April 22, 2024

Institute for Clinical and Economic Review
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Lykos Therapeutics (Lykos) appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft report for the assessment of 3,4-Methylenedioxymethamphetamine Assisted Psychotherapy (MDMA-AP) for Post-Traumatic Stress Disorder (PTSD). We ask that ICER consider the following in developing the final report on midomafetamine.

Lykos is a public benefit company committed to addressing unmet needs in mental healthcare. The Company's initial focus is on developing midomafetamine capsules used in conjunction with psychological intervention (MDMA-assisted therapy) as a potential treatment for PTSD*.

In January 2017, Lykos initiated a Special Protocol Assessment (SPA) process with the U.S. Food and Drug Administration (FDA). Lykos received an SPA Agreement Letter from the FDA in July 2017** and was granted Breakthrough Therapy Designation in August 2017. The company submitted a New Drug Application (NDA) to the FDA for MDMA-Assisted Therapy in December 2023, which was accepted and granted Priority Review on February 9, 2024. The FDA is currently reviewing the NDA, including the data from the MDMA-Assisted Therapy clinical program, to determine if it is safe and effective for use in adult patients with PTSD. The target date for the completion of the FDA's review of the NDA is August 11, 2024.

Lykos is disappointed by the ICER draft report as it discounts the significant unmet medical need for patients living with PTSD, relies on a limited number of stakeholder perspectives, and focuses on areas squarely within the FDA's purview on the evaluation of safety and efficacy of drugs in the United States.

Significant Unmet Need for Patients with PTSD

PTSD currently affects more than 13 million adults in the United States[1] with patients experiencing their PTSD symptoms on average for more than six years.[2] Despite this significant need, there have been no new PTSD medications determined to be safe and effective by the FDA in more than 20 years.[3] Furthermore, available approved medications treat individual *symptoms* associated with the PTSD diagnosis but do not treat the *core pathology* of PTSD. Available

* Please note that although the ICER report uses the term "MIDMA-AP," the Lykos-sponsored research and submission currently under consideration with the U.S. Food and Drug Administration (EDA) is for midomafetamine (the U.S. established name for the substance) used in conjunction with psychological intervention (MDMA-assisted therapy) and is referenced as such herein.

** A SPA agreement indicates concurrence by FDA with the adequacy and acceptability of specific critical elements of overall protocol design (e.g., entry criteria, dose selection, endpoints, and planned analyses) for a study intended to support a future marketing application.

evidence-based psychotherapies and pharmacotherapies are often difficult for patients to tolerate[4][5][6] or ineffective for many individuals with PTSD. As a result, an estimated 40-60% of patients remain symptomatic despite treatment,[7][8] and 48% of patients go untreated entirely, due to the lack of available and accessible treatment options.[9] The field has acknowledged for years that patients need better options so they can experience symptom relief and ensure the resumption of (or sustained) successful function in daily life. Effective interventions that address the core pathology of PTSD are desperately needed.

Lykos has a long history of engagement with a broad cross-section of groups representing people living with PTSD and their caregivers. The ICER report neglected to include meaningful input from veterans, first responders, survivors of domestic violence and physical trauma, and other groups representing patients, caregivers, and providers who have valuable perspectives to share on the needs of those living with PTSD.

FDA Review

Lykos' design and execution of the clinical development program for midomafetamine addresses the scientific and regulatory requirements to support a marketing application. Given the novel nature of midomafetamine treatment, Lykos has consistently sought and received feedback from the FDA throughout the development program.

Because the FDA is the regulatory agency tasked by Congress with the authority to evaluate the safety and effectiveness of all drugs distributed in the United States, and Lykos' NDA is currently under review by the FDA, the company will refrain from discussing details of the application in public comments on the ICER report. Unfortunately, the issues in the ICER report were not raised during the three meetings held between ICER and the Lykos management team prior to issuance of the draft report.

Cost Effectiveness Analysis

Lykos is conducting its own cost-effectiveness analysis of MDMA-assisted therapy, leveraging real-world cost estimates from a retrospective claims analysis along with data from its Phase 3 and long-term follow-up studies, the latter for which data will be published in the coming months. The clinical trial data and claims analysis will serve to enable the demonstration of cost-effectiveness when treating appropriate PTSD patients with MDMA-AT.

In conclusion, Lykos is working closely with the FDA as the Agency reviews its application. Given the substantial unmet need and results from the clinical development program, the company is hopeful that patients will soon have access to this potential new treatment.

Sincerely,

Amy Emerson
Chief Executive Officer
Lykos Therapeutics

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[9] Rodriquez et al., 2003.

Otsuka

Otsuka-people creating new products for better health worldwide

April 22, 2024

Submitted electronically to publiccomments@icer.org

RE: Institute for Clinical and Economic Review (ICER) Draft Evidence Report on 3,4-Methylenedioxymethamphetamine-Assisted Therapy (MDMA-AT) For Post-Traumatic Stress Disorder (PTSD)

Otsuka America Pharmaceutical, Inc. (Otsuka) appreciates the opportunity to submit comments on ICER's Draft Evidence Report on MDMA-AT For PTSD.

Otsuka and its affiliates oversee research and development and commercialization activities for innovative products in North America. At Otsuka, our driving philosophy is to defy limitation, so others can too. We seek to serve those with unmet medical needs in three important treatment areas: nephrology, central nervous system, and digital therapeutics. Otsuka is proud to be at the forefront of the research and development of new therapies designed to help patients with Alzheimer's disease, mental illness, and chronic kidney disease. We respect the value within every mind—whether it's a grand idea that changes the world, a simple human connection that changes someone's life, or something in between.

Otsuka offers comments on various elements of the Draft Evidence Report below, including the patient and caregiver perspective, comparative clinical effectiveness, and long-term cost effectiveness.

A. Patient and Caregiver Perspective

Otsuka appreciates ICER's involvement of the patient and caregiver community in development of this report, and shares several of ICER's concerns, as noted below.

Concerns About Trials. ICER cites potential threats to the validity of the trials, including:

- The community of therapists and patients involved in the trial holding very positive beliefs about the therapy prior to participation
- Lack of standardization of the trial
- Possible pressure to suppress negative outcomes of the trial
- Safety concerns regarding follow-up care

Otsuka agrees that all these issues are concerning and may have skewed the results of the trial and efficacy/safety data of the drug. We understand that ICER attempted to gather as much information as possible, and we are hoping that some of these issues become more apparent as this process continues.

B. Comparative Clinical Effectiveness

- Regarding the economic models for MDMA-AP versus Lykos-Specific Non-Assisted Psychotherapy and versus Trauma-Focused Therapies, we agree with many of the methodological issues identified by ICER that cause uncertainty in the models. It was unclear if costs related to the caregiver were included in the societal perspective model. The potential for increase in care/support partner burden needs to be considered since there may be an increase in the need to monitor patients or to accompany them to the psychotherapy sessions.

Additionally, Otsuka would like to comment on the following longer-term considerations:

- Persons with active alcohol and substance abuse disorders, eating disorders and major depressive disorder were excluded from the MAPP1 trial. These are common comorbid conditions for persons with PTSD. It will be critical to determine if the harms of potential addiction outweigh the risks of this therapy in people with co-occurring substance abuse issues.
    - Along those same lines, including the costs of treatment for substance abuse and costs related to withdrawal may need to be added to the model in the future.
- While ICER was only able to model the clinical effectiveness and safety concerns that were reported in the trials, as ICER noted, the follow-up period was likely not long enough to fully understand the benefit/risk profile in the longer term. As new data become available, ICER should update the model.
- While treatment discontinuation was included in the model, the larger question of treatment durability remains. As ICER pointed out, the long-term durability of MDMA cannot be adequately assessed given the current evidence in the public domain. Since the number of treatments will have a large effect on cost to the healthcare system, this will also be important to monitor in the future.

Otsuka appreciates the opportunity to comment on the Draft Scoping Document. If you have any questions about these comments, please contact Heidi Waters at Heidi.Waters@Otsuka-us.com.

Sincerely,

Kaan Tunceli, PhD
VP Global Value & Real World Evidence

April 22, 2024

Foluso Agboola, MBBS, MPH
Vice President of Research
Institute for Clinical and Economic Review (ICER)
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Re: Draft Evidence Report, 3,4-Methylenedioxymethamphetamine Assisted Psychotherapy for Post-Traumatic Stress Disorder (PTSD)

Dear Ms. Agboola,

We, the undersigned, comprise clinical investigators, clinicians, supervisors, trainers, and medical monitors who worked on the Phase 3 clinical trials of MDMA-Assisted Psychotherapy (MDMA-AP) for PTSD. We share a deep commitment to scientific inquiry, ethical research practices, and the integrity and validity of research outcomes. Drawing from our extensive research and clinical experience at major teaching institutions, hospitals, and individual practices, we are compelled to share our concerns about ICER's March 26, 2024 draft evidence report, entitled 3,4-Methylenedioxymethamphetamine Assisted Psychotherapy for Post-Traumatic Stress Disorder (PTSD). The report draws attention to a number of important issues in psychedelic therapy research, such as the problem of functional unblinding, the potential role of expectancy in clinical outcomes, and the importance of ethical practice. However, certain aspects of the Phase 3 MAPP1 and MAPP2 trials of MDMA-AP for PTSD (Mitchell et al., 2023, Mitchell et al., 2021) are misrepresented in the draft report. We are writing to correct and contextualize some of the assertions made there, as failing to do so would represent a disservice to both the scientific endeavor and the patients it aims to benefit.

One hundred and nine therapists and principal/co-investigators contributed to the Phase 3 trials of MDMA-AP for PTSD. To our knowledge, none of them were consulted before the preliminary report was issued. However, this group is in the strongest position to describe the studies and address accusations related to inappropriate study design and conduct. In the absence of such input, a number of assertions in the ICER report represent hearsay, and should be weighted accordingly. This consideration is particularly important because the two sources referenced in section 2.1, “Concerns About Trials of MDMA-AP,” are a podcast and an online article written and produced by individuals who have repeatedly and publicly expressed strongly negative views about the medicalization of psychedelic substances (see Devenot, 2024; Nickles, 2018, 2020), underscoring the high risk of bias in the current draft report.

Choice and validity of the primary outcome measure

The draft report calls into question the validity of the primary outcome measure of the Phase 3 trials, namely, the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). The CAPS-5 is the gold-standard measure of symptom severity used in clinical trials for PTSD (Weathers, et al., 2013). Closely adhering to diagnostic criteria in the DSM-5, the CAPS-5 measures PTSD symptomatology anchored to a specific index trauma (or series of traumatic events) that meets DSM-5 Criterion A for a PTSD diagnosis. Although many participants may have had multiple

distinct life events that contribute to their overall experience of PTSD, rigorous research demands that outcome measures be standardized. As such, the traumatic event selected as the index trauma for the baseline CAPS-5 assessment was also used for subsequent assessments. The ICER report notes that a limitation of this measure is the fact that a participant's symptoms may improve with respect to their identified index trauma, while actually worsening with respect to one or more other traumatic memories; that is, a positive CAPS-5 result might inaccurately represent the patient's overall clinical status. We do not dispute this possibility. However, the accusation that it undermines the validity of the Phase 3 data supporting the use of MDMA-AP for PTSD could be leveled against any other clinical study using this outcome measure—which again, though flawed, is the gold-standard in the field of PTSD clinical research. We do not dispute that some participants may have experienced worsening psychological distress; however, secondary outcome measures (e.g., the Sheehan Disability Scale, the Beck Depression Inventory) and adverse event reporting (e.g., exacerbation of anxiety, suicidality, insomnia) would have captured that distress, even if it was not associated with the index trauma identified on the CAPS-5. However, results from these secondary outcome measures did not show statistically significant worsening; on the contrary, they favored active treatment with MDMA.

Functional unblinding

The ICER report raises the concern that functional unblinding in the Phase 3 trials of MDMA-AP for PTSD may have biased, and might therefore invalidate, the reported outcomes. Though frequently discussed in psychedelic research, functional unblinding is also a concern in conventional clinical research. For example, pharmaceutical interventions are frequently unblinded due to medication side effects, and neither the patient nor the clinician is blinded to treatment in a comparative-efficacy psychotherapy trial (e.g., EMDR vs. CPT). The fact of functional unblinding therefore cannot undermine efforts to approve new treatments for PTSD. Instead, study design should take measures to minimize the effect of functional unblinding. To do so, the study design in the Phase 3 trials of MDMA-AP for PTSD (Mitchell et al., 2023; Mitchell et al., 2021) used independent raters blind to the participant's treatment to assess the primary outcome, obviating any concerns of bias that might emerge if the main efficacy endpoint was administered by a participant or their study therapist.

Standardized intervention

The draft report notes that the challenge of standardizing psychotherapy is not unique to the Phase 3 trials of MDMA-AP for PTSD. However, the draft report relies on hearsay (Institute for Clinical and Economic Review, 2024, page 6) to call into question the generalizability of the Phase 3 MDMA-AP results. It does not note the many measures taken to train, support, and evaluate therapists on those trials—measures that met, and in some cases exceeded, the accepted standards in the field of psychotherapy research (Roth et al., 2021; Wang, 2021; Schoenwald & Garland, 2013;). In addition to therapist training, adherence was rigorously assessed in the Phase 3 trials. Over a number of years, many individuals were trained to rate therapists on their adherence to the MDMA-assisted therapy treatment manual (Wang et al., 2021). Rater cohorts went through a rigorous standardization process to establish strong inter-rater reliability before they were certified for Phase 3 trials (Mithoefer, 2017, 2021). By rating therapist adherence to the treatment manual, a standard of fidelity and quality was assured.

Phase 3 clinical trials are highly structured and standardized by design, and the rigidity of clinical research protocols may not be able to meet all patients' needs. As stated in the draft report, the MAPP1 and MAPP2 protocols did allow for additional integration therapy sessions if these were clinically indicated. Although this flexibility could introduce the potential confound of variable "dose" of therapy, it was driven by the ethical imperative to protect participants and minimize harm. Indeed, our Phase 3 trial experience suggested that some patients might benefit from an extended treatment arc; however, the need for standardized dosing cycles and clear termination time points was a limiting factor, as it is in any clinical trial. Should MDMA-AP receive approval for clinical use, we hope that clinicians will be able to individualize treatment to meet a patient's unique needs in a way that is not possible within the more rigid framework of a Phase 3 clinical trial.

Expectancy and Accurate Reporting

Given the enormous unmet clinical need that PTSD represents, patients and clinicians are predictably enthusiastic about the prospect of a novel treatment for this life-threatening disorder. This phenomenon is by no means unique to MDMA-AP research. In any clinical trial, the pre-treatment hope for, and expectation of, a clinical benefit may account for a substantial proportion of the overall therapeutic effect (Colloca et al., 2023; Weimer, Colloca, & Enck, 2015). In the Phase 3 trials, therapists discussed with participants what their expectations were regarding the study, and took measures to manage them. In some cases, the expectations might have applied to the acute MDMA experience itself—e.g., a participant may have hoped for an experience of euphoria or relaxation. While such experiences did happen, they were not universal, and the Phase 3 protocols called for significant time to be spent discussing the broad range of possible medication-day experiences, which may have helped limit expectancy bias.

Some who benefit from an investigational treatment, or clinicians who see participants do so, may be tempted to idealize the treatment experience, exaggerating any clinical improvements while minimizing any adverse events in an effort to accelerate other patients' access to the treatment in the future. In initial research training and monthly clinical investigator meetings, therapists on the Phase 3 trials of MDMA-AP for PTSD discussed the possibility of biased reporting, which might be well-intentioned, but ill-informed. Therapists encouraged participants to be comprehensive in their description of their acute and long-term experiences in the study, noting that Phase 3 trials are designed to identify not only the potential efficacy of a novel treatment, but also its risks. Therapists noted that the participant's candor in describing the full spectrum of their experience during the study would allow the therapists to support them as fully as possible for the duration of the trial. Moreover, participants were reassured that such candor—and the accurate documentation of adverse events that followed—would allow future patients and clinicians to engage in a comprehensive discussion of risks and benefits that allowed for shared, and patient-centered, decision-making.

Of note, the psychotherapy platform in the Phase 3 trials took a non-pathologizing approach to the participant's emotional experience and expression, whatever its intensity or valence. As practiced in those trials, MDMA-AP comprises elements from a number of other psychotherapies, but particularly exposure therapies, as participants were invited to access and process traumatic memories. Short-term destabilization was therefore expected, as it is in any psychotherapy incorporating elements of exposure. This was discussed with Phase 3 participants

in the informed consent process and throughout the treatment. The ICER draft report intimates that study therapists might have underreported adverse events. Though this seems unlikely, another safeguard against intentional or unintentional bias in the Phase 3 trials was that the *entire* study team was trained in, and collectively responsible for, adverse event reporting. Clinically significant destabilization (e.g., worsening depression or anxiety) was always documented as an adverse event, either by the study therapists or other study staff.

Ethical Concerns

The draft report indicates that one or more participants in MDMA-AP trials suffered significant boundary violations at the hands of study therapists, and suggests that such experiences would alter the risk/benefit analysis for this combination treatment. Unfortunately, the report relies heavily on one particular, well-publicized case of ethical misconduct in a Phase II trial, as well as anecdotal comments made by a small number of undisclosed study participants and unnamed "experts" rather than validated research outcomes (for validated research see Mitchell et al., 2023; Mitchell et al., 2021; Wagner et al., 2021; Jerome et al., 2020). Moreover, treatment-emergent adverse events should not be confused or conflated with malpractice. That being said, the potential for ethical transgressions in this emerging field should not be minimized.

The Phase 3 trials of MDMA-AP for PTSD included a number of features that were intended to protect the participants from undue harm. First, the principle of active, ongoing informed consent was embedded in the research protocols, and explicitly assessed in therapist training and adherence rating. Second, the therapeutic approach centered the participant's autonomy and empowerment, and aimed to minimize power imbalances between participants and therapists. Third, Phase 3 therapists were either licensed psychotherapists or on the path to licensure, which ensured a level of personal and professional training and accountability even outside the study framework. Finally, study-specific therapist training and supervision efforts addressed ethical considerations in the practice of MDMA-AP; therapists were expected to adhere to the MAPS Code of Ethics (Carlin et al., 2019); and challenging cases were discussed in multi-site consultation calls during the Phase 3 trials. Indeed, several of the signatories here have dedicated significant time, energy, and scholarship toward education and advocacy regarding ethical practice, safety, and consent so as to prevent future violations (see Luoma et al., 2024; Rosa et al., 2023; Stauffer et al., 2022; Carlin et al., 2019). We remain committed to self-examination and peer supervision, cultivating self-awareness and seeking out guidance to ensure the safe, ethical practice of MDMA-AP if this treatment receives federal approval.

Conclusion

We appreciate ICER's efforts to evaluate the strength of the evidence in MDMA-AP research, and to prioritize transparency and collaboration in doing so. We appreciate the opportunity to comment on the draft report, which draws attention to some known challenges in psychedelic research design. It also draws attention to some important considerations related to the practice and implementation of MDMA-AP for PTSD, which will require rigorous training of ethical therapists who are held accountable by clinical practice standards and licensing boards. These challenges and considerations do not undermine the dramatic efficacy data and favorable safety profile seen in the rigorous Phase 3 trials to which we contributed. We hope that the final report will take into consideration our input, which draws on the collective effort and scientific data

amassed by hundreds of contributors across over a dozen sites, all under the oversight of institutional, state, and federal regulatory bodies.

Post-traumatic stress disorder is a debilitating mental health condition that significantly disrupts the lives of the 13 million patients who suffer from it, and the many more who care for them. New treatments are urgently needed. Robust primary outcomes in two Phase 3 trials support a positive benefit-risk ratio for MDMA-AP in patients with PTSD, even in severe cases where other treatments have failed. Future research will help quantify whether the benefit-risk profile changes when studying different patient populations, treatment protocols, and/or models of care. But given the enormous unmet need, coupled with robust Phase 3 efficacy data and a favorable drug safety profile, the 13 million patients with PTSD have good reason to hope that access to the combination treatment of MDMA-AP could change their symptoms and their lives. We look forward to reading a future version of the ICER report that more accurately represents the weight of the evidence behind that hope.

Sincerely,

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I am writing to provide public comments on a number of points raised in the ICER report on the use of MDMA-AT for the treatment of PTSD. These comments come from my perspective as an investigator involved in the phase 3 studies. Given this involvement, I believe I can comment on the veracity and interpretation of the phase 3 data, but not on earlier studies.

Research oversight and investigation

To begin, the studies termed MAPP1 and MAPP2 were FDA-guided international phase 3 trials and, as such, were overseen by a number of regulatory and compliance bodies including Institutional Review Boards, Human Research Protection Programs, and Federal Health Administrations. These governing bodies are also those typically tasked with the investigation and remediation of participant complaints. Outside entities, such as ICER, that would like to conduct an independent investigation should work with these governing bodies to ensure that such investigation is conducted properly and involves accurate sampling of the data. In the case of the ICER report, this does not appear to have happened.

Proper evaluation of data requires the inclusion of a complete data set. As ICER notes, their report is informed by a select group of subjective interviews and, although alleging to be based on phase 3 findings, also involves participants and events from earlier studies. As an example, the ICER report notes that, “sexual boundaries were severely crossed with at least one patient”, and that when a “patient was struggling, they were told to take their own supply of MDMA at home”. I have no knowledge of such events in phase 3. The ICER report also notes speaking with “a therapist who had been involved in one of the trials”. I have no knowledge of any of the phase 3 therapists being approached or interviewed for this report.

Functional unblinding

With respect to the phase 3 findings, the ICER report notes that “functional unblinding is a particular concern in this trial”. It is indeed especially difficult to blind a study that uses a psychedelic medication. However, because this point was acknowledged by the team designing the phase 3 trials nearly a decade ago, everyone who evaluated phase 3 primary and secondary outcome measures was blinded; the study therapists were not involved in collecting these data. Indeed, none of the study sites collected primary and secondary outcome measures, which were instead collected by a separate telehealth assessment pool that had no knowledge of where the study participant was located (e.g. which study site), how much of the trial they had completed (e.g. initial, middle, or final evaluation), or whether the participant believed they had received MDMA or placebo. This was the best means of ensuring that the main outcome measures would not be influenced by staff at the various study sites and would also be collected homogeneously between the study sites.

The ICER report goes on to state that, “the pool of therapists… appears to have pulled heavily from the existing community of those interested and involved in the use of psychedelics for possible psychological benefits”, and that, “this led to some participants feeling pressured to report good outcomes and suppress bad outcomes when they were in the MDMA arms of the trials”. While it is possible that there were participants who felt compelled to please their therapy team, outcome measures were never collected in the presence of therapy team members, mitigating the desire for a participant to misrepresent their experience.

Therapist pool

In evaluating a novel medication that could, as the ICER report notes, make participants "susceptible to context" it is important to strike a balance between therapists with prior knowledge and experience regarding the safe administration of the compound and those with no prior knowledge or expectation who themselves are still learning to provide novel clinical care. The phase 3 studies sought to strike this balance by including practitioners both familiar and unfamiliar with the administration of psychedelics. No significant differences were found between individual study sites and no significant differences were found between private practice and institutional study sites, suggesting that practitioners with prior knowledge and experience regarding psychedelics were not unduly influencing the study results.

Inclusion of follow-up data

The ICER report states that, "Some patients were prevented from entering the long-term follow-up study and felt this was done to keep these negative outcomes out of the data set". This is untrue. No participants were prevented from entering the phase 3 long-term follow-up study (MPLong). Indeed, we went through great pains to locate and include all phase 3 study participants in order to evaluate the durability of the study drug. Approximately 70% of phase 3 participants contributed long-term follow-up data, the rest either declined to participate or never responded to our repeated requests for contact.

Comment on ICER's draft evidence report on MDMA-assisted treatment for PTSD

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1. The main conclusion in ICER's draft evidence report that the evidence for MDMA-assisted psychotherapy (MDMA-AP) is "insufficient" is in line with the evaluation of a number of independent, non-partisan organizations, including the American Psychiatric Association (American Psychiatric Association, 2022), the expert committee established by the Therapeutic Goods Administration (TGA) in Australia (Kisely, 2023; Kisely et al., 2023) and the VA/DoD Clinical Practice Guidelines (Department of Veterans Affairs (VA) & Department of Defense (DoD), 2023).
2. It is welcome to see that ICER in addition to the scientific literature also draws on knowledge from other sources, especially interviews with individuals with firsthand or secondhand knowledge of the trials.
3. Given the lack of comparative clinical trials it is difficult to adequately assess relative efficacy and cost-effectiveness. As pinpointed by the draft report, if we compare outcomes across trials, with all the inherent limitations this entails, there is limited indication that MDMA-assisted psychotherapy will confer better outcomes relative to existent evidence-based trauma-focused psychological treatments for PTSD (Halvorsen et al., 2021). A meta-analysis of trauma-focused psychological treatments for PTSD compared to active controls estimated a standardized mean difference (SMD) of 0.83 (95% CI 0.69 - 0.97) in favor of trauma-focused psychological treatments (Lee et al., 2016; see also Merz et al., 2019). In a meta-analysis of the six phase 2 trials of MDMA-AP, the estimated SMD of MDMA-AP compared to control conditions was 0.80 (no 95% CI given; Mithoefer et al., 2019), and in the meta-analysis conducted for the ICER draft report of the two phase 3 trials (Mitchell et al., 2021; Mitchell et al., 2023) the estimated SMD was 0.80 (95% CI 0.49 – 1.10). As discussed in the draft report, dichotomous outcomes, such as response and remission rates, paints a similar picture of the relative benefits of existing evidence-based psychological treatments for PTSD and MDMA-AP (see Halvorsen et al., 2021). Outcomes in terms of change in functional impairment also seems to be relatively equivalent. The ICER draft report estimates a SMD of 0.42 (95% CI 0.17 – 0.66) between MDMA-AP and "LSNAP". A recent meta-analysis estimated an overall SMD of 0.426 (95% CI 0.26 -0.59) between psychotherapy and waitlist or treatment-as-usual in functional outcomes (Bonfils et al., 2022). Of note, there was considerable variability in functional outcomes between specific therapy models, with the best outcomes for existent evidence-based trauma-focused treatments.
   However, as underlined in the draft report, the comparison across trials is associated with a number of substantial limitations, and there is a pressing need for head-to-head comparative clinical trials.

4. Given the combination of functional unblinding and expectancy effects (Aday et al., 2022; Burke & Blumberger, 2021; Flameling et al., 2023; Muthukumaraswamy et al., 2021), in addition to the issues raised by the ICER draft report in relation to "the community", it could potentially be argued that the trials of MDMA-AP conducted to date has many of the same methodological limitations as psychotherapy trials with inactive control conditions, such as waitlist (e.g. differential expectations of benefit between patients randomized to the experimental vs. control condition).
5. Furthermore, the amount of psychological treatment in MDMA-assisted psychotherapy is substantially larger compared to existent evidence-based trauma-focused psychological treatments for PTSD (see Halvorsen et al., 2021). The ICER draft report pinpoints that the amount of psychotherapy is equivalent to 84 therapist hours (p. 10), clearly indicating that the amount of therapist resources needed to provide MDMA-AP is substantially larger than that of existent evidence-based trauma-focused treatments.
6. Not surprisingly, the costs of MDMA-assisted psychotherapy seem to be higher than existent evidence-based trauma-focused psychological treatments for PTSD. The cost of MDMA-assisted psychotherapy is estimated to be between $ 7,543 (Marseille et al., 2020) and $ 11,537 per patient (Marseille et al., 2022), whereas the cost of existent evidence-based trauma-focused psychological treatments for PTSD is estimated to be between approximately £ 2,047 (≈ $ 2,608) and £ 3,140 (≈ $ 4,000) per patient (Mavranezouli et al., 2020). Although these estimates must be interpreted with caution as they are not based on comparative trials directly comparing MDMA-AP and trauma-focused psychological treatments and differences in the model input parameters (e.g. differences in clinician salary in US vs. UK), they give a preliminary, tentative indication that MDMA-AP is a resource demanding treatment. Whether the potential costs of MDMA-AP are reasonably aligned with the potential benefits compared to existent evidence-based trauma-focused psychological treatments remains to be assessed.
7. In line with the aforementioned, the VA/DoD Clinical Practice Guidelines (Department of Veterans Affairs (VA) & Department of Defense (DoD), 2023) has pinpointed that the substantial amount of resources needed to implement MDMA-assisted psychotherapy "could have negative impacts on access for other patients" (p. 69).
8. It is also worth noting that although Marseille et al. (Marseille et al., 2020; Marseille et al., 2022) conclude that MDMA-AP is a cost-effective treatment for PTSD, this is compared to *no treatment* and not placebo or existent evidence-based psychological treatments. Marseille et al. (Marseille et al., 2020) write that since "[t]he control condition in the phase 2 trials does not represent a feasible, real-world treatment option (…) we therefore modeled the costs and benefits of the active treatment group after receiving MAP with the same group at baseline, i.e., as if they had not received MAP." (p. 3-4) In the same line, Marseille et al. (Marseille et al., 2022) explains that "[b]ecause the control condition does not represent a feasible treatment option, we modeled the costs and benefits of the active treatment group after receiving MDMA-AT with the same group at baseline assuming no change in their treatment." (p. 3). Although many patients with PTSD does not receive evidence-based treatment and care for their disorder, it is questionable whether it is reasonable to assume that they do not receive any care or treatment. As such it is good to see that ICER took a different approach to the cost-effectiveness analysis and included the "LSNAP" condition as a comparator. However, it should be stressed, as pinpointed in the draft report, that the "LSNAP" condition is a

bespoke psychological treatment that has not been independently investigated in clinical trials (Cristea et al., 2022). Furthermore, when considering implementing a new treatment into clinical practice we need high-quality comparative trials of the new treatment vs. treatment-as-usual or existent evidence-based treatments in order to perform cost-effectiveness analyses third-party payers can rely on.

9. The resource demanding nature of MDMA-AP can be justified if the treatment helps patients who do not benefit from existing evidence-based psychological treatments. Indeed, it has been argued that MDMA-AP is effective for patients with treatment resistant PTSD and comorbidities that confer treatment resistance, e.g. dissociation. Although a minority of the patients recruited into the clinical trials of MDMA-AP reports to have been offered existent evidence-based trauma-focused treatment previously, there is no explicit evaluation whether they meet criteria for "treatment resistance". There is no consensus-based definition of treatment-resistant PTSD. Treatment-resistant depression is often defined as the patient not having responded to or benefited from at least two to three different evidence-based treatment methods for depression. In accordance with this, a proposed definition of treatment-resistant PTSD is that the patient has not responded to two to three evidence-based treatment methods of adequate dose and quality, where at least one of the treatment courses has been a full course of treatment with trauma-focused treatment (Sippel et al., 2018). There is no information whether patients who have been recruited into the trials of MDMA-AP has received at least one full course of trauma-focused psychological treatment of adequate dose and quality.
10. Furthermore, it has been argued that MDMA-AP might confer benefit for patients with the dissociative subtype of PTSD relative to existent evidence-based trauma-focused treatments (e.g. Mitchell et al., 2021). However, again this has not been formally tested in comparative trials with stratified randomization. Furthermore, there is limited evidence for the assumption that dissociative symptoms moderate the outcomes and benefits of already existent evidence-based trauma-focused treatments (Hoeboer et al., 2020).
11. The draft report also mentions the low dropout rate from trials of MDMA-AT and compare this to what seems to be a larger dropout rate from existent evidence-based trauma-focused treatments. Two recent meta-analyses estimated the dropout rate from existent evidence-based trauma-focused treatments to be between 18% (Lewis et al., 2020) and 20,9% (Varker et al., 2021). This is in line with the dropout rate from psychotherapy in general, which is estimated to be 19,7% (Swift & Greenberg, 2012). However, it is also important to note that different delivery formats might influence dropout rates for existent evidence-based trauma-focused treatments, where intensive or massed treatment formats is associated with a substantially lower overall dropout rate of 5% (Sciarrino et al., 2020).The report pinpoints that a potential explanation for the seemingly low dropout rate from MDMA-AT might be related to the combination of functional unblinding and expectation effects, in addition to the issues the report identifies in relation to "the community". This underlines the need for comparative trials of MDMA-AT and existent evidence-based trauma-focused treatments in psychedelic-naïve patients in order to also assess differential acceptability and tolerability. It is also important to stress that we should be mindful not to equate dropout rates with acceptability and tolerability or poor treatment outcomes (Bisson & Olff, 2021; Szafranski et al., 2017)

12. In conclusion, there is currently limited evidence that the benefits of MDMA-AP for patients with PTSD offset the potential resources needed to provide this treatment.

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To whom it may concern,

I am submitting the following text from a "Petition for the FDA to Convene an Open Advisory Committee Meeting to Hear Concerns on MDMA-Assisted Therapy." The concerns outlined in this petition corroborate some of the details included in ICER's "Draft Evidence Report on Treatment for Post-Traumatic Stress Disorder," as we indicate below.

Each of the authors of this petition have many years of experience working in the field of psychedelic studies; as lead author, I have been active in the field since 2010.

I will add one additional note about this line from the draft report: "Of note, those with concerns about the MAPP trials also have strong beliefs, and this needed to be considered when evaluating information received by ICER" (p.6). It is my position that lived experiences of harm in a clinical trial cannot be equated with the community's strong belief in the healing powers of MDMA-assisted psychotherapy as defined by the MAPS/Lykos protocol.

Sincerely,

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Senior Lecturer
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The text of the petition begins below, with signatories included as an appendix (current as of April 22, 2024):

Petition for the FDA to Convene an Open Advisory Committee Meeting to Hear Concerns on MDMA-Assisted Therapy

We, the undersigned, **call for the FDA to schedule an open advisory committee meeting** on Lykos' application for MDMA-assisted therapy for PTSD. It is imperative that this meeting prioritizes contributions from stakeholders who are concerned about the application's shortcomings and risks.

The approval of a drug-psychotherapy combination would be precedent-setting for the FDA. This is a high-stakes decision with significant consequences. A public advisory committee meeting is essential to preserve the FDA's mandate of protecting and promoting public health. As such, we call for the FDA to organize an advisory meeting for MDMA-assisted therapy (MDMA-AT) with an extended open public hearing (OPH).

The decision to extend the OPH beyond the minimum standard is at the discretion of the committee Chairperson. Given the novelty and public interest of this application, the OPH must include sufficient time for participants who can speak to the concerns identified in this petition.

We are aware that the FDA informed Lykos (formerly MAPS Public Benefit Corporation) of a planned meeting in June 2024, but this meeting was not publicly announced by the time of posting this petition. This advance notice allows Lykos to organize advocates in preparation for the meeting. Although the FDA stipulates that meetings must be publicly advertised at least 15 calendar days before the meeting date, other stakeholders should also be afforded the opportunity to prepare for this meeting. Additionally, given that some former clinical trial participants are disabled, advance notice is a reasonable accommodation for their full participation in the OPH. In light of strong public interest in FDA's decision, this meeting should also be made available by webcast.

If the FDA convenes an advisory committee OPH without sufficient notice or time allotted for other stakeholders, the FDA would be risking public safety and favoring industry interests. While the minimum OPH duration is set at 1 hour, the committee Chairperson has wide latitude to establish a longer OPH schedule. The novelty of MDMA-AT necessitates an extended OPH due to a constellation of special factors, including:

1. Novelty of the drug application: Since MDMA is a psychedelic/entactogen, this application is the first in a new medicine class. As an additional novelty, the FDA has never considered a drug-psychotherapy hybrid application. Further, Lykos purports that MDMA-AT involves a new mechanism of action involving the "inner healing intelligence." MAPS/Lykos' protocols explicitly theorize that "surrendering" to the "inner healer" is "the method of therapeutic action." This construct attributes healing to "ordinarily hidden spiritual dimensions of existence" that are accessed through non-ordinary states of consciousness (Grof, 2006).
2. Significant safety concerns: Evidence from multiple sources indicates that the sponsor has engaged in a pattern of systematic and deliberate omission of adverse events from the public record while minimizing documented harms. **This creates "substantial concerns about the validity of the results"** submitted to the FDA (ICER, 2024). Although we take no position on the ultimate approval of MDMA or MDMA-AT, we have serious concerns about the safety of the therapeutic adjunct to MDMA proposed by Lykos.
3. Unresolved scientific issues regarding safety/efficacy: The March 2024 Institute for Clinical and Economic Review (ICER) report catalogs numerous issues with MAPS/Lykos clinical trials, including issues with blinding, unvalidated uses of

psychometric tools, boundary violations, and inadequate trial designs. As a result of these issues, trial reporting is "unlikely to represent all adverse effects" or to reflect actual treatment efficacy (ICER, 2024).

4. Strong public interest requiring transparency and public input: There are indications that coordinated industry narratives may be skewing public perception of MDMA-AT's safety and efficacy. MAPS/Lykos employs former participants to engage in public relations and political lobbying campaigns, which raises concerns about the impartiality and objectivity of advocacy efforts. These concerns are heightened by reports from veterans who described feeling "used" as political pawns by MAPS/Lykos. There are also allegations that MAPS's lobbying campaign was kickstarted by funds acquired through elder abuse employing the drug under review.

The urgency of convening an advisory committee meeting is also supported by the FDA's own 2008 draft guidance document, which identifies three determining factors. If "one or more" of these factors is met, the issue "should generally be referred to an advisory committee." All three factors are met by Lykos' MDMA-AT application:

1. Is the matter at issue of such significant public interest that it would be highly beneficial to obtain the advice of an advisory committee as part of the agency's regulatory decision-making process? — **Yes.** If approved, MDMA-AT would be offered to some of the most vulnerable patient groups. Applications for psychedelic-assisted therapy are also anticipated to be transdiagnostic, which means that marketing is anticipated for large cross-sections of the public. As a result, this matter holds significant public interest, and the FDA has a responsibility to ensure the safety of potential patients
2. Is the matter at issue so controversial that it would be highly beneficial to obtain the advice of an advisory committee as part of the agency's regulatory decision-making process? — **Yes.** Lykos' application is highly controversial due to evidence (reported below) of data fraud and systematic misreporting of adverse events. Lykos' MDMA-AT protocol is also controversial due to concern that the therapy increases risks to participants.
3. Is there a special type of expertise that an advisory committee could provide that is needed for the agency to fully consider a matter? — **Yes.** Personal, professional, and financial conflicts of interest permeate the research at MAPS/Lykos. As a result, the FDA should solicit testimony from cross-disciplinary experts without such industry ties. The FDA should also hear from trial participants whose experiences are not reflected in official reports. The FDA should not rely on accounts from researchers who are personally and financially invested in the MAPS/Lykos spiritual ideology of the "inner healing intelligence."

The stakes of this petition are emphasized by recent disclosures from a former MAPS PBC employee, who prefers to maintain anonymity at this juncture. The identity of the former employee is known to two of the undersigned authors, and we share this information with their consent. We consider the former employee's accounts to be highly credible.

We believe that these accounts from the former MAPS PBC employee, combined with our collective research and personal experiences, are essential for understanding the implications of regulating the model of MDMA-AT proposed by Lykos. **We emphasize that this petition is**

agnostic to the ultimate decision of the FDA on regulating MDMA-AT. However, we believe that the FDA and the public should be informed about the current evidence base for the proposed psychotherapeutic adjunct.

MAPS/Lykos are alleged to have an internal culture of silence that explains the organizations' limited public acknowledgment of pervasive issues with MAPS/Lykos' data collection and reporting, despite being known to many MAPS/Lykos employees. Accounts have described a "culture of fear" surrounding widely-recognized concerns about the organization's operations.

These concerns include **an organizational culture that normalized violations of IRB, HHS, and FDA regulations**. An account provided by the former MAPS employee suggests that clinical trial investigators would phone Rick Doblin (then MAPS Executive Director) in the event of an incident so that Doblin could determine whether an adverse event should be reported. In turn, Doblin would often respond with justifications for why adverse events should not be filed.

In one account from a clinical trial session involving MDMA, a participant made a serious suicide attempt during a dosing session. **Doblin reportedly instructed the investigators not to report the incident, since he attributed the suicide attempt to the participant's personal circumstances rather than to the MDMA.** Despite Doblin's alleged instructions, this event would have qualified as an "unexpected serious adverse event related to the study" based on the definitions from 21 CFR 312.32(a) (FDA, 2023), which legally obligated MAPS to notify regulatory authorities within seven (7) calendar days. Further, according to the United States Department of Health and Human Services, this event would meet requirements for classification as an "unanticipated problem" or "unanticipated adverse event" and require reporting under HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) (HHS, 2018; HHS, 2007). In another alleged unreported incident, a participant was kept overnight for observation because they remained in a "regressed" state at the end of the MDMA dosing session.

In addition to the internal reports of unreported adverse events, Rick Doblin asserted during a March 2024 SXSW presentation that suicidality only increased in participants in the placebo groups. However, we are aware of records that Doblin was directly informed of increased suicidality in participants in the MDMA groups. We also note that on the public record, multiple participants have described increased suicidality attributable to MDMA therapy.

In another March 2024 panel at SXSW, Lykos CEO Amy Emerson described that increased suicidal ideation is "actually part of the process" involved in psychedelic therapy, but that the existing medical and regulatory systems need to be "taught" to embrace this.

Based on the preceding information, **we cannot rule out the possibility that MAPS/Lykos manipulated clinical trial data to hide adverse events from regulatory agencies,** motivated in part by a belief that these agencies would not understand that these adverse events are a necessary part of their MDMA-AT.

There are additional concerning signs of unacknowledged safety issues in the MAPS/Lykos therapy protocol itself, to the extent that several experts suggest that Lykos' MDMA-AT protocols may *increase* the risk of harm from MDMA relative to other forms of therapeutic support. Multiple researchers have raised concerns that the protocol's emphasis on the "inner healing intelligence" establishes a vocabulary for minimizing participant complaints when real harm is occurring. Multiple accounts of harm in MAPS's clinical trials have already been associated with the spiritually-rooted "inner healer" construct, which has never been scientifically validated.

The MAPS/Lykos therapeutic manual encourages patients to "let go" and "surrender" to the inner healing intelligence, which may amplify the risk of harm associated with increased openness and vulnerability from the effects of MDMA. Directing patients to let go of boundaries is not consistent with contemporary trauma-informed practice, which emphasizes building personal boundaries and increasing a sense of control in patients who have experienced trauma.

There are several well-documented cases of high-profile therapists who have exploited the increased vulnerability of patients in MDMA therapy, including incidents of entrapment, sexual abuse, and coercive control. In the aforementioned case of elder abuse, MAPS board chair Vicky Dulai sent records to George Sarlo's family about his participation in a MAPS clinical trial. These records included the dates of three MDMA dosing sessions between September and December 2020. When Sarlo's health care agent later requested his medical records, MAPS lawyers denied the existence of this trial. This incident raises concerns that clinical trial records might have been hidden, or that a MAPS clinical trial might have been faked as part of a sales pitch to a MAPS funder.

We hold serious concern that these allegations of entrapment, sexual abuse, and coercive control are directly connected to the organisational culture and psycho-spiritual beliefs around "healing" that are encoded in the MAPS/Lykos protocol. Aspects of the psycho-spiritual beliefs associated with the MAPS/Lykos protocol have been employed by high-control therapy groups, where patterns of harm have been linked to their framing of distress as a necessary component of healing and spiritual development.

Since the expertise necessary to evaluate these risks lies outside of the FDA's purview, the FDA must solicit input from outside researchers in order to evaluate the full risks of this protocol. We urge the FDA to investigate the psychotherapeutic protocols while considering the application for MDMA-AT.

We also concur with the ICER report on the current evidence base for MDMA-AT. **We do not have high confidence in the validity or accuracy of MAPS/Lykos' reporting to FDA.** While MDMA-AT may have potential therapeutic utility, there are numerous indications that Lykos' experimental protocol poses significant risks to vulnerable patient groups.

The FDA must take action to ensure that this does not amount to another regulatory scandal like the opioid crisis, where widespread harm retroactively illuminated substantial regulatory failures. If the FDA again prioritizes industry interests over public health, the outcome could mirror the trajectory of OxyContin, which was also once promoted as a wonder drug offering relief from chronic suffering. If an unsafe therapeutic adjunct is sanctioned by the FDA, the resulting harm could result in corrective restrictions that ultimately limit MDMA's potential utility as a therapeutic.

Even if MDMA-AT is approved, the FDA should hold a public hearing to discuss latitude on the psychotherapeutic component. As this petition illustrates, there are serious potential risks in tying the administration of MDMA to the Lykos protocol.

Other concerned parties who support a thorough vetting of the MAPS/Lykos MDMA-AT application by the FDA are encouraged to sign the petition. Click here to become a signatory.

APPENDIX
Signed by Authors:

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Senior Lecturer
Johns Hopkins University

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Independent Researcher

Alaina M. Jaster, PhD
Virginia Commonwealth University

Kayla Greenstien
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Lecturer
The Ohio State University

List of Signatories:

1. Sasha Sisko, Independent Journalist/Researcher
2. Rev. Joe Welker
3. Joar Øveraas Halvorsen, Associate Professor and Consultant Clinical Psychologist, Norwegian University of Science and Technology and St. Olav's University Hospital
4. Hilary Marusak, PhD, Assistant Professor of Psychiatry, Wayne State University
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6. Mike Rabin, Lead Researcher, Corporate Purpose Project
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10. Eiko Fried, PhD, Leiden University
11. Steven Hassan, PhD, Freedom of Mind Resource Center, Inc.
12. Elizabeth S. Geisler, PhD Student, Virginia Commonwealth University
13. Jimmy Smrz, Psyched 4 News
14. Jules Evans, Director, The Challenging Psychedelic Experiences Project
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32. Daniel Garcia, SSDP, Attorney
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54. Robert Forte Independent Scholar, Researcher, & Editor
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62. Tahlia Harrison, MA, MFTA; Therapist, Bioethicist, and PhD Candidate, University of Ottawa
63. Treasure Lundskog, Clinical Social Work Intern, The Ohio State University
64. Carmen Ostrander, MA, Narrative Therapist, Independent Practice
65. Katherine Kaelin, U.S. Army Veteran
66. Nakul Raval, Postdoctoral Associate, Yale University
67. Magen Todd Southam
68. Ethan Solomon, MD, PhD, Resident Psychiatrist, Stanford Health Care

Comment on

MDMA-assisted psychotherapy for PTSD report issued on 3/26/24

To whom it may concern:

I am one of the Principal Investigators on the recently published Phase II and Phase III trials of MDMA-AP for PTSD. I read the recent report with interest. I find the summary to be unreflective of the current science and the nature of our psychiatric research.

I will take issue with two topics: functional unblinding and investigator bias.

Functional unblinding:

Functional unblinding is a well-known element of anti-depressant trials and this accounts for a significant challenge in trial design and outcome interpretation (Walsh et al, 2002). It accounts for as much as 75% of the medication effect documented in SSRI trials and less so, but as much as 50% of the medication effect in anxiety trials for FDA approved psychiatric medications in current use (Mora et al, 2011). Functional unblinding is made up of both expectancy and conditioning effects. Expectancy may be heightened with MDMA and psychedelics and these are most pronounced in depression trials in general. In fact, the response seen to fluoxetine in FDA trials was closely linked to the appearance of adverse effects likely indicating an unblinding effect (Greenberg et al, 1994). Conditioning effects are most pronounced in anxiety trial subjects (closest published studies to PTSD), who in general exhibit less expectancy and placebo responses in trials. The conditioning effects of people with years of failed medications trials would likely constitute a nocebo or negative influence on outcome as the unblinding could trigger a negative conditioning response (Mora et al, 2011). Thus, unblinding is both common and unlikely to purely augment response in this case. Placebo responses are much more of a concern with depression trials with its elevated spontaneous remission rate and much less likely with chronic PTSD which has much lower spontaneous remission rate. The average participant in our studies suffered with PTSD for an average of 14 years. Given this data point, we would expect a very low spontaneous remission rate and a much more limited placebo response.

If these results are called into question because of functional unblinding then all of the results for FDA approved psychiatric medications must be challenged as well. The large effect size found in these results would more than compensate for the minor shifts that could be attributed to unblinding. Paroxetine and sertraline were approved by the FDA and brought into widespread use in spite of similar issues. They exhibited less than of the effect size found in these trials. They remain a cornerstone of medication-based care for PTSD and are wholly inadequate. The comments found in your report on unblinding are biased in nature and unconvincing.

Investigator Bias:

Section 2.1 outlines concerns about investigator bias. All of the study therapists and physicians underwent thorough instruction in investigator bias and this was a constant intention for all of our staff who participated in the trial. This was constantly reiterated at our investigators meeting

and supported with in-depth training on these issues. I can assure you this study was launched with a focus on data integrity and the minimization of bias on many levels. It is interesting to note that many to most of the psychiatric medication trials run by the pharmaceutical industry are led by investigators with deep commercial ties to that industry. I suspect that is not called into question. The effect sizes found consistently in this work represent a breakthrough therapy for chronic PTSD.

Concluding remarks:

The overall tilt of this report does seem quite imbalanced and frankly a bit insulting to those of us involved in this work. This report does not reflect the tone and nature of our research and is highlighted in such a manner to minimize the value of this work for those deeply suffering with chronic PTSD. Please revise this report to better reflect the data and the significant effect size found for those suffering from our inadequate current treatment options.

Scott Shannon, MD
Assistant Clinical Professor, University of Colorado Department of Psychiatry
Board Certified Psychiatrist

KEEPING OUR PROMISE TO AMERICA'S VETERANS

Washington Headquarters
1300 I Street NW, Suite 400W
Washington, DC 20005
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April 22, 2024

Public Comments
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108

Re: 3,4-Methylenedioxymethamphetamine Assisted Psychotherapy for Post-Traumatic Stress Disorder (PTSD) Draft Evidence Report

Dear ICER Team:

DAV (Disabled American Veterans) is grateful for the opportunity to respond to the Institute of Clinical and Economic Review's (ICER) draft report assessing the clinical effectiveness of 3,4 Methylenedioxymethamphetamine-assisted psychotherapy (MDMA-AP), released on March 26, 2024.

As a Congressionally chartered veterans service organization representing more than 1 million wartime service-disabled veterans, DAV is committed to ensuring all who have sacrificed for this nation are afforded the best, most effective health care options available.

While DAV appreciates ICER's efforts in gaining "patient and caregiver perspectives," we believe the three paragraphs contained in section 2 of the draft report are woefully lacking in the complexity and perspectives of those living with post-traumatic stress disorder (PTSD) and their caregivers. PTSD is among the signature disabilities for post-9/11 veterans. According to the Department of Veterans Affairs (VA), nearly 30% of veterans who served in the Iraq and Afghanistan wars report having PTSD at some point in their lives, with 15% reporting the ailment in the past year. These lifetime estimates are higher than veterans who served in the Persian Gulf War (21%) and Vietnam War (10%).

Risk factors for PTSD among veterans include combat deployments, military sexual trauma and training accidents. Experiencing a traumatic event in service does not occur in a vacuum, and many of these incidents can negatively impact a veteran's mental health for months, and even years following the trauma. Living with PTSD can also mean a veteran reexperiences the traumatic event repeatedly. In many cases, these troubling experiences are constantly replayed in their minds, causing severe limitations in everyday life.

PTSD disrupts what many people take for granted. For example, people living with PTSD may find it difficult to leave their homes to perform daily tasks such as grocery shopping, running household errands and attending appointments. They often report memory problems, focusing, and concentrating, or remaining attentive. Those with complex PTSD (C-PTSD) may exhibit chronic hypervigilance or a heightened awareness of their surroundings. These symptoms may prevent driving, for example, if they had been subjected to an improvised explosive device attack, which makes getting to and from work a challenge. These symptoms can also significantly affect one's ability to maintain steady employment or relate to close family members and friends. As they attempt to avoid reliving the trauma, they may seem disengaged, distant, or emotionally detached.

Apart from physically evading physical spaces, avoidance behaviors can negatively impact their overall mental well-being and lead to other co-occurring conditions like depression, extreme anxiety and suicidal ideation. A 2022 study in the *Journal of Clinical Psychiatry* reflects the economic impact of this brain disorder.

According to the article, researchers estimated the total excess economic burden of PTSD as $232.2 billion for 2018. This staggering figure indicates a pressing need for more effective treatments and evidence-based exploration to reduce the clinical and economic strain PTSD has on individuals and healthcare systems. The study also notes an emergent need for new drug developments, as no new medication has received FDA approval for PTSD in two decades.

The guidelines of the Department of Veterans Affairs, Department of Defense and World Health Organization include evidence-based trauma-focused psychotherapy as a first-line treatment. Emotionally processing the trauma memory and integrating new perspectives learned in this therapy aims to disarm the threat imposed by such memories.

However, dropout rates among veterans participating in this type of therapy are high. While rates have varied across studies, a meta-study analyzing PTSD treatments from Iraq and Afghanistan war veterans found the dropout rate to be 36%.

The VA announced new funding of studies to investigate the efficacy and safety of the psychedelic compounds MDMA and psilocybin when taken in conjunction with psychotherapy to treat PTSD and depression, respectively. These studies will be the VA's first in nearly 70 years to investigate psychedelic compounds.

Veterans are desperate for new treatment options and DAV believes more research is needed to verify effectiveness and ensure the safety of any new treatment options. The systematic pharmaceutical development process is necessary, but its glacial pace means often results in veterans taking it upon themselves to seek symptom relief with other drugs and substances. DAV has spoken to veterans who travel overseas searching for treatments that are currently unavailable in the United States. Longing for healing, they are turning to compounds that are often deemed dangerous, illegal or untested for efficacy. Anecdotal evidence among some veterans suggests they are indeed being helped. DAV supports more veteran-related research to answer critical questions of efficacy and safety of alternative treatments such as MDMA and that any medications the FDA approves expeditiously be made available to the men and women who served.

The United States has a solemn duty to make those who return from service forever changed whole again, while understanding, in many cases, this noble pursuit can never be fully realized. However, we know that more treatment options, especially for those veterans with treatment resistant PTSD, will be invaluable in the fight to effectively treat PTSD and improve the lives of those who served us all.

RE: Draft Evidence Report on Treatment for Post-Traumatic Stress Disorder

To whom it may concern,

In the MAPS Study Protocol Document there is reference to a paper titled Gender Differences in the Subjective Effects of MDMA which states the following:

"The fact that equal doses of MDMA per kilogram body weight produce stronger responses in women compared to men is consistent with an increased susceptibility of women to the [serotonin] 5-HT-releasing effects of MDMA."

110. Liechti, M.E., A. Gamma, and F.X. Vollenweider, Gender differences in the subjective effects of MDMA. Psychopharmacology (Berl), 2001. 154(2): p. 161-8.

It's unclear why this paper was referenced by MAPS in the protocol document, but the menstrual cycle was not factored into the study design. A large literature suggests that the menstrual cycle plays a key role in the serotonergic system. A large literature also suggests that the serotonergic system plays a key role in the effects of MDMA.

It's also unclear why outcomes are not reported by sex. This leaves many questions unanswered regarding the safety and efficacy of MDMA for both men and women.

The Evaluation of Gender Differences in Clinical Investigations, which is referenced in the Special Protocol Assessment states the following:

"The guideline identifies three specific pharmacokinetics issues to be considered when feasible: (1) effect of the stages of the menstrual cycle; (2) effect of exogenous hormonal therapy including oral contraceptives; and (3) effect of the drug or biologic on the pharmacokinetics of oral contraceptives."

It's unclear if this data exists at all in the broader psychedelic literature. Phenotypic differences in women related to mental health, the menstrual cycle, and serotonergic fluctuations - which may impact bioavailability and subjective effects - is also not well-represented in the broader literature. This general lack of data is being addressed further in an open letter to the FDA.

All of this said, we do believe that novel treatments such as MDMA, and natural psychedelics hold immense potential for healing mental health ailments. There are many women who have benefited from these treatment modalities for trauma-based conditions stemming from sexual assault, domestic violence, and many other traumatic experiences that are more prevalent in women.

Risk is relative, and for some women battling suicidality, these treatments may be a last resort. Our intent with these comments is not to prevent access to these treatment options, but rather, to reduce harm and to prevent adverse drug reactions. Historically, women have been at a greater risk for adverse drug effects, and we have an opportunity and responsibility to prevent this in psychedelic medicine.

It's unfortunate that MAPS did not consider the paper that they themselves referenced regarding increased susceptibility of women to the [serotonin] 5-HT-releasing effects of MDMA. It is well-documented that women are at a greater risk for developing PTSD and depression - conditions that MDMA is being used to treat.

More information on this topic can be provided upon request. We hope that these discrepancies will be addressed in future trials. We also hope that research which considers female biology will be prioritized as more credible, especially when compared to research that does not account for these variables.

Best regards,

Tina A. Williams

U.S Army Veteran, OIF Campaign

Director, ~~Dysphoric~~ Project

Hailey Llewellyn

Menstrual Health Researcher, Consultant

Director, ~~Dysphoric~~ Project

Mental Health America

April 22, 2024

Institute for Clinical and Economic Review
Two Liberty Square
Ninth Floor
Boston, MA 02109

Dear Members of the New England Comparative Effectiveness Public Advisory Council:

Mental Health America (MHA) thanks the Institute for Clinical and Economic Review (ICER) for inviting public comment on the Draft Evidence Report for 3,4-Methylenedioxymethamphetamine Assisted Psychotherapy for Post-Traumatic Stress Disorder (PTSD).

Mental Health America (MHA), founded in 1909, is the nation's leading national nonprofit dedicated to the promotion of mental health, wellbeing, and illness prevention. Our work is informed, designed, and led by the lived experience of those most affected. Operating nationally and in communities across the country, Mental Health America advocates for closing the mental health equity gap while increasing nationwide awareness and understanding through public education, direct services, tools, and research. Our mental health data reports, based on our National Screening and Prevention program, are among the most widely recognized in the nation.

Upon reviewing the draft report, MHA would encourage ICER to glean additional input from those with lived experience of PTSD, which would serve to address some of the uncertainties about the "frequency of harms and benefits" and the "reliability of reports and benefits" identified by ICER, which resulted in an "insufficient" rating and the exploratory economic analyses. We assert that additional feedback from the patient community is warranted, as doing so will offer a more complete picture of the burden of illness that PTSD presents, as well as insight into how currently approved treatments often fall short of mitigating PTSD symptomatology or offering remission of diagnosis.

Since 2014, MHA has offered free, anonymous, clinically-validated mental health assessments to the general public (https://www.mhascreening.org). Over 24 million screens have been completed for conditions like depression, anxiety, ADHD, and PTSD. Our data around PTSD offers an especially compelling rationale for including additional patient insight into the burden of illness and treatment options and outcomes. Our screeners report many different types of trauma associated with PTSD, including family conflict, child abuse/violence, traumatic event, death of a loved one, intimate partner violence, serious illness/injury/assault, and more. This highlights the complex etiological nature of PTSD and the challenges associated with current treatments. In short, there remains an unmet need within this population.

According to the draft report, those undergoing the MDMA assisted psychotherapy achieved remission at a rate significantly higher than the comparison group, with the trial meeting its

endpoint goal. Moreover, the exploratory results that indicate that the total discounted costs, life years (LYs), quality-adjusted life years (QALYs), equal value of life years (evLYs) gained, and the proportion who achieved response over the lifetime time horizon also were positive for the trial group compared to placebo. Adding additional input from the voice of lived experience might help, in part, to address the "frequency of misreporting of benefits and/or harms and thus the overall balance of net benefit with MDMA-AP."

We thank you, again, for the opportunity to submit these comments. If you have any questions, please feel free to contact me at ntatro@mhanational.org.

Sincerely,

Nathan A. Tatro, MA
Vice President of Alliance Development
Mental Health America

April 4, 2024

To Whom It May Concern:

I am writing in response to ICER's assessment of MDMA-assisted therapy as a patient who healed from childhood trauma-induced PTSD with MDMA-assisted therapy in 2021.

To be transparent, my therapy mirrored the MAPS protocol, but I was not part of a trial. I documented my therapy in my memoir *Rescuing Jill – How MDMA with a Dash of Mushrooms Healed My Childhood Trauma-Induced PTSD*. I also have a YouTube channel where I talk about this therapy. From what I can tell, the biggest difference in my experience versus the trials was the time between therapeutic journeys depended on my progress versus an artificial timeline that is needed for testing. My three MDMA-assisted journeys and integrations had a full-year timeline with months between journeys supplemented with talk therapy.

The therapy saved my life. That statement sounds dramatic because it is. My PTSD symptoms were edging me closer to suicidal behavior when my therapist diagnosed me. I "knew" the universe was against me, I had no control over my life, and I was exhausted in trying to escape what I knew would be a terrible fate.

MDMA-assisted therapy allowed me to look at my childhood memories without the physical trauma responses created when I was a toddler. I could then reframe those memories and realize that my toddler-created understanding that the "universe" was my adversary was the result of an abusive father and a neglectful mother.

I ask when you further review this therapy you keep in mind that MDMA-assisted therapy works differently than any other FDA-approved medicine for PTSD. The speed at which it works can create enthusiasm and hope. I knew this therapy's potential an hour after my first therapeutic journey.

Millions of people suffer from PTSD just in the US. Please be diligent and avoid looking at the MAPS data/anecdotal information with any stigma that surrounds psychedelics.

Sincerely,

Jill Sitnick

The Journey Sage

Cell: 267-446-6772 | www.thejourneysage.com |linkedin.com/in/jillsitnick

Joe Welker
April 20, 2024

RE: Institute for Clinical and Economic Review (ICER) Draft Evidence Report on 3,4- Methylenedioxymethamphetamine-Assisted Therapy (MDMA-AT) For Post-Traumatic Stress Disorder (PTSD)

I am submitting a brief public comment on the draft evidence report for "Post-Traumatic Stress Disorder: An assessment of MDMA-assisted therapy." I comment as someone who used to be involved in the psychedelic industry before becoming a whistleblower.

I would like to focus my comments on Section 2, Patient and Caregiver Perspectives, in deep support and solidarity for the perspectives of those harmed in these trials. The issues described represent similar patterns of abuse across the psychedelic industry. I have also personally encountered the "religious movement" dynamics cited in the report in section 2.1.2 and wish to speak more to them. I share the opinion of other industry critics who have been disturbed by the religious fervor, dogma, and social punishments in this field that evoke the worst of my own religion.

I share concerns that spiritual and religious motives have significantly impacted the quality of Lykos' data. As has been publicly discussed, one stated mission of Lykos' founder Richard E. Doblin, Ph.D., is to "spiritualize humanity,"[i] and researchers with close ties to Lykos admit a decades-long strategy of using science as a vehicle to promote their spiritual beliefs.[ii] While one may argue the legitimacy of these spiritual beliefs on their own merits and the legal issues involved in prohibition, this presents a unique problem: how do we trust data when a company not only has financial conflicts of interest that may impact research quality, but open spiritual and religious conflicts of interest? As an analogy, I believe that if a hypothetical pharmaceutical company with evangelical Christian beliefs made the same application, with the same concerns arising about evidence, and with the same harms happening at the hands of pastors instead of nominally secular therapists, the issues would be even more clear.[iii]

I support research into psychedelics on the principle of supporting scientific research writ large, and I believe extensive future research could bear better fruit. As the report notes, there are people who have experienced healing from PTSD thanks to MDMA, and I support them in their healing journeys. But regarding Lykos and this specific application, I strongly support and echo the concerns of patients harmed in these trials.

Thank you,

Rev. Joe Welker

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[i] Skipper, Clay, "Where the Psychedelic Revolution Is Headed, According to the Guy Who (Arguably) Started It," in *GQ*, October 26, 2021. https://www.gq.com/story/rick-doblin-interview-where-the-psychedelic-revolution-is-headed
[ii] Welker, "The Religious Science of Johns Hopkins: Spiritual Directions," in *Psychedelic Candor*, https://www.psychedeliccandor.org/p/the-religious-science-of-johns-hopkins-4cd.
[iii] Welker, Joe, "Miraculous Shadows," in *Psychedelic Candor*, https://www.psychedeliccandor.org/p/miraculous-shadows.

PIPC Partnership to Improve Patient Care

April 22, 2024

Sarah K. Emond, MPP
President and Chief Executive Officer
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Ms. Emond,

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) assessment on post-traumatic stress disorder (PTSD).

As ICER acknowledges, PTSD is a deeply challenging condition that puts extensive stress on both patients and their caregivers. Current treatment options for PTSD are limited and many patients do not respond to them. Given this urgent need, it will be important for ICER to take an unbiased approach to this assessment to evaluate the potential value of treatments reflecting the diversity of PTSD patients.

ICER should approach this assessment from the societal perspective.

The burden of PTSD impacts patients, their families and caregivers and others. We are concerned that ICER neglects to incorporate the wider indirect costs of PTSD, such as the financial and emotional costs to caregivers and the wider societal impact of the disease, despite relying on sources that describe in detail the significant burden of PTSD.

We urge ICER to consider the robust data that exists on the life effects and day-to-day burden experienced by family members and informal caregivers when caring for someone with PTSD.[1] As PIPC has commented to ICER previously, for diseases that have a considerable caregiver burden and high societal costs, like PTSD, the societal perspective presents a clearer picture than only using the health care perspective. A societal perspective is also recommended for cost-effectiveness models by the 2nd panel on cost-effectiveness[2] convened by ISPOR, the Professional Society for Health Economics and Outcomes Research.[3]

[1] Thandi G, Harden L, Cole L, Greenberg N, Fear NT. Systematic review of caregiver burden in spouses and partners providing informal care to wounded, injured or sick (WIS) military personnel. BMJ Military Health. 2018 Sep 1;164(5):365-9.
[2] Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. Jama. 2016 Sep 13;316(10):1093-103.
[3] Garrison Jr LP, Mansley EC, Abbott III TA, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ispor drug cost task force report—Part II. Value in Health. 2010 Jan;13(1):8-13.

Though ICER acknowledges PTSD to be a highly heterogeneous condition, it still focuses its report on an "average" patient.

ICER states early on that PTSD is a highly heterogenous condition. PTSD's complexity is widely acknowledged, both in terms of PTSD sub-types[4], how its experienced[5] and how it can be treated.[6] ICER chooses, however, to focus its assessment on a hypothetical "average" patient. If ICER intends to provide insight into decision-making around the value of a new therapy for beneficiaries, it should to produce an estimate – or a range of estimates – for as many of that wide range of patients, or patient types, as possible. ICER's methodology falls short of doing this. Providing an estimate of the value of a new drug to a hypothetical "average" patient is not useful information on value, particularly for this diverse of a patient population in which one patient is not representative of most other patients.

It is well established that generating and reporting on differential value assessment estimates across subgroups captures substantial health gains that would not otherwise be considered, both through treatment selection and coverage.[7,8] For ICER's work to be informative to health policy decision makers about the value of new therapies for the diversity of patients seeking treatment, it needs to move away from assuming all patients are the same and the value to each patient can be determined by estimating average value to a patient archetype.

ICER Continues to Use the Discriminatory QALY and the Similar Measure evLYG.

Multiple studies have shown that cost-effectiveness models using the quality-adjusted life year (QALY) discriminate against patients with chronic conditions[9] and people with disabilities.[10] There is widespread recognition that the use of the QALY is discriminatory, reflected in laws that bar its use in government decision-making. The National Council on Disability (NCD), an independent federal agency advising Congress and the administration on disability policy, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that

[4] Campbell-Sills L, Sun X, Choi KW, He F, Ursano RJ, Kessler RC, Levey DF, Smoller JW, Gelernter J, Jain S, Stein MB. Dissecting the heterogeneity of posttraumatic stress disorder: differences in polygenic risk, stress exposures, and course of PTSD subtypes. Psychological medicine. 2022 Nov;52(15):3646-54.
[5] DiMauro J, Carter S, Folk JB, Kashdan TB. A historical review of trauma-related diagnoses to reconsider the heterogeneity of PTSD. Journal of anxiety disorders. 2014 Dec 1;28(8):774-86.
[6] Bonanno GA, Mancini AD. Beyond resilience and PTSD: Mapping the heterogeneity of responses to potential trauma. Psychological trauma: Theory, research, practice, and policy. 2012 Jan;4(1):74.
[7] Basu A. Economics of individualization in comparative effectiveness research and a basis for a patient-centered health care. Journal of health economics. 2011 May 1;30(3):549-59.
[8] Espinoza MA, Manca A, Claxton K, Sculpher MJ. The value of heterogeneity for cost-effectiveness subgroup analysis: conceptual framework and application. Medical Decision Making. 2014 Nov;34(8):951-64.
[9] Paulden M. Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable?. Expert review of pharmacoeconomics & outcomes research. 2017 May 4;17(3):239-42.
[10] Nord E, Pinto JL, Richardson J, Menzel P, Ubel P. Incorporating societal concerns for fairness in numerical valuations of health programmes. Health economics. 1999 Feb;8(1):25-39.

policymakers and insurers reject QALYs as a method of measuring value for medical treatments.[11]

Additionally, we share the concerns of the NCD about the equal value of life year gained (evLYG), a similar measure created by ICER to supplement the QALY. The evLYG is a simplistic fix attempting to address criticism that the QALY devalues life years lived with a disability, yet it fails to account for oversimplified measures of quality-of-life gains in expected life years (not extended life years) and it does not account for any health improvements in extended life years. Like the QALY, the evLYG relies on average estimates based on generic survey data and obscures important differences in patients' clinical needs and preferences, particularly those with complex diseases and from underrepresented communities.[12] It assumes that people value life year gains more than quality of life improvements, giving a lower value to health interventions in patient populations that have a lower life expectancy or fewer life years gained from treatment, which may include people with disabilities, underlying chronic conditions, the elderly, and certain communities of color.[13] With the evLYG and the QALY, ICER promotes two compromised and flawed measures of health gain. Deciding which to choose is confusing and inconsistent.

ICER assumes a linear relationship between severity of disease and utility increments, which is no longer best practice in value assessment.

In recent years, in an effort to ensure that value assessments are portraying an accurate picture, there has been a widespread questioning of several of the assumptions that underpin cost utility analysis.[14] One flaw that has been widely criticized is the assumption that every unit of health gain – measured here in health-related quality of life - is equal in value.[15] In other words, a single unit of health generates the same utility whether that health is accrued to someone with considerable disease burden, or to someone with minimal disease burden.[16] Many HTAs have moved away from this system and apply multipliers to capture the benefit of treatments that provide relief from high levels of burden from disease or disability. HTA systems the world

[11] https://www.ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf
[12] DiStefano MJ, Zemplenyi A, Anderson KE, Mendola ND, Nair KV, McQueen RB. Alternative approaches to measuring value: an update on innovative methods in the context of the United States Medicare drug price negotiation program. Expert Rev Pharmacoecon Outcomes Res. 2024 Feb;24(2):171-180. doi: 10.1080/14737167.2023.2283584. Epub 2024 Jan 25. PMID: 37961908.
[13] Mike Paulden, Chris Sampson, James F. O'Mahony, Eldon Spackman, Christopher McCabe, Jeff Round, Tristan Snowsill, Logical Inconsistencies in the Health Years in Total and Equal Value of Life-Years Gained, Value in Health, Volume 27, Issue 3, 2024, Pages 356-366.
[14] Beresniak A, Medina-Lara A, Auray JP, De Wever A, Praet JC, Tarricone R, Torbica A, Dupont D, Lamure M, Duru G. Validation of the underlying assumptions of the quality-adjusted life-years outcome: results from the ECHOUTCOME European project. Pharmacoeconomics. 2015 Jan 1;33(1):61-9.
[15] Sund B, Svensson M. Estimating a constant WTP for a QALY—a mission impossible? The European Journal of Health Economics. 2018 Jul;19(6):871-80.
[16] MacKillop E, Sheard S. Quantifying life: understanding the history of quality-adjusted life-years (QALYs). Social Science & Medicine. 2018 Aug 1;211:359-66.

over, such as in Norway, the Netherlands and the United Kingdom,[17] are known to adjust their models to account for severity of illness. PIPC suggests ICER also account for the value of health improvements for people experiencing a higher burden of disease or disability.

Conclusion

PIPC urges ICER to consider evolving its value assessment methodology to better account for value to patients and move away from the use of blunt tools that fail to capture the reality of patients' experiences and the benefits of treatment for heterogenous populations.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

[17] Phelps CE, Lakdawalla DN. Methods to Adjust Willingness-to-Pay Measures for Severity of Illness. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research.:S1098-3015.

I'm new to psychiatry, however my mentor shared his every thought process with me during my residency and I have a few thoughts to share regarding your report on MDMA-AT.

First of all, instilling hope when speaking to people with depression, particularly treatment resistant depression, is necessary. A depressed brain is unable to create its own hope, unable to see the brighter side of life, unable to see any way out of misery. Therefore, in speaking to people with severe, treatment resistant depression, it should be considered STANDARD OF CARE to instill hope that the treatment will work. If one does not believe that a treatment will be successful, it is less likely to be so. Frankly, we are also able to see signs of treatment efficacy before the client is able to determine improvement in themselves because of how a depressed brain 'sees'.

Secondly, where the hell was a review like this when the STAR-D study was performed? Have you reviewed Esketamine in this manner? We would have been able to call bullshit on the data presented & years of brainwashing about pharmaceuticals could have been eliminated. This failure of evidence based medicine, once considered by all to be the standard of care, has led to nothing but false beliefs that society continues to cling to & disempowers the patient, distilling their agency.

I agree that this is a particularly important FDA decision that should be critiqued, given significant consideration, and viewed from all sides & angles. I'm grateful for the opportunity that the report presents to do so. However, when presenting your principles, here say & private, anonymous reports, should be explored yet weighed for what they are worth: word of mouth.

As the report admits, it was written through the lens of those who carry significant bias. My ask for this is to set aside your own internal beliefs & motivators (as we are supposed to be capable of in medicine) - and open to new ideas. Review all of the data about MDMA and listen to the incredible testimony of those who have received it. I challenge that its therapeutic potential outscales this narrow medicalized, diagnosis-based application.

I would also like to note and raise concern about the moral fiber & ethical consideration of this report specifically. It's main financial support being that of Arnold Ventures leads me to question the framing of the organization, one led by a former oil company executive & investor. The mission of Arnold Ventures is to use this research to leverage this sponsored research for political & legal gain in pursuit of 'opprutunity' likely within the capitalistic context that its leadership is rooted.

For the purpose of ethical disclosure regarding the ICER report, I present these questions as a challenge: If patients no longer had to attend regular appointments with psychiatry or psychology, would the authors and/or sponsors of the research be affected negatively? If patients no longer required multiple pharmaceuticals on a regular basis, would the authors

and/or the sponsors of the research be negatively affected? If the medical paradigm were to shift away from an allopathic medical model, would the authors and/or the research sponsors be negatively affected? If the cultural paradigm were to shift away from a capitalist society, would the authors and/or the research sponsors be negatively affected?

My guess is that there is much on the line.

The I found the ethical disclosure in the report to be significantly lacking and perhaps others overlooked the authors ties to the pharmaceutical industry, however I did not and question the integrity of this publication, its authors, and the money from the foundation that paid for it to be written.

Thank you for the opportunity to share my opinions, thoughts, and questions regarding this piece of research. I appreciate the oppressed to open additional conversations regarding the issue and look at this large decision from all angles.

Warmest regards,

Rebecca Nedden, PMHNP

To researchers at the Institute for Clinical and Economic Review,

I hope this letter finds you well. I am writing to you today with a matter of utmost importance regarding egregious research misconduct within the realm of pharmaceutical research. As an individual dedicated to clinical research evaluation, I believe your insight and expertise are invaluable in addressing the issues I am about to present.

For the past 38 years, the pharmaceutical research organization known as the Multidisciplinary Association for Psychedelic Studies (MAPS) has been at the forefront of groundbreaking studies investigating the therapeutic potential of MDMA-assisted psychotherapy. However, amidst its achievements, a troubling pattern of research misconduct has emerged, raising serious concerns about the ethical foundation of its endeavors. My extensive investigation, encapsulated in a comprehensive 40,000-word preprint manuscript, delves deep into these ethical and regulatory violations spanning approximately a decade. The manuscript is entitled "Omission Of Serious Adverse Event(s) Within MAPS-Sponsored Clinical Trial Publications Examining MDMA-Assisted Psychotherapy For PTSD" (available at https://osf.io/4tf2s).

The purpose of this letter is to provide ICER with a succinct overview of the broader points highlighted in my research and to elucidate why I believe it is imperative for ICER to consider briefly reviewing the detailed findings encapsulated within the manuscript. By shedding light on these issues, I aim to initiate a dialogue that not only addresses past transgressions in MAPS-sponsored clinical research but also promotes accountability and transparency within the landscape of MDMA-assisted psychotherapy.

In the subsequent pages, I will outline key findings and observations, elucidating the gravity of the situation and underscoring the urgent need for thorough scrutiny of MAPS-sponsored clinical trials. I am confident that your organization's commitment to promoting ethical standards in clinical research aligns with the objectives of my inquiry, and I eagerly anticipate any opportunity to engage in further discourse on this matter.

Before I begin summarizing key research findings, I wish to thank ICER for their previous draft report concerning MDMA-assisted psychotherapy as well as the virtual public meeting set to take place on May 30th. These discussions are essential for promoting increased awareness of the shortcomings/limitations related to this investigational form of drug assisted-psychotherapy.

Thank you for considering my letter, and I look forward to the possibility of collaborating with ICER in addressing these critical issues.

A Prolonged Incident Of Patient Abuse In A MAPS-Sponsored Clinical Trial

My investigations of MAPS-sponsored clinical trials started in December/January of 2021/2022 when I began publicly discussing MAPS' omission of discussions pertaining to a prolonged incident of MDMA-facilitated patient abuse that occurred during a MAPS-sponsored Vancouver-based clinical trial examining MDMA-assisted psychotherapy for chronic, treatment-resistant PTSD.

Specifically, the information which triggered this research was that MAPS researchers publicly offered "heartfelt gratitude" to the abusive study therapists subsequent to MAPS' awareness of the incident. Following more than two years of independent fact-finding missions, I have concluded that the available evidence indicates that MAPS researchers knowingly omitted details of the incident of patient abuse from the relevant clinical literature (and repeatedly deceived the public), potentially as a means to obscure the severity of the incident.

In following this trail of evidence, I came to realize that the apparent majority of the widespread issues/shortcomings related to MAPS research facilitated the Vancouver trial participant's abuse. Specifically, I discuss in my manuscript how MDMA's psychopharmacological properties, the incorporation of touch within MDMA-assisted psychotherapy, and methodological inconsistencies/shortcomings related to MAPS' treatment approach can (in combination) readily facilitate acts of patient abuse/mistreatment. Despite the available evidence pointing in a different direction, MAPS Founder has publicly affirmed his "belie[f]" that MDMA-assisted psychotherapy (as practiced by MAPS therapists) is "safer than" traditional (non-drug) forms of psychotherapy.

In light of the extraordinary amount of evidence indicating that the Vancouver trial participant's abuse was facilitated by the psychopharmacological properties of MDMA and MAPS' therapeutic protocols, I seek to briefly clarify these factors for analysis by ICER and other interested researchers.

After witnessing the Vancouver trial participant's published treatment session footage, MAPS founder Richard Doblin publicly criticized reporters for giving others "the impression" that the participant was being "actively abus[ed]" by her therapists, offering his perspective that the conduct depicted in the footage represents a "technique" involving "psychodrama" which (he believes) "can be beneficial" in the context of psychotherapy. In my investigations, I have determined that the 'technique' described by Doblin is described as a viable approach to psychedelic psychotherapy within Stanislav Grof's book *LSD Psychotherapy,* an opus published by MAPS and utilized as a "primary reference material" in formal discussions with the Food and Drug Administration.

In addition to this, I am presently in possession of rare footage of the Vancouver trial participant telling an audience of several MAPS researchers that she engaged in suicidal behaviour during her MAPS-sponosored clinical trial, yet the available evidence does not indicate that MAPS reported this incident to the relevant authorities. Specifically, the participant stated that she began

walking towards an approaching train in an attempt to throw herself on the tracks. I am willing to provide ICER with this footage.

Following the participant's MDMA treatment sessions in 2015, the participant moved hundreds of kilometers away to live on a remote island inhabited by her MAPS therapists in order to receive follow-up treatment. During this time, the participant was repeatedly exploited by her MAPS therapists, including in the form of sexual abuse. Subsequent to the participant's departure from the island in 2017, she reported this misconduct to MAPS' Senior Medical Director Michael Mithoefer, but MAPS summarily released a public statement that repeatedly described her exploitation as a "sexual relationship" and denied that the reviewed trial footage depicted "signs of ethical violation".

In response to the publication of the trial participant's footage, MAPS' founder Richard Doblin denied that the footage depicted "sexual abuse" despite the fact that the footage clearly depicts one of the therapists pushing their groin against the (drugged) participant's posterior. Two months prior to the release of the participant's disturbing treatment session footage, MAPS Senior Medical Director Michael Mithoefer denied that the abusive therapists' violation of the Vancouver trial participant's boundaries took place "during" her treatment sessions.

Boundary Violations, MDMA's Psychopharmacology, & The Omission Of Adverse Events

As one can tell, there appears to be an observable pattern of behaviour related to MAPS researchers publicly downplaying the severity of the Vancouver trial participant's on-camera abuse and subsequent exploitation. This pattern of behaviour comports with the findings detailed in a recently-released petition concerning allegations of MAPS researchers engaging in a "pattern of systematic and deliberate omission of adverse events from the public record while minimizing documented harms."

Beyond the disturbing allegations detailed in the petition, I have assembled compelling evidence of MAPS researchers omitting descriptions of treatment-emergent adverse events (related to anxiety and insomnia) within previous trial publications. As I detail in my manuscript, I offer a first-of-its-kind analysis of this omission of TEAEs in MAPS trial publications, thereby providing indisputable evidence regarding inconsistencies in the reporting of adverse events across MAPS-sponsored clinical trial publications.

In my manuscript, I also discuss allegations of MAPS-affiliated Swiss study therapists "cuddling on the floor" with trial subjects and how the principal investigator of the Swiss trial has repeatedly endorsed the supposed therapeutic value of therapists "cuddling" with trial subjects.

Just as well, I highlighted the pervasive use of touch within MAPS-sponsored clinical trials while emphasizing the absence of its empirical validation and the potential exacerbation of power dynamics within therapeutic relationships. Despite positive media portrayals, the ethical dimensions surrounding touch remain inadequately addressed with insufficient guidelines and formal training for

therapists, thereby posing significant risks to participant well-being and undermining the credibility of psychedelic therapy research. Perhaps most importantly, I offer an original analysis of how the psychopharmacological properties of MDMA can diminish trial subjects' ability to identify sexualized forms of touch offered by therapists as 'sexual' in nature.

In light of the potential for MDMA's psychopharmacological properties to increase the risk profile of psychotherapy, I discuss in my manuscript how MAPS researchers have continuously highlighted the positive potential of MDMA's psychopharmacology while downplaying or otherwise ignoring how these factors can exacerbate the risks within the context of psychotherapy. The ten psychopharmacological domains identified for analysis in my manuscript consist of (1) impaired detection of external threats and/or negative emotions (2) increased suggestibility/affectability (3) profound personal vulnerability (4) the use of touch and its perceived pleasantness and/or benefits (5) diminished amygdala/fear response (6) decreased defensiveness (7) increased trust (8) increased sexual desire, arousal, and/or "loving feelings" (9) increased transference and countertransference and (10) potentially decreased capacity for consent.

Shortcomings/Limitations Related To MAPS' Therapeutic Approach

In my manuscript, I enumerated several shortcomings/limitations related to MAPS' therapeutic approach. As found within the MAPS Treatment Manual, these shortcomings include the implementation of a non-standardized combination of up to thirteen "psychotherapeutic approaches", offering therapists "creative latitude" to "apply their own intuition" in the treatment room, the implementation of a pseudoscientific concept known as the "inner healing intelligence", and the contextual reframing of MDMA-associated adverse events as a "natural progression of the therapeutic process". In brief, these limitations provide therapists an extraordinary degree of flexibility within the treatment room, so extraordinary that MAPS study therapists retain the ability to manipulate trial subjects into believing that increased anxiety (and even suicidal ideation) is a "part of the[ir] healing process".

Beyond this, it has been independently verified that at least three MAPS trial subjects have experienced simultaneous, paradoxical increases in PTSD-related symptoms (including suicidal ideation/behaviour) during and after heir clinical trial, yet their standardized symptomatology scores (as captured by the Clinician-Administered PTSD Scale) suggested significant symptom alleviation. Despite acknowledging this issue, MAPS researchers have not announced formal investigations into this paradoxical phenomenon. Instead, MAPS has paradoxically announced that while this "limitation" is beyond their "control", MAPS therapists do not intentionally "carry those limitations into the treatment room". Just as well, MAPS founder Richard Doblin has directly implied that MAPS trial subjects who experienced increased suicidality as a result of the medical intervention can purchase "more" MDMA treatment sessions "once" the FDA approves MDMA in the treatment of PTSD.

In addition to this, my manuscript discusses the extent to which Czech psychiatrist Stanislav Grof has influenced MAPS' therapeutic approach. Although Grof is credited by MAPS as having partially "laid the foundation" of their treatment approach, the pervasive influence of Grof's unvalidated hypotheses on the patient-therapist dynamics within psychedelic psychotherapy raise significant concerns regarding the scientific integrity and ethical standards of MAPS-sponsored clinical trials.

Despite lacking empirical validation, Grof's concepts such as 'inner healing intelligence' and 'inner radar' are foundational to MAPS' therapeutic approach, potentially misleading both therapists and patients. Most importantly, my research indicates that the concept of the 'inner healer' has been redefined by MAPS researchers to include the adverse events within MAPS-sponsored clinical trials. According to the aforementioned petition, the inclusion of such MDMA-associated adverse events into this construct "establishes a vocabulary for minimizing participant complaints when real harm is occurring".

The uncritical acceptance of Grof's speculative hypotheses underscores the need for rigorous scrutiny and independent validation of therapeutic practices within MAPS-sponsored clinical trials. Moving forward, it is imperative for researchers to prioritize evidence-based approaches while ensuring that patient well-being remains paramount and (moreover) untethered from unsubstantiated metaphysical claims endorsed by the Czech psychiatrist.

Conclusion

Overall, the evidence compiled within the manuscript submitted to ICER warrants immediate review as it succinctly summarizes the systematic omission of one or more adverse events from MAPS-sponsored trial publications, the organization's disinformation concerning the Vancouver trial participant's abuse, and the organization's widespread violation of professional boundaries within clinical settings. Simply put, my attached manuscript provides significant support for ICER's previous conclusion that there exist "substantial concerns about the validity" of the outcomes obtained from MAPS-sponsored trials examining MDMA-assisted psychotherapy.

It is my hope that ICER views the information presented within these public comments (and my attached manuscript) to be worthy of consideration for future analyses of MAPS-sponsored MDMA clinical trials. I am grateful that ICER has brought attention to these matters and thank your organization for promoting ethical standards in clinical research. Please do not hesitate to reach out for any inquiries.

Warm regards,

Sasha Sisko

Sasha Sisko

Public Comment on ICER's Draft Evidence Report on MDMA-Assisted Psychotherapy for PTSD

I. Introduction

We are grateful for the opportunity to provide feedback on ICER's draft evidence report concerning MDMA-Assisted Psychotherapy (MDMA-AP) for PTSD. Our team comprises four graduate students specializing in neuroscience, biotechnology, and pharmacy. We are committed to enhancing the accessibility and affordability of innovative treatments for those in need. Having thoroughly reviewed the draft report, we outline our detailed comments in the subsequent document.

These comments reflect concerns with the final evidence report's timeline and underlying methodology. Specifically, ICER plans to release the final evidence report based on incomplete data before an FDA assessment has been made, and thus, by design, producing insufficient results. Further, the underlying methodology omits real-world data relevant to treatment benefits to both patients and society. We urge ICER to incorporate the recommendations below and update your methodology and timeline accordingly, enabling policymakers to make more informed decisions regarding drug reimbursement and access.

II. High-level feedback

ICER should wait to release the evidence report until an FDA decision has been made.
In the draft report, ICER gives MDMA-AP the lowest certainty rating, "Insufficient," that the intervention provides a substantial net benefit over the standard of care. The low certainty rating is based on potential concerns about the clinical evidence. ICER goes to great lengths to describe potential concerns, acknowledging that a "limited investigation" had been conducted to verify them. The assessment of clinical evidence should be deferred to the FDA, which, unlike ICER, will have full access to the clinical trial data. The FDA is not expected to decide on the approval of MDMA-AP until August 11, 2024, which will factor in their assessment of the clinical evidence. Yet, ICER plans to release its final evidence report "on or about May 14, 2024". Further, ICER states that should the "insufficient" rating remain unchanged by then, the final evidence report will exclude benefit price benchmarks.

ICER releasing a final evidence report based on incomplete data before the FDA comprehensively evaluates the clinical evidence is premature and could jeopardize patient treatment access. Doing so increases the probability of payers denying coverage based on ICER's "insufficient" rating, even if the FDA later deems the clinical evidence sufficient. This directly contradicts the very purpose of ICER, which is to provide "fair pricing, fair access, and future innovation across the entire US healthcare system."

Concluding that a potentially cost-saving medicine has low efficiency before collecting real-world data is a major disservice to the U.S. healthcare system and patients.
It is worth noting that ICER's exploratory analysis predicts MDMA-AP to be **cost-saving,** assuming the clinical evidence is accurate. On page 29, the exploratory results predict MDMA-AP to yield a total discounted cost saving of $36,000 per patient compared to the placebo (Lykos-specific psychotherapy only). MDMA-AP is also predicted to be more efficient, where patients in the MDMA-AP arm gain more LYs, QALYs, and evLYs, with 219 fewer PTSD-related deaths by suicide per 100,000 compared to the placebo. Applying cost savings per

patient to ICER's potential budget impact of treating 1,893,168 patients per year for the first five years means the U.S. healthcare system could stand to save $341 billion while preventing up to 20,730 suicides by introducing MDMA-AP. Even if the real-world efficiency of the treatment turns out to be only a fraction of this, the impact on the U.S. healthcare system and patient lives would be significant.

The potential real-world impact of MDMA-AP could be even higher than ICER's exploratory analysis when accounting for omitted values.

When accounting for the omitted factors presented in this document, the real-world impact and cost savings could be even *more favorable* than the aforementioned estimates. The draft report acknowledges that it is "common that individuals living with PTSD feel that not one aspect of their life has gone untouched by this condition." As such, ICER's assessment of the intervention should logically extend *beyond* the current framework limited to direct medical costs and productivity measures. While the ICER report has identified some additional considerations subject to voting, **several additional factors are omitted, including dynamic pricing, family/caregiver spillover, community spillover, comorbidity impact, disease-modifying potential, and severity-based mortality risk.**

III. "Benefits Beyond Health and Special Ethical Priorities" subject to voting

We value ICER's willingness to contemplate adding additional value factors beyond direct healthcare and productivity costs to their model. We understand the factors listed below will be subject to a vote to determine the extent to which they should be considered in assessing the long-term value of the intervention. We believe each of these to be crucial for a comprehensive assessment of the intervention's value. Given the evidence, it is challenging to justify the exclusion of either of these factors from the final model.

1. ICER vote: "There is substantial unmet need despite currently available treatments."

We recommend the appraisal committee vote in a way that acknowledges the promising clinical evidence showing improved retention and efficacy rates of MDMA-AP compared to the high nonresponse and dropout rates of current PTSD treatments.

Despite the availability of current interventions, many patients diagnosed with PTSD either do not respond to these treatments or discontinue them prematurely. Nonresponse rates can be as high as 50%,[1,] and dropout rates range from around 20% in RCTs[2] and up to 90% in real-world practice.[3,4] Additionally, after completing an entire course of traditional treatments, around 60% of patients continue to experience clinically significant PTSD symptoms, and only about 31% achieve recovery in military-related PTSD treatment trials.[5] The FDA has approved no new pharmacological treatments for PTSD in over twenty years. Considering that in the MAPP-1 and 2 trials, up to two-thirds of patients in the MDMA-AP arm no longer met the criteria for PTSD after completing treatment, and only 5% of patients discontinued MDMA-AP treatment, this underscores the critical need for innovative therapeutic options like MDMA-AP.

2. **ICER vote: "This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the health care system."**

We recommend the appraisal committee vote in a way that incorporates MDMA-AP's potential to reduce health inequities by providing highly effective treatment for traditionally underserved populations who experience higher PTSD rates and worse outcomes with standard treatments.

PTSD disproportionately affects demographics that have historically been underserved by the healthcare system, such as women,[6] racial and ethnic minorities,[7] who often find current therapies ineffective. Often, they display severe or treatment-resistant PTSD,[8] and have higher drop-out rates and lower treatment retention,[9,10] as well as higher nonresponse rates.[11] Clinical trials of MDMA-AP have shown high efficacy rates, particularly in patients who have not responded to existing treatments. MDMA-assisted therapy offers a promising new avenue for treatment that could be particularly effective for these vulnerable groups. Its potential to provide more effective relief where other treatments may have failed aligns with societal goals to reduce health inequities.

3. **ICER vote: "The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life."**

We recommend the appraisal committee vote in a way that acknowledges that the treatment value of PTSD extends far beyond the affected individual by reducing caregiver burden, family strain, and generational trauma.

Research has indicated that PTSD can lead to more marital problems, family violence, and distress for partners. It has also been shown that children whose parents suffer from mental illness are at an increased risk of experiencing mental health symptoms themselves.[12] Unpaid caregivers, typically direct family members, are especially vulnerable to *both* emotional and financial distress related to caregiving. The excess costs of PTSD in informal caregivers are estimated to be >$80 billion,[13] while excess costs for productivity loss alone are $36.7 billion.[14] Beyond the loss of productivity, caregivers face severe personal and emotional challenges, resulting in the heightened risk of developing depression and secondary trauma. By providing significant psychological breakthroughs more rapidly and effectively than traditional methods, MDMA-AP could potentially reduce the duration and intensity of care required from caregivers, as well as improve caregivers' quality of life while lowering the risk of caregivers themselves developing related health issues.

4. **ICER vote: "The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery."**

    - **Additional information provided by ICER associated with the vote:** "Multiple experimental, preparatory, and integration sessions with at least two therapists leave questions about the feasibility of MDMA-AP administration. Additionally, some participants in the trials have discontinued MDMA- AP treatment due to adverse events."

We recommend the appraisal committee vote in a way that incorporates MDMA-AP's unique action and delivery in enhancing PTSD treatment access, especially for patients with incomplete relief from standard therapies.

MDMA-AP facilitates significant psychological breakthroughs by enhancing emotional engagement during therapy, allowing patients to directly address their underlying trauma,

potentially leading to enduring changes in the patient's psychological state and reducing or eliminating the need for ongoing treatment. With MDMA-AP's potential to modify the disease course of PTSD, the treatment could notably shorten the overall therapy duration, thus easing the burden on mental health systems and improving access to care. By addressing these elements, ICER would not only recognize MDMA-AP's ability to improve PTSD treatment efficacy significantly but also its potential to reduce future medical healthcare expenditures by decreasing the need for continuous treatment and reducing PTSD-related complications.

Feedback on discontinuation concern: As demonstrated in the MAPP1 and 2 trials, the MDMA-AP treatment arm had a low (5%) rate of treatment discontinuation, with a reduced risk of dropout compared to psychotherapy without MDMA. This rate is also significantly lower compared to standard treatments for PTSD, where about 1 out of 5 patients discontinue treatment.[2] Thus, the discontinuation rate appears to be *lower* for MDMA-AP than standard of care (5% and 20% respectively).

Feedback on feasibility concern: While MDMA-AP does require more sessions than typical psychotherapy in the short term, the treatment's potential to provide significant, enduring relief could reduce the overall number of sessions needed in the long term. For instance, while standard psychotherapy often necessitates extended treatment durations across many years for severe PTSD cases, MDMA-AP has shown promise in achieving substantial improvements within a condensed timeframe, particularly crucial for those with severe or treatment-resistant PTSD, who often incur the highest treatment costs and experience the least improvement with traditional therapies.[15]

III. Additional factors omitted from the draft evidence report

The current ICER model employs a static drug pricing approach, which does not account for the significant reductions in drug costs post-generic entry, particularly in cases like MDMA where traditional patent protections do not apply.

We recommend that ICER integrate dynamic pricing models into its MDMA-AP evaluations to accurately reflect the post-exclusivity economic impact, considering the absence of traditional patent protection in this special case.

Dynamic pricing is a critical component in the economic evaluations of new drugs, especially given the substantial cost reductions following generic market entry. While typical U.S. drug patents offer 20 years of protection, potentially extended under certain conditions, the effective exclusivity is often only around 14 years due to the lengthy pre-market clinical trials required. MDMA, lacking traditional patent protection, is subject to an even shorter exclusivity period, with Lykos Therapeutics to be granted about five years of data protection following a potential FDA approval.[16] By adopting a dynamic pricing model, ICER can better align its evaluations with the actual market conditions expected for MDMA-AP, ensuring more accurate and equitable drug pricing strategies to enhance long-term healthcare sustainability.

ICER's model excludes widespread comorbidities, which likely underestimates the overall benefit of intervention.

At a minimum, ICER should incorporate proxies to evaluate the effect of alcohol and substance use disorder on the treatment of PTSD based on existing research.

Over 90% of people diagnosed with PTSD suffer from at least one lifetime comorbid mental disorder, whereby the most common comorbidities are major depressive disorder, alcohol or substance use disorder, and anxiety disorder, as well as eating disorders and chronic pain.[17-19] While the ICER report acknowledges the reduction in depressive symptoms from the MAPP1 trial (although unclear if factored into the final QALY calculations), ICER fails to acknowledge and assess the impact of any other comorbidity associated with PTSD, with the rationale that patients with conditions such as alcohol-, substance use, and eating disorders were excluded from the MAPP1 trial. However, eligible patients in the MAPP1 trial could meet the criteria for mild (current) or moderate (early remission) alcohol use disorder, and MDMA-AP was associated with a significant reduction in alcohol consumption and risk for hazardous use.[20] Although participants in the MAPP1 trial did not meet the diagnosis of an active eating disorder (ED), 31,5% had ED symptoms in the high-risk range, and there was a significant reduction in ED symptoms following MDMA-AP treatment.[21] Extensive knowledge also exists that individuals suffering from PTSD have a much higher risk of self-medicating and subsequently developing alcohol and substance use disorders.[22-26]

ICER's model underrepresents real-world mortality risks associated with different severity levels of PTSD.

We urge ICER to incorporate severity-based mortality rates consistent with the existing literature to account for reduced suicide risk among patients who improve their severity score without going into remission.

The ICER draft report contains inconsistencies in its mortality risk analysis as described on pages 27 and E7. While it initially states that mortality risk was measured "*across severity states (from mild to severe)*," the model validation segment later states that their model "*did not primarily consider varying probabilities linked to changes in the condition but rather emphasized that being asymptomatic lowers the risk of suicide."* ICER acknowledges that this diverges from prior models that *"place greater emphasis on quality of life improvements and significant variations in mortality rates across different severity states."* By not incorporating severity-based mortality adjustments, ICER fails to account for the reduced suicide risk in patients who experience decreases in PTSD severity without fully reaching remission. This illogically assumes that a patient who reduces their severity score from severe to mild as a result of the intervention has *not* reduced their suicide risk.

V. Closing Statement

We appreciate the opportunity to contribute to the discourse on ICER's draft evidence report. ICER's perspective on this issue appears to overlook some of the clear benefits of treating PTSD coupled with a timeline for which the final evidence report will be based on incomplete data and, thus, by design, producing insufficient results. This raises concerns about ICER's approach and underlying motive for this discourse. We are concerned that the focus may not be on achieving a constructive outcome but rather on hindering progress. Despite these concerns, we have sincerely tried to present our arguments, hoping those reviewing this will consider them openly and guide their decisions towards the most beneficial course of action.

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