials.gov, but with no current marketing approval, it would imply a significant lengthening over the 20 years evaluated. The average number of estimated days to completion of a trial not already marked completed is  $953 \pm 152$  or  $\sim 2.6$  years. However, reported completed trials actually averaged 3.3 years start to finish, approximately 1.3 times longer than the reported prediction. Two trials have primary completion dates set less than 10 days after the start date of the trial with an average enrollment of 45 participants, and another 3 additional trials set to finish in under 90 days, implying great efficiency around recruiting, running, and finishing a trial. This paints a relatively dismal picture for potentially promising technology with respect to implementation as a therapeutic treatment, most likely related to any or all the following issues: clinical trial design, availability of test product, and/or participant recruitment.

The current estimated timeline to FDA approval of any approvable drug, after inception research and development, in-vitro and *in-vivo* studies, and anything additional necessary to be granted approval for a human clinical trial Phase 1, is averaging 10.5 years, with transition timelines from Phase 1 to Phase 2 at 2.3 years, Phase 2 to Phase 3 at 3.6 years, Phase 3 to New Drug Application (NDA) submission at 3.3 years, and NDA submission to marketing approval at 1.3 years.<sup>14</sup> The four trials listed as Phase 2/3 or Phase 3, based on these estimations, are currently the closest to possible FDA approval with  $\sim 3.6$  years left assuming positive outcomes with the trial, the FDA not requesting additional data or requiring additional studies to be completed, and all other aspects of the NDA are complete (see Figure 2). All other current active or completed trials have timelines considerably longer averaging 9.3 years for Phase 1 and 6.6 years for Phase 2. It is important to stress that these average timelines are calculated for a variety of drugs, from a variety of sponsors, and over various years. Given the Schedule 1 classification, the abuse potential and the first in class status of psilocybin, the likelihood of its timeline exceeding the average is very high.

The FDA has provided guidance on the generally accepted number of participants for each clinical trial phase to include Phase 1, 20 to 100, Phase 2, up to several hundred, and Phase 3, 300 to 3,000.<sup>15</sup> This review demonstrates a targeted enrollment at or below this typical guideline, with average targeted enrollment for Phase 1 trials at  $34 \pm 13$ ,  $49 \pm 11$  for Phase 2 trials, although 19 trials deemed Phase 2 described a targeted enrollment of 20 or less participants, and  $284 \pm 672$  for Phase 3 trials. Considering the inverse relationship between sample size and standard error, meaning as the sample size decreases, the variability of sampling distribution increases, a higher number of participants seems necessary. Also, the uptick in media hype surrounding the use of psychedelics to potentially treat mental health disorders should presumably increase public awareness and likely facilitate enrollment into any clinical trial.



**Figure 2** Proposed Years Remaining Before Possible FDA Approval.

- Completed Phase 1
- Completed Phase 2
- ▲ Active Phase 1
- ▲ Active Phase 2
- ▲ Active Phase 3

Psilocybin has been awarded FDA Breakthrough Therapy designation for the indications of TRD and MDD indications. This designation is meant to allow expedited development and review of drugs intended to treat serious conditions. Preliminary psilocybin clinical evidence indicates it may demonstrate substantial improvement over current available therapy.<sup>9</sup> This designation also makes psilocybin eligible for all Fast Track designation features which provides facilitation of the development and expedition of the review of drugs to treat serious conditions and fill an unmet medical need, with the purpose of getting important new drugs to patients earlier.<sup>16</sup> These designations should unburden the psilocybin field and provide a clear and faster path to FDA approval. However, the 54 distinct therapeutic indications reported in these clinical trials seem large and diffuse for a field awaiting its first approval. The largest grouping, 39 of the 134 trials evaluated, fall under the umbrella of “depression” with the remaining two-thirds of trials focused elsewhere.

Psilocybin has been sometimes given in conjunction with psychological support, although only 9 studies on ClinicalTrials.gov listed “therapy” as an intervention with psilocybin. The FDA recently issued draft guidance stating, “this additional variable (therapy) both complicates the assessment of effectiveness and presents a challenge for any future product labeling” for psychedelics. Furthermore, “the psychotherapy component to any efficacy observed with psychedelic treatment has not been characterized”.<sup>17</sup> This review was not designed to and has no psychotherapy-related data post-FDA guidance, and thus will not address further the psychotherapy component but will continue to discuss the advancement of psilocybin as a therapeutic agent.

Of the trials listed, there are some significant issues that could further delay approvals for this potentially important therapy. Blinding is a crucial feature of clinical trials, and a previous systematic review observed significant differences when trials were not double-blinded yielding 1) a larger estimate of effects ( $P = 0.01$ ) and 2) an odds ratio exaggerated by 17%.<sup>18</sup> Unblinded clinicians may be more unknowingly susceptible to provide assistance differently between treated and untreated groups and could pass their own thoughts on relief of symptoms to these participants. Likewise, unblinded participants could show bias in patient-reported outcomes (PROs), may be less compliant with the trial protocol, and more likely to seek another form of treatment elsewhere. While the need for blinding, particularly in Phase 2 trials, is well known, this review demonstrates that 50% of clinical trials with recorded start dates in the last 3 years alone have been designed without the inclusion of blinding. Unfortunately, the results from these trials may suffer from this preventable bias and eventually prove unreliable. Since the average reported time to completion of a psilocybin trial is over 3 years, this will not be observed nor accurately reported quickly and will likely delay any potential regulatory approval while sufficiently blinded studies are completed and analyzed.

The large disparity in clinical trial inclusion age ranges for these trials is interesting considering 1 in 5 adults/older adults experience mental illness each year and 75% of all lifetime mental illness begins by age 24 in the US.<sup>19</sup> A total of 30 trials evaluated specifically excluded participants aged 18 to 24 years old, which is somewhat perplexing considering that is 22.4% of all the trials listed. This age exclusion, while not explained on ClinicalTrials.gov, could potentially be based upon a fear of undiagnosed schizophrenia in this age group, although the additional monitoring and evaluation involved in clinical trials conducted under Good Clinical Practice (GCP) would not only be able to exclude individuals with this condition from participation but would allow the undiagnosed schizophrenia to begin to be diagnosed, thus benefiting the individual desiring to participate in the trial. Broadening the age range seems prudent as there is no apparent purpose to participants enrolled in the trial based upon age alone and street usage of this fairly popular compound is not regulated or restricted to individuals over the age of 24. While there are certainly more hurdles to involving individuals under the age of 18, it will ultimately become a necessity given the lack of adequate therapies for this age group. To date, there have been no clinical trials recorded enrolling individuals under the age of 18, however, 1 in 6 youths aged 6–17 experience a mental health disorder each year and 50% of all lifetime mental illness begins by age 14 in the US.<sup>19</sup> Putting aside fears of illicit drug use in youths for an adequately studied and approved medication, if the psilocybin field truly believes in the potential mental health benefit of its use, then future trials in pediatric aged participants will be required, should the adult trials demonstrate sufficient safety and efficacy.

Compliance with FDAAA 801 requires the posting of results for completed studies. For 19 psilocybin studies marked as completed, no results were provided, limiting the potential impact, both positive and negative, garnered from those participants for the advancement of the field. More importantly, lessons learned and not shared limit advancement throughout the field and potentially prevent unnecessary or redundant clinical trials from being initiated. This is further compounded considering the average overdue time to post these much-needed results is 2.3 years, delaying access even when those results are finished. Additionally, 11 unfinished trials have not been updated on the registry for over 366 days averaging 791 ±353 days, providing another gap in what could amount to critical knowledge for a potentially important therapeutic in a field in need of new and improved therapeutics.

There are numerous companies and academic researchers actively pursuing psilocybin clinical trials. Although it is beneficial to see competition in the field, many of these trials with start dates in 2023 and 2024 have an Early Phase 1 or Phase 1 status and are small, underpowered trials, with ten of them listed as open-label, and most still examining safety and tolerability of psilocybin. This is interesting given the psilocybin safety profile has been well established for decades, albeit current safety guidelines are more stringent than those of the past. Academic pursuits in both basic and applied research are meaningful and necessary, however, the ultimate goal for any potential therapeutic agent must be approval. This is particularly relevant for those participants who benefited from being on active drug during a trial to be able to (legally) continue effective therapy post-trial and on a larger scale for society who is awaiting a better solution to these conditions. Clinical trials need to be ethically conducted and non-futile. Trials that do not meet this goal beg the question: do these trials push the field closer to FDA approval or are they merely a self-serving approach to join the current trend without apparent strategy or desire to actually obtain approval and marketing authorization to help those who suffer from the condition.

It remains difficult to substantiate how, with no FDA approved indications and a Schedule 1 (defined as drugs with no currently accepted medical use and a high potential for abuse) DEA categorization, the projected market size is expected to exceed \$10 billion dollars by 2027.<sup>5,6</sup> The typical median completion time for a Phase 3 trial is 3.8 years and given there has been no completed psilocybin Phase 3 trials there is no better information available.<sup>20</sup> The typical FDA review time before granting marketing approval after successful completion of a Phase 3 trial and subsequent submission of the comprehensive NDA is 6–10 months. Following approval, numerous additional hurdles remain prior to the first sale on the path to revenue generation which is typically calculated when projecting market size and timing, including a DEA Schedule change, CMS drug code(s), and price negotiation. For the myriad indications and descriptive studies in early phase, open-label, the time for those approvals, assuming successful clinical trial conduct and data quality, is considerably longer, making their contribution to the market size even less obvious and certainly not occurring by 2027.

To fully evaluate the actual potential of psilocybin, purposeful human clinical trials need to be designed well, executed efficiently and professionally, and analyzed utilizing sequential and statistically valid processes for each potential indication. This will require a change from the current exploratory forays across 54 unique indications to defined, well-funded, regulatorily

defined, sequential pharmaceutical development practices, including adequate and appropriate blinding of studies, statistical design to determine the number of participants and more importantly, professional expertise in conducting multicenter trials. This will require savvy investors funding appropriate developmental studies if sufficient progress is desired.

## Limitations

The primary limitation to this study was that it used only information available from the ClinicalTrials.gov registry by design, which was also the primary goal of this study to analyze the available information provided by study sponsors on ClinicalTrials.gov as regulatorily required. Another limitation was the assumption that every record was added and amended with the same understanding of terms as defined by ClinicalTrials.gov and required by the FDA. For example, the Recruitment Status, Recruiting, is defined as “The study is currently recruiting participants”.<sup>21</sup> This definition could be interpreted as 1) the first participant has been recruited, or 2) we can recruit, but have not recruited the first participant. This leaves a broad understanding of the real status of the trial considering, finding people willing to participate in clinical trials is notoriously difficult due to a rising number of new drugs and a dwindling pool of potential subjects due to saturation in the clinical trial market.

<sup>22</sup> Lastly, the information in the registry is fluid, can change at a given moment, and analysis was done on a single snapshot of the data. This analysis shows that overall trends not easily altered in a day, a week, or even a month. However, while writing this paper, some interesting updates to the registry were found such as changing the gender qualification from female only to female and male for one trial, a Phase 1/2 study suddenly becoming a Phase 3, and multiple accounts of trial end dates occurring before their respective start date, mercifully fixed before our final analysis.

## Conclusion

The resurgence of psilocybin as a potential therapeutic has spurred more than a hundred and thirty clinical trials in the last twenty years, but no FDA marketing approval for psilocybin has been achieved yet. Although ClinicalTrials.gov has been a required platform for study sponsors to register and update said trials and is considered an important source of information, the breadth of knowledge attained from the site demonstrates a surprisingly slow progression towards and a less than focused direction in the field to psilocybin approval, not due to lack of interest or scientific merit by investigators or the staggering number of small, eager companies, but rather from lack of sufficient, knowledgeable funding and trial design to move the field forward to benefit those in need.

## Abbreviations

CAGR, compound annual growth rate; CI, confidence interval; CMS, Centers for Medicare & Medicaid Services; DEA, US Drug Enforcement Agency; FDA, US Food and Drug Administration; FDAAA 801, Food and Drug Administration Amendments Act; GCP, Good Clinical Practice; IRB, institutional review board; MDD, major depressive disorder; N/A, not applicable; NCE, new chemical entity; NDA, new drug application; PRO, patient-reported outcomes; TRD, treatment-resistant depression; US, United States of America.

## Data Sharing Statement

The dataset generated and analyzed during the current study is available from the corresponding author on reasonable request.

## Ethics Approval

As this study utilized public, non-human subject data not constituting human participant research, does not require IRB or ethics committee approval, it was therefore not submitted for review, nor did it receive an approval by any IRB.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.



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## Disclosure

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