INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

MDMA-Assisted Therapy for Post-Traumatic Stress Disorder (PTSD)
Response to Public Comments on Draft Evidence Report

May 14, 2024
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Manufacturers		
Lykos Therapeutics		
1.	*Significant Unmet Need for Patients with PTSD* PTSD currently affects more than 13 million adults in the United States with patients experiencing their PTSD symptoms on average for more than six years. 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. Furthermore, available approved medications treat individual symptoms associated with the PTSD diagnosis but do not treat the core pathology of PTSD. Available evidence-based psychotherapies and pharmacotherapies are often difficult for patients to tolerate or ineffective for many individuals with PTSD. As a result, an estimated 40-60% of patients remain symptomatic despite treatment, and 48% of patients go untreated entirely, due to the lack of available and accessible treatment options. 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.	Thank you for highlighting the importance of speaking with relevant stakeholders during this review. We want to emphasize that ICER did reach out to Lykos multiple times and asked to engage with Lykos throughout the review. Unfortunately, Lykos declined to collaborate with us, and did not provide us with any relevant contacts to engage with (clinicians, patient advocates, researchers in the MAPP trials, etc.). However, as part of ICER's standard process, we did reach out numerous experts in the PTSD space. We reached out to over 20 clinicians, 15 patient advocacy organizations, and hosted a focus group with individual patients. Our full list of stakeholders can be found here: https://icer.org/wp-content/uploads/2024/05/PTSD_Stakeholder-List_051424.pdf
2.	*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	Nearly every review that ICER conducts involves therapies under review by FDA. In the vast majority of those cases, companies find that they are able to engage with ICER and discuss reasons for specific design decisions. Lykos to refer to "three meetings" where "issues in the ICER report were not raised". The first of these meetings occurred in August 2023, prior to the start of ICER's review, when MAPS PBC (now Lykos) communicated that they felt the ICER review was early, and, in response, ICER delayed the review by a month. A

	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.	second was held in September 2023, many weeks before publication of even a draft scoping document. The third was in March 2024 where the only engagement Lykos was willing to provide was to suggest that the price for MDMA used in a prior MAPS cost-effectiveness analysis should not be assumed as a placeholder price. Over that time period, ICER asked to engage with Lykos and receive input and feedback, but Lykos chose not to engage. As for the most difficult to assess of those "issues", ICER sent an email to Lykos in early December 2023 stating: *As part of our discussions with experts, we were pointed to the Cover Story podcast that addresses the MAPP trials in its later episodes.* *As follow up to that, we spoke with Lily Kay Ross and Dave Nickles who, as I'm sure you are aware, have a number of concerns about the MAPP trials.* *As we continue our look at the evidence, I wanted to make sure you had the opportunity to address the issues they raise if you want to do so. I understand that MAPS has felt that they have limited bandwidth to engage with ICER's review, but it would also feel unfair to you and the trials not to make you aware that these concerns were brought to us.* As with other outreaches from ICER to Lykos, we received no substantive response. Given this, it seems disingenuous to suggest that Lykos was unaware that ICER would be trying to evaluate concerns about the MAPP trials or that ICER did not try to provide Lykos an opportunity to engage.
3.	*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	Authors related to MAPS previously published a cost-effectiveness analysis on this, and MAPS PBC asked us to disregard said analysis. Furthermore, we reached out to MAPS PBC/Lykos with a data

	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.	request after publishing the revised scope, asking them to provide us with data and inputs for our model and analyses.
Otsuka America Pharmaceutical, Inc.		
1.	**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.	Thank you for this comment.
2.	**A. 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.	The modified societal perspective analysis included indirect cost estimates from Davis et al 2022 which included the costs of caregiving. We have revised Section E2 of the report to offer more clarity regarding indirect cost inclusions.

3.	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. o 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.	We agree that the costs of treatment associated with substance abuse disorders may need to be added to future modeling efforts. However, given exclusions for moderate to severe alcohol and cannabis use in addition to exclusions of other substance abuse in MAPP1 and MAPP2, short-term and long-term research on substance abuse and changes in substance abuse from MDMA-AP is needed to advance modeling in this area. We added text to the controversies and uncertainties section to signal its importance to the research community. We agree that it is important to assess long-term durability of MDMA-AP, and we hope to see additional long-term follow-up studies in the future.

#	Comment	Response/Integration
Clinical Experts		
Casey Paleos, MD and Clinical Investigators Who Participated in the Phase III Trials		
1.	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.	Please see the response to Lykos above. It is typically the case that investigators in manufacturer-sponsored trials will only engage in ICER reviews when the manufacturer gives permission and connects those investigators with ICER. As such, when Lykos did not engage, ICER did not attempt to directly contact investigators. As you can see from the quoted email in the response to Lykos above, Lykos was informed of the concerns ICER was hearing. ICER would have been happy to engage with any investigators or therapists that Lykos had connected us with as a way to work through these concerns. Despite all this, as noted in the Draft Report, ICER did speak with a therapist involved in the trials.
2.	*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,	Thank you for your comment. We agree broadly with your comments, however, that does not mean that there are no limitations to using CAPS-5.

	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.	
3.	*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.	Important levels of functional unblinding are relatively uncommon in drug trials, but when it may have occurred, ICER discusses it as a concern. See, for instance, ICER's reviews of therapies for Alzheimer's Disease.
4.	*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,	Independent of the information we received from patients in section 2.1, it is recognized that establishing a standard therapy in psychotherapeutic trials poses difficulties. While we acknowledge the efforts made by Lykos, it does not completely alleviate the concerns of generalizability.

	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.	
5.	*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.	We heard from multiple experts, and reviewed multiple publications on this topic and it is established that there are issues around expectancy when using MDMA-AP in this unblinded trial. The impact of expectancy bias is well documented in the literature. This raises uncertainties in relation to the true clinical effectiveness.

	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.	
6.	*Ethical Concerns* The draft report indicates that one or more participants in MDMA-AP trials suffered significant boundary violations at	We believe that the Report is quite clear that we are uncertain about the frequency of harms. It is concerning that we heard

	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.	first-hand reports of harms that were not described in published reports of the MAPP trials, but we recognize that we do not have the resources to examine primary data to determine the balance of benefits and harms. We believe that regulatory agencies with authority to review such data should be sure to carefully review these issues. It seems unusual in a phase III trial to have therapists "on the path to licensure", but we recognize that many psychotherapies have not been evaluated in adequate trials.
Jennifer Mitchell, PhD		
1.	*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	Typically, ICER works with the manufacturer around data concerns. Please see the discussion above about ICER's interactions with Lykos.

	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.	The mention of sexual boundaries being crossed refers to an event in a phase II trial. The wording in the Draft Report was ambiguous and has been revised to make this clear. That you are unaware of an event of a patient being told to take their own MDMA does not alter our evaluation of the event. As mentioned in the Report, we have chosen to maintain anonymity of people we spoke with, even though it does somewhat decrease the transparency we would typically want in an ICER report.
2.	*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	We agree that attempts were made to mitigate functional unblinding. We remain concerned that functional unblinding may have had important effects on reports of benefits and harms despite these mitigation efforts.

	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.	
3.	*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.	This is the sort of data (with specific numbers and statistical analyses) that we would have appreciated receiving from the manufacturer, Lykos. This is why we engage with manufacturers whenever possible.
4.	*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.	We had first-hand reports of such events. We cannot be certain that these reports were accurate, but we do wonder whether Dr. Mitchell is certain that this could not have occurred.
Joar Halverson, PhD.		
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	Thank you for this comment.

	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.	Thank you for this comment.
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.	Thank you, we agree with your comment regarding 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	Thank you for this comment.

	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.	Thank you for this comment.
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.	Thank you for this comment. Our exploratory cost-effectiveness analysis can be useful in interpreting the additional costs associated with MDMA-AP as well as the potential benefits. Please also find more details on our cost by severity calculations in the Supplement.
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).	We hope to discuss topics such as access and coverage at the policy roundtable on May 30th.
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	Thank you for this comment.

	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	Thank you.

	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).	We agree that more evidence is needed on the relationship between MDMA-AP and treatment outcomes among patients with dissociative subtype of PTSD.
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)	Thank you for this comment. We revised a portion of our report to reflect the potential for lower dropout rates among intensive treatment formats.
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.	Thank you.

Nese Devenot, PhD		
1.	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. [Full Petition available via https://docs.google.com/forms/d/e/1FAIpQLSf1z9uJAdYxKGgv-pMGUL_e0wHKC_4YrzN33ZYu9E-Ka-8Cfw/viewform]	Thank you for sharing your petition with us. As Dr. David Rind said in ICER's press release on March 26, "Current therapeutic options are insufficient for many people with PTSD. While MDMA-AP may be a promising therapy for PTSD, functional unblinding in the clinical trials and additional concerns around trial design and conduct leave many uncertainties about the balance of benefits and harms. It will be incumbent on regulators with complete access to primary data to carefully assess whether MDMA-AP has been proven safe and effective."
Scott Shannon, MD		
1.	**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	Important levels of functional unblinding are relatively uncommon in drug trials, but when it may have occurred, ICER discusses it as a concern. See, for instance, ICER's reviews of therapies for Alzheimer's Disease.

	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.	
2.	**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.	Concerns around investigator bias were pervasive when we spoke with experts in the field. This came from many more people than the small number who raised many of the other issues discussed in section 2.1. In most trials, blinding protects against nearly all investigator biases during the intervention period of the trial. Investigator actions during the design phase and then during the evaluation phase of trials (after blinding has been broken) are routinely raised as concerns.
3.	**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.	We note that, after publication of the Draft Report, ICER heard concerns from those who felt the Report was unbalanced by focusing mainly on possible biases among those who are proponents of MDMA-AP and also heard concerns from those who felt the Report was inappropriately trying to appear balanced by also highlighting possible biases in those who have raised concerns about the MAPP trials. While receiving concerns from those on both sides does not prove that ICER struck an appropriate balance, it

		does suggest that some perceptions of bias may be in the eye of the beholder.

#	Comment	Response/Integration
Patient/Patient Groups		
Disabled American Veterans		
1.	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%).	Thank you for bringing this to our attention. We have contacted your representatives and asked your organization to participate in the public meeting on May 30th to provide further details on the lived experience of veterans.
2.	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-	Thank you for your comment. We've added additional material to our Patient and Caregivers Perspectives to reflect inputs received from Disabled American Veterans and other patient groups since the posting of our Draft Report.

	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.	

3.	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.	Thank you for your comments. We hope to discuss access to novel therapies such as MDMD-AP at the policy roundtable on May 30th.
Dysphoric Project		
1.	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.	Thank you for your comments.
2.	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.	Thank you for your comments.

	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.	
3.	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.	Thank you for your comments.
Mental Health America		
1.	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.	In addition to adding language to our report, we reached out to multiple patient organizations to invite them to share their stories and lived experience at our public meeting on May 30th.

2.	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 agree that if the remission rates are unbiased, this looks like an effective therapy. Unfortunately, we have some concerns around the certainty of these data. We look forward to hearing additional patient testimony at the public meeting on May 30th.
The Journey Sage		
1.	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.	Thank you for sharing your story with us.
2.	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	Thank you for your comment.

	enthusiasm and hope. I knew this therapy's potential an hour after my first therapeutic journey.	
3.	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.	Thank you. We can assure you that we base all of our reviews on the same framework and methodological practices, regardless of any controversy surrounding the disease space or therapies.

#	Comment	Response/Integration
Other Stakeholders		
Joe Welker		
1.	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.	Thank you for your comments.
2.	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," and researchers with close ties to Lykos admit a decades-long strategy of using science as a vehicle to promote their spiritual beliefs. 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.	Thank you for your comments.
3.	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 for your comments.
PIPC		
1.	**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	Thank you for your comments. We did include productivity changes and other indirect costs in a separate modified societal perspective analysis in the Supplement, Table E10.

	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. 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 convened by ISPOR, the Professional Society for Health Economics and Outcomes Research.	
2.	**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, how its experienced and how it can be treated. 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. 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.	Thank you for your comments. ICER reports evaluate drugs (therapies or treatments) and we look at the average price for these drugs in our analyses.
3.	**ICER Continues to Use the Discriminatory QALY and the Similar Measure evLYG.**	Thank you for this comment. We invite you to review our Value Assessment Framework for a detailed overview of the

	Multiple studies have shown that cost-effectiveness models using the quality-adjusted life year (QALY) discriminate against patients with chronic conditions and people with disabilities. 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 policymakers and insurers reject QALYs as a method of measuring value for medical treatments. 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. 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. With the evLYG and the QALY, ICER promotes two compromised and flawed measures of health gain. Deciding which to choose is confusing and inconsistent.	different methods and concepts we use in our reviews: https://icer.org/our-approach/methods-process/value-assessment-framework/ The quality-adjusted life year (QALY) is the academic standard for measuring how well all different kinds of medical treatments lengthen and/or improve patients' lives, and therefore the metric has served as a fundamental component of cost-effectiveness analyses in the US and around the world for more than 30 years. If evidence shows that a treatment helps lengthen life or improve quality of life, these benefits are comprehensively summed up to calculate how many additional QALYs the treatment provides, and this added health benefit is then compared to the added health benefit of other treatments for the same patient population. To complement the use of the QALY, ICER's reports also include a calculation of the Equal Value of Life Years Gained (evLYG), which evenly measures any gains in length of life, regardless of the treatment's ability to improve patients' quality of life. In other words, if a treatment adds a year of life to a vulnerable patient population – whether treating individuals with cancer, multiple sclerosis, diabetes, epilepsy, or a severe lifelong disability – that treatment will receive the same evLYG as a different treatment that adds a year of life for healthier members of the community. By understanding a treatment's cost per evLYG, as well as its traditional cost per QALY, policymakers can take a broader view of cost-effectiveness and be reassured that they are considering information that poses no risk of discrimination against any patient group.

4.	**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. 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. 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. 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 over, such as in Norway, the Netherlands and the United Kingdom, 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.	ICER has begun looking into novel ways to quantify preferences related to severity, methods that often are framed as abandoning an assumption of a linear relationship between health gain value and replacing it with a formula that can capture risk aversion, severity, and the value of insurance. We will focus on exploring the Generalized Risk-Adjusted Cost-Effectiveness framework and methods adopted by several international HTA programs that now weight health gains in relation to severity. In this effort to examine these methods, we will engage our Health Economics Council, Methods Advisory Group, and other researchers and stakeholders including international HTA bodies prior to testing the feasibility and impact of shifting to differentially weighting cost-effectiveness findings. We will also continue to monitor advances in methods as well as monitor changes made in the health technology assessment ecosystem on this topic. And, as a result of this special focus, ICER may entertain making an interim update to its Value Assessment Framework on this topic prior to the next overall update.
5.	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.	Thank you. You are welcome to submit comments on our methods and value assessment framework during the next update cycle.
Rebecca Nedden		
1.	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'.	Thank you for your comments. You can find our previous work on treatment-resistant depression here: https://icer.org/assessment/depression-2019/ It seems common today, and perhaps in the past as well, to assume that those who disagree with us must have corrupt motives. ICER and its funders have no stake in the results of our reports.

2.	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.	All of ICER staff, and our external collaborators, adhere to strict conflict of interest policies that you can find here: https://icer.org/our-approach/policies/policies-to-manage-conflicts-of-interest/. At the public meeting on May 30th, all speakers have to disclose any conflicts.
3.	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.	
4.	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.	
5.	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.	
6.	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.	
7.	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.	
Sasha Sisko		
1.	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).	Thank you for this detailed overview. ICER does not have any regulatory, investigative or law enforcement authority. We hope that you are able to share your materials with the appropriate organizations who conduct investigations into alleged trial misconduct.
2.	**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.	
3.	**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.	
4.	**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.	
5.	**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.	
Therese Dalebrant, Michelle Müller, William Hsieh and Hyeongeun Cho		
1.	**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	ICER's Final Evidence Report will be published after the public meeting. The report will be published on June 27, 2024. This is six weeks prior to the expected date the FDA will make a decision. You are welcome to review the ICER Evidence Rating Matrix™ in further detail on our Value Assessment Framework: https://icer.org/wp-content/uploads/2024/02/ICER_2023_2026_VAF_For-Publication_021324.pdf

	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.	The founder of MAPS had contacted ICER previously to suggest that MDMA-AP might be an appropriate topic for an ICER review. When ICER was about to begin its review we again connected with the founder of MAPS to share our interest in a near-term review of this topic. The founder of MAPS felt that it was "good to learn" of our near-term interest in this topic and he did not convey any concerns at all about the timing of our interest.
2.	**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."	ICER strives to complete most drug assessments around the time of FDA approval because this is when an independent assessment of value is most helpful in informing the critical decisions that stakeholders across the US health system need to make around pricing, coverage, and prescribing. While it may seem premature to assess the value of a treatment before it has been given to a population in a real-world environment, this is precisely what pharmaceutical companies do when they set the treatment's initial price. ICER provides an independent and transparent analysis of comparative clinical effectiveness and cost-effectiveness for any stakeholder to review. While we appreciate your inquiry into these aspects of our work, it appears that all of the authors of this public comment are affiliated with No Patient Left Behind, but this organization is not listed as an author in your comment. We invite you to clarify whether these comments were drafted in collaboration with No Patient Left Behind. We believe that transparency is important when participating in public discussion on these topics. ***Updated on May 17, 2024:*** *The authors of the public comment clarified that they participated in a fellowship at No Patient Left Behind but submitted the public*

		comment independently from the organization.
3.	**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.	We are not aware of any decision-makers using real-world data at the time of FDA approval. Real-world data can only be collected and synthesized after the treatment has been on the market, and available to patients.
4.	**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.**	We agree that there may be spillover effects and the costs of treatment associated with substance abuse disorders may need to be added to future modeling efforts. However, given exclusions for moderate to severe alcohol and cannabis use in addition to exclusions of other substance abuse in MAPP1 and MAPP2, short-term and long-term research on substance abuse and changes in substance abuse from MDMA-AP is needed to advance modeling in this area. We added text to the controversies and uncertainties section to signal its importance to the research community. We agree that it is important to assess long-term durability of MDMA-AP, and we hope to see additional long-term follow-up studies in the future. There is no direct evidence on mortality risk by PTSD health state with treatment effects that suggest reductions in mortality risk based on short-term

		therapies. However, we did include increased risk of death associated with PTSD. A review of the available evidence showed that individuals with PTSD have a higher risk of mortality compared to the general population. Part of this increased risk can be attributed to deaths from suicide. Although the MDMA phase three clinical trials have not measured mortality endpoints, there may be an indirect benefit of reductions in mortality from avoiding severe PTSD health states. We retrieved data from the Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database for the USA in 2020 to calculate the baseline all-cause and suicide crude death rates by age. After identifying the increased risks of both all-cause (RR 1.47) and suicide (RR 2.09) mortality linked to PTSD, we calculated the mortality risk across PTSD states (from mild to severe) by multiplying the increased PTSD mortality ratio with the baseline crude death rate. Subsequently, we estimated the mortality risk in the asymptomatic state by multiplying the PTSD-related suicide mortality risk with the baseline suicide mortality rate and subtracting this risk from the increased PTSD-related (all-cause) mortality. In the results, we present deaths averted as a function of PTSD-related deaths by suicide which may occur each cycle across mild, moderate, and severe PTSD states. These estimates of PTSD-related deaths by suicide isolate the indirect effect of MDMA-AP on mortality and are comparable to reported CDC estimates. Therefore, despite no treatment effects on mortality measured in MDMA-AP trials, we still modeled decreases in mortality from this short-term intervention.

5.	**"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.	We invite you to review our Value Assessment Framework for a detailed overview of how these domains are used in our deliberations: https://icer.org/wp-content/uploads/2024/02/ICER_2023_2026_VAF_For-Publication_021324.pdf
6.	**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.	Thank you for providing these references for the independent appraisal committee to consider prior to the public meeting on May 30th.
7.	**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.*	Thank you for providing these references for the independent appraisal committee to consider prior to the public meeting on May 30th.

	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.	
8.	**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.	Thank you for providing these references for the independent appraisal committee to consider prior to the public meeting on May 30th.
9.	**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	Thank you for providing these references for the independent appraisal committee to consider prior to the public meeting on May 30th.

	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.	
10.	**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).	Our report highlights the challenge of directly comparing MDMA-AP to other trauma-focused psychotherapies due to lack of head-to-head trials and variations in trial design, duration, and patient population across studies.
11.	**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]	Even therapies that, in the long run, save costs and provider time can be infeasible in the near term if there are inadequate resources to implement those therapies.
12.	**III. Additional factors omitted from the draft evidence report**	Thank you for this recommendation. You are welcome to review our rationale for

	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.	considering dynamic pricing in our Value Assessment Framework. Prior to changing our approach to include price dynamics within a mandated scenario analysis, we commit to engaging our Health Economics Council, Methods Advisory Group, and other researchers and stakeholders including international HTA bodies to test the feasibility and impact of how best to include pricing dynamics within cost-effectiveness analyses. Although academic contributions are emerging in the dynamic pricing arena, best practices across health technology assessment entities do not exist. Further, public comments received on this topic supported additional deliberation on the methods prior to implementing them in ICER's Value Assessment Framework. We are willing to make updates to ICER's Value Assessment Framework on this topic if and when engagement and testing support making a change.
13.	**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	We agree that the costs of treatment associated with substance abuse disorders may need to be added to future modeling efforts. However, given exclusions for moderate to severe alcohol and cannabis use in addition to exclusions of other substance abuse in MAPP1 and MAPP2, short-term and long-term research on substance abuse and changes in substance abuse from MDMA-AP is needed to advance modeling in this area. We added text to the controversies and uncertainties section to signal its importance to the research community.

	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]	
14.	**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.	There is no direct evidence on mortality risk by PTSD health state with treatment effects that suggest reductions in mortality risk based on short-term therapies. However, we did include increased risk of death associated with PTSD. A review of the available evidence showed that individuals with PTSD have a higher risk of mortality compared to the general population. Part of this increased risk can be attributed to deaths by suicide. Although the MDMA phase three clinical trials have not measured mortality endpoints, there may be an indirect benefit of reductions in mortality from avoiding severe PTSD health states. We retrieved data from the Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database for the USA in 2020 to calculate the baseline all-cause and suicide crude death rates by age. After identifying the increased risks of both all-cause (RR 1.47) and suicide (RR 2.09) mortality linked to PTSD, we calculated the mortality risk across PTSD states (from mild to severe) by multiplying the increased PTSD mortality ratio with the baseline crude death rate. Subsequently, we estimated the mortality risk in the asymptomatic state by multiplying the PTSD-related suicide mortality risk with the baseline suicide mortality rate and subtracting this risk from the increased PTSD-related (all-cause) mortality. In the results, we present deaths averted as a function of

		PTSD-related deaths by suicide which may occur each cycle across mild, moderate, and severe PTSD states. These estimates of PTSD-related deaths by suicide isolate the indirect effect of MDMA-AP on mortality and are comparable to reported CDC estimates. Therefore, despite no treatment effects on mortality measured in MDMA-AP trials, we still modeled decreases in mortality from this short-term intervention.