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Date: April 16, 2019

RE: ICER Treatment-Resistant Depression (TRD) Draft Evidence Report – Response to Request for Public Comment

The following key feedback is provided in response to request for public comment and is not intended as an endorsement of any usage not contained in the Prescribing Information. For complete information, please refer to the full SPRAVATO™ Prescribing Information. Additional corrections will be sent separately to ICER.

CONTACT INFORMATION

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EXECUTIVE SUMMARY

ICER should assign a grade of "A" to esketamine (ESK) plus new oral antidepressant (oAD) compared with new oAD alone in the comparative clinical effectiveness matrix based on the high certainty in the evidence and the substantial net benefit as demonstrated below.

The ICER model does not accurately reflect the heterogeneous natural course of illness and treatment response in Major Depressive Disorder (MDD) and TRD. For example, the ICER model does not allow for a meaningful proportion of patients in long-standing remission to exit an episode; and it does not incorporate a declining risk of symptom relapse/episode recurrence the longer a patient stays in remission which is contrary to findings from research. These clinical aspects of the disease were emphasized in Janssen's original comments to ICER during the open input period at the start of this process, and these factors are critical to fully evaluating the cost effectiveness of TRD treatments. In contrast, the UK NICE[1] modeling framework does incorporate these important clinical aspects in their model. Janssen proposes that the ICER model be modified to be more flexible and to better align with the NICE modeling framework. Our comments below focus on aspects of the ICER model that we believe ICER can reasonably update at this late stage of the process to better assess the value of antidepressant treatment; however, even if these comments are accepted it should be noted that the ICER model still has critical structural deficiencies.

Given the current structure of the model, the following inputs should be modified (further rationale below):

- Change the probability of receiving an effective treatment with alternative treatment to better capture the diminishing effectiveness of later lines of therapy identified in a TRD population.[2]
- Change the treatment discontinuation rate assumption to better reflect the American Psychiatric Association guidelines[3] for MDD and real-world treatment patterns.
- Change the proportion relapsing after discontinuing effective treatment with ESK as indicated in the SUSTAIN-1[4] trial.
- Correct the probability of patients with partial response with maintenance treatment subsequently achieving complete response.
- Use TRANSFORM-2[5] data alone to inform the initial treatment effect with flexible dosing as ESK nasal spray is approved for use as a flexibly dosed medication which is consistent with real world practice.
- Correct the probability of patients with partial response losing response to match the SUSTAIN-1[4] trial.
- Adjust excess mortality to better reflect a population with TRD.

Janssen recommends removal of the cost-analysis comparing ESK to off-label IV ketamine from the draft evidence report as it is not in the best interest of patients and runs contrary to health economic principles.

3. COMPARATIVE CLINICAL EFFECTIVENESS

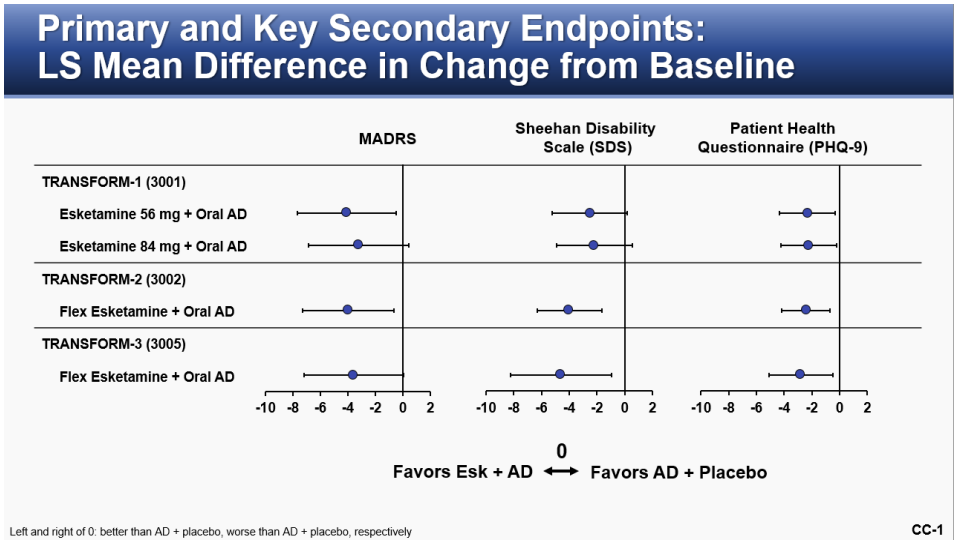
3.3 Results; Pages 32-36, Figures 3.1, 3.2, and 3.3: Meta-analysis of TRANSFORM-1 & -2:

- **We recommend ICER only use the TRANSFORM-2[5] data in its quantitative assessment of the acute effectiveness of ESK + oAD.** Flexibly-dosed TRANSFORM-2, was the short-term trial that formed the basis of SPRAVATO approval. Based on this, the SPRAVATO™ USPI[6] recommends flexible

dosing which is consistent with real world practice. Therefore, we do not consider it appropriate to pool the data from TRANSFORM -1[7] (fixed doses; 84 mg and 56 mg) and TRANSFORM-2[5] (flexibly dosed; 56-84 mg per session). Historically, flexibly-dosed antidepressant trials are more likely to be successful compared with fixed-dose antidepressant trials (59.6% successful vs. 31.4%) which underscores the value of allowing the clinician to adjust and individualize the dose.[8] Pooling the remission and response rates from the 2 studies reduces or masks the significant benefit of the flexible dose observed in the TRANSFORM- 2[5] trial and diminishes the real-world applicability of ICER's cost effectiveness analysis.

3.4 Summary and Comment; Pages 49-50, Table 3.9:

- **We recommend ESK + oAD receive an "A" grade in the subjective grading system based on 2 positive pivotal phase 3 studies (TRANSFORM-2[5] and SUSTAIN-1[4]), which are further supported by the FDA advisory committee vote (14 yes, 2 no, 1 abstain)[9] and subsequent FDA approval**.
  Supporting Rationale:
  - Two positive phase 3 studies provide evidence of short- and long-term efficacy of ESK within a population with TRD in whom it has been identified in STAR*D are less likely to respond and remit to treatment. Specifically, in TRANSFORM-2[5], the Number-Needed-to-Treat [NNT] for response for ESK plus oAD was 6 and the NNT for remission was 5 [Calculated]. Similarly, for SUSTAIN-1[4], ESK + oAD, had a significantly delayed time to relapse versus those treated with placebo (PBO) + oAD after 16 weeks of treatment with ESK + oAD (stable remitters: NNT=6; stable responders: NNT=4 [Calculated]). Based upon this substantial net benefit versus a newly initiated oAD, we consider this level of evidence to correspond to a grade "A" for ESK + oAD.[10]
  - In the TRANSFORM-2[5] trial, patients with treatment-resistant depression (TRD) achieved clinically meaningful and statistically significant improvement (based on change in Montgomery-Asberg Depression Rating Scale [MADRS] total score after 28 days) in depressive symptoms after being switched to ESK + new oAD vs. PBO + new oAD. It is notable to mention that the group treatment difference of -4.0 was against a newly initiated oAD and not PBO alone (difference of LS means: -4.0, 95% CI: 7.31, -0.64; 2- sided *P*=0.020). This observed -4.0 difference exceeded Minimum Clinically Important Difference thresholds reported in the literature.[11, 12]
  - Highlighting the importance of improving functioning in this vulnerable population, a consistent numerical trend favoring ESK + oAD on the primary endpoint (MADRS) and patient reported measures of depression and function (Patient Health Questionnaire [PHQ-9] and Sheehan Disability Scale [SDS], respectively) was observed across all 3 short-term studies.[13]



  - Maintenance of effect was established in a dedicated ESK maintenance of effect study (SUSTAIN-1[4]).

SUSTAIN-1	Relapse Event
Stable Remitters	HR: 0.49 (95% CI: 0.29, 0.84); *P*=0.003
Stable Responders	HR: 0.30 (95% CI: 0.16, 0.55); *P*<0.001

  - In conclusion, the efficacy data across the phase 3 double-blind studies demonstrates a consistent effect both in short and long-term efficacy (see Primary/Key Secondary Endpoint Forest Plot and

SUSTAIN-1 Table). The trial program in totality demonstrates a high certainty of substantial net health benefit of ESK + oAD.

3.4 Summary and Comment; Page 49, Table 3.9: **Correct labels in table referring to "Esketamine Plus Background Antidepressant" vs. "Background Antidepressant Alone" to "Esketamine plus New Oral Antidepressant" vs. "New Antidepressant Alone."** The initiation of a new oAD in the study design is an important factor to emphasize, as it presents a higher hurdle to demonstrating a difference between the treatment groups compared with a design evaluating an adjunctive treatment added to an existing treatment to which the patient has not responded. Unlike other cost-effectiveness analyses that are based on indirect comparisons, this comparison is based on head-to-head data across a series of trials, increasing confidence in the conclusions of the comparison.

4. LONG-TERM COST EFFECTIVENESS

4.2 Clinical Inputs Page 60-62: TRD is a complex disease and patient experiences and treatment responses are highly heterogeneous. The structure of the economic model oversimplifies the natural history of the disease and the treatment decisions; therefore, resulting in underestimation of the value of ESK. The following inputs are biased and should be modified as recommended below.

- **Initial treatment effect: TRANSFORM-2[5] data alone should be used to inform the initial treatment effect**. As noted in the comparative clinical effectiveness section, it is not appropriate to include TRANSFORM-1[7] fixed dose study data in the meta-analysis.
- **Probability of patients in maintenance treatment with partial response subsequently achieving complete response: We recommend the use of the correct SUSTAIN-1[4] estimates: i.e. 48.6% for ESK and 32.8% for oAD alone.** The estimates of 19.9% for ESK + oAD and 12.4% for oAD alone were provided by Janssen, which equals the transition probability based on a 1-month cycle, vs. a 3-month cycle.
- **Probability of patients in maintenance treatment with partial response subsequently losing response: We recommend the use of the correct SUSTAIN-1[4] estimates, i.e. 13% for ESK + oAD and 40.7% for oAD alone.** The current inputs of 21% for ESK + oAD and 47.6% for + oAD alone do not match SUSTAIN-1 estimates.
- **Probability of effective treatment with alternative treatment: We recommend adjustment be made for subsequent lines of treatment and a lower range of remission rates used. In the base case, we propose to use 11.9% for 1st alternative treatment, 9.3% for 2nd alternative treatment and 7.3% for 3rd alternative treatment.** The current data used by ICER is based on STAR*D[13] Step 4, a patient population who had failed 3 prior lines of antidepressants. In the current model the efficacy rate remains constant as patients move to more lines of treatment (i.e. alternative treatments line of 1-3). STAR*D data showed significant reduction in remission/response rates with sequential treatment from Step 1 to Step 4 (i.e. response and remission rates are lower with increasing levels of treatment resistance). The proposed numbers are extrapolated from remission rates across each sequential treatment step from STAR*D[2] data, which on average declined by 22%/step (resulting in an estimated remission probability of 10.2%, 8.0%, and 6.3% at lines 5, 6, and 7, respectively). The target patient population treated in the clinical trials of ESK had failed at least 2 treatments in the current major depressive episode, with a considerable number of patients failing 3 or more oAD treatments (e.g. 41% patients in SUSTAIN-1[4] had failed 3 or more prior treatments). The simulated patients in the 4th treatment of the ICER model should have failed at least 5 or more treatments. Using the same STAR*D[2] Step 4 remission for sequential lines of treatment in the model therefore significantly overestimates the effectiveness of the subsequent treatments in real world, and consequently biased against ESK.
- **The ICER model includes a health state "Initial Tx discontinued No depression" but in any model cycle significantly fewer than 1% of ESK patients are in this health state, which is an implausibly small proportion. The ICER model requires adjustment to increase the proportion entering this health state and decrease the proportion exiting it to better model the disease state.**
    - Probability of patients with long-term effectiveness discontinuing treatment: We recommend using at least 21%-41% (vs 1.3%/cycle) as the proportion of patients with long-term effectiveness discontinuing treatment per 3-month cycle. The current value of 1.3% per cycle results in a median duration of treatment in patients who remit and do not relapse, of 13 years. Applying 21% per cycle results in a more plausible median duration of treatment among patients with remission who do not

relapse (9 months). Nine months is better supported by the SUSTAIN-1[4] trial and guidelines. After 6-months of treatment in the maintenance phase of SUSTAIN-1[4] (10 months since treatment initiation) there is an observable inflection point in the slope and the risk of relapse decreases in patients in both treatment arms and many patients on ESK could potentially have discontinued ESK and persisted with oAD alone. Additionally, both ACNP Task Force[14] and the APA[9] guideline suggest that most patients need 4-9 months of continuation treatment for relapse prevention. Applying 21% per cycle results in a median duration of 9 months (upper end of APA guideline) and 41% per cycle results in a median duration of 4 months (lower end of APA guideline). Of note, even if 21% is applied, it remains conservative as half of the patients in long standing remission for 9 months will continue with ESK treatment beyond 9 months.

  - The proportion with "patient relapse" out of this health state should be 13% based on the SUSTAIN-1[4] trial, as the current value of 40% is derived following acutely remitted patients in the STAR*D[2] trial. Clinicians will select patients at lower risk for discontinuation, and the STAR*D rate does not reflect the lower risk of relapse/recurrence among patients in long-standing remission. Even if the transition probability into this state is increased as recommended above, these patients would still have been in remission for much longer (e.g. 9 months) than in the STAR*D trial.

- **Mortality adjustment: A recent study by Bergfeld et al (2018)[15] reported that the overall incidence of completed suicide among TRD patients is 0.47 per 100 patient years. We request this number be added to the general mortality risk during depression health states to accurately account for excess mortality TRD could cause.** The ICER model attempted to adjust the excess mortality associated with depression. However, the adjustment did not fully consider the suicide risk associated with TRD. The reference used in the model is based on a long term follow up study of patients with depression, which would include both a depression period and a healthy period. A more reasonable adjustment should be done by adding the average completed suicide risk to each age cohort's mortality during depression health state.

4.2 Methods; Page 68-69, Cost-Analysis: We recommend that the cost-analysis comparing esketamine to IV ketamine be removed.

- **Supporting Rationale:** ICER acknowledges that IV ketamine was excluded from the formal cost-effectiveness analysis due to lack of comparable data; however, the draft report includes an inappropriate comparison of cost vs. ESK. It is inappropriate to compare an approved treatment with 1) an established risk/benefit profile, 2) established acute and maintenance efficacy and long-term safety data, including guidance on dosing, and 3) a REMS to ensure safe use, to an alternative off-label treatment lacking any of these elements. ICER cites both APA and Canadian Agency for Drug and Technologies (CADTH) statements on off-label IV ketamine. The cited reference from APA recognizes, "major gaps…remain in our knowledge about the longer-term efficacy and safety of ketamine infusions,"[16] while the CADTH, recommend "restricting access to ketamine to the research setting."[17]

4.3 Results; Page 69-70: Table 4.12: We recommend to use the full time horizon of the cost effectiveness model to estimate the cost of a depression free day.

- ICER reports cost per depression free day based on a 2-year time horizon. We believe this time horizon is unable to capture the benefits of ESK and therefore overestimates the cost per depression free day.

5. POTENTIAL OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

5.1 Potential Other Benefits; Table 5.1 on Page 77: **We recommend clarifying to readers that these 3 benefits may be particularly relevant for ESK**: 1) a novel MOA for the treatment of TRD, 2) tested in a population with confirmed TRD, and 3) potential impact on productivity.

5.1 Potential Other Contextual Considerations; Table 5.1 on Page 77: We recommend deletion of two items in the text: 1) there is significant uncertainty about the long-term risk of serious side effects of this intervention and 2) there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.

Supporting Rationale:

- Unlike standard oral antidepressants at approval, the ESK phase 3 data package was approved with a comprehensive clinical trial package including a positive maintenance of effect study (Study 2 in the SPRAVATO™ USPI[6]).

- As noted in the SPRAVATO™ USPI[6], the safety of ESK was evaluated in 1709 patients diagnosed with TRD, with a cumulative exposure of 611 patient-years of esketamine.[18] The safety of long-term treatment, of up to 1 year, has been well characterized.
- As an example, Zoloft (sertraline) is one of the most widely prescribed antidepressants for MDD. Similar to ESK, the Zoloft USPI notes 1 longer-term maintenance study. The safety data in the Zoloft USPI is informed by ~5,000 patients, but this data comes from studies conducted for multiple indications. The total number of Zoloft- and placebo-treated patients in the Clinical Studies section of the Zoloft USPI under the MDD indication is 840.

7. POTENTIAL BUDGET IMPACT; PAGES 81-82; TABLE 4.11

As noted, we consider treatment duration within the ICER model assigned to ESK as unrealistic compared with prescriptive guidelines or descriptive real-world practices, which impacts the Budget Impact Analysis by overestimating the cost of ESK.

- Mean Length of Therapy: The draft evidence report includes a number of assumptions that likely result in a length of therapy inconsistent with guideline recommendations, typical treatment patterns for MDD/TRD in real-world data (RWD), the SPRAVATO™ USPI[6], and precedents set in CEA in depression. Table 4.11 on page 70 lists the mean cost of ESK as $42,600. The draft evidence report does not state the mean length of therapy but based on the reported mean we estimate this corresponds to a mean length of therapy of 13 months.
- Treatment Guidelines: APA guidelines[3] recommend patients successfully treated with antidepressant medication continue with those agents for 4-9 months for relapse prevention. Those who do not initially respond or who relapse would only decrease the mean length of therapy.
- RWD: In the absent of RWD for ESK treatment persistence, the current treatment persistence data for oAD are the best proxy for ESK utilization in the real-world setting. In RWD, typical patients with MDD/TRD persist with an antidepressant line of therapy for 4-6 months[19-22] The ICER model overestimates typical treatment durations observed in RWD by at least 2-fold.

ICER made the Excel-based model available to Janssen for review. Janssen used that model to estimate the impact on the cost/QALY for those inputs that can be modified in the ICER model and, in the spirit of transparency, report the results below for your consideration.

Modified ICER Input	**Rationale**	**New ICER**
Apply all steps listed below		55k/QALY
Decrease effectiveness of later lines of treatment to 11.9%, 9.3% and 7.3% for 1st, 2nd, and 3rd subsequent treatments.	Remission rates declined with line of therapy during the STAR*D trial, so inputs should be decreased to at least these values. It is unrealistic to assume the trend would not persist beyond lines of therapy evaluated in STAR*D	173k/QALY
Increase treatment discontinuation rate assumption to 21% per cycle	At a minimum, this value better reflects the SUSTAIN-1 trial and APA guidelines	152k/QALY
Change proportion relapsing after discontinuing ESK to 13% per cycle	Reflects SUSTAIN-1 results	184k/QALY
Correct probability of patients with initial partial response to maintenance treatment achieving complete response to 48.6% for ESK and 32.8% for oAD.	Reflects SUSTAIN-1 results	189k/QALY
Use TRANSFORM-2 data to estimate acute effectiveness of ESK	Effectiveness of flexibly-dosed ESK is diluted by meta-analysis combining with fixed-dose TRANSFORM-1 trial	182k/QALY
Correct probability of losing partial response to 13% for ESK and 40.7% for oAD	Reflects SUSTAIN-1 results	196k/QALY
Adjust mortality to reflect excess risk in TRD	Better reflect indicated patient population	183k/QALY

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April 17, 2019

Attn: Midwest Comparative Effectiveness Public Advisory Council (CEPAC)
Institute for Clinical and Economic Review
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Dear Members of the Midwest CEPAC:

Mental Health America (MHA) thanks Institute for Clinical and Economic Review (ICER) for inviting public comment on the draft evidence report for a review of esketamine for treatment-resistant depression, and for the opportunities for ongoing engagement.

Consistent with our comment on the draft scoping document, MHA asks that ICER consider in the modeling the possibility of future loss of eligibility for means-tested public health care programs (Medicaid and disability Medicare) due to increased earnings resulting from reduced behavioral health challenges. This scenario is different than modeling increases in productivity and taking a societal perspective on benefit. This continues to take a narrow payer perspective on benefit, but recognizes that public payers have different costs and benefits than commercial insurers.

As we noted in our previous comment: federal and state governments are the largest payers of depression care in the United States. Because governments only cover individuals when they reach certain thresholds of income or disability, public health care payer cost-effectiveness works differently than commercial payer cost-effectiveness. When a public payer invests in effective depression care for an individual, the individual may be more able to work and increase their earnings. If the increased earnings causes the individual to cross over the thresholds of income or disability (or not reach them in the first place), the individual will no longer be eligible for public health care coverage, and be able to seek commercial coverage instead. From the perspective of the public payer then, the cost in the cost-effectiveness of depression care is not just driven by a potential decrease in later health care utilization related to better depression outcomes, but also the possibility of not having to pay for any further health care services as the individual transitions to commercial coverage. Thus, meaningfully investments in depression care can be extremely cost-effective for public payers, and modeling should reflect this where possibly.

Modeling public payers is important not only to ensure descriptive accuracy, but also to advance an important normative goal – that the government invest in the long-term functioning of its citizens. By making the analysis described here common practice, it can shift the paradigm for how CMS and state Medicaid agencies view costs and benefits – away from trimming health

care costs and toward making critical investments that alleviate poverty and disability. Where there is not good evidence for these relationships in the literature, MHA urges the use of estimates in scenario analyses, and would assist with any attempts to parameterize such models.

MHA thanks ICER for its consideration on how additional scenario analyses could enrich the field's understanding of costs and benefits. For additional information, please do not hesitate to contact us.

Sincerely,

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National Alliance on Mental Illness

Comments on Draft ICER Evidence Report on Esketamine for Treatment-Resistant Depression

April 17, 2019

On behalf of the National Alliance on Mental Illness (NAMI), the nation's largest grassroots organization dedicated to improving the lives of people with mental illness and their families, I am pleased to offer the following comments on the Institute for Clinical and Economic Review (ICER) Draft ICER Evidence Report on Esketamine for Treatment-Resistant Depression, released on March 21, 2019. NAMI appreciates the opportunity to offer its thoughts on this review.

As this evidence report makes clear, treatment-resistant depression (TRD) is a devastating condition associated with an enormous public health burden in terms of both mortality and morbidity, as well as lost productivity and poorly managed co-morbid chronic medical conditions. People living with TRD often experience months and even years of trial and error with multiple medications without significant symptom relief and regaining quality of life. Further, this is not an isolated or narrow population – about one-third of patients diagnosed with depression are considered to have TRD.[i]

The economic impact of higher costs of care and decreased productivity alone total about $64 billion.[ii] According to the World Health Organization, depression is the leading cause of disability in the world and a major contributor to the global burden of disease.[iii] It is also important to recognize that chronic mental illnesses, such as TRD, often incur a significant strain on family caregivers. In fact, there are about 8.4 million family caregivers of adults with mental illness in the United States. According to the National Alliance for Caregiving report (2016), *On Pins & Needles,* 74% of caregivers report feeling high emotional stress and four in ten say they find it difficult to take care of their own health. Only one in three (33%) report having excellent or very good health. These impacts on both patients and caregivers underscore the need for new treatment options to improve the effectiveness and tolerability of treatments for TRD.

While there are numerous medications approved to treat depression in several therapeutic classes – SSRIs, SNRIs and MAO inhibitors—the common experience for people living with TRD is a repetitive cycle of trial and error with multiple combinations of these existing medications. It is significant that antidepressants can take 4-6 weeks to show any clinical effect – prolonging an individual's suffering with severe symptoms that negatively impact on work, relationships and engagement with life activities, as well as management of other health conditions and risk of suicide.

Given this high level of mortality and morbidity associated with TRD and the enormous public health burden, it was with enormous excitement that we learned on March 5 that the Food and Drug Administration (FDA) had approved Esketamine under breakthrough status as an on-label treatment for TRD. Up until now, the only FDA-approved adjunctive therapy (a supplemental therapy added onto an antidepressant) for TRD are antipsychotic medications that carry significant risk of negative side effects such as weight gain, sedation, metabolic syndrome and akathisia. Beyond these treatment options, individuals living with TRD are forced to seek out interventions such as Electroconvulsive therapy (ECT) and Transcranial Magnetic Stimulation (TMS). While these interventions can provide some clinical

benefit in symptom relief for an acute episode, they have significant limitations as tools for managing TRD as a chronic condition. This is especially the case with ECT where side effects include memory loss.

In short, NAMI members are extremely excited about the approval of Esketamine as an on-label treatment. People living with TRD have been desperate for novel therapies that offer immediate symptom relief. With over 4 million adults in the U.S. estimated to live with TRD, it is imperative that they are able to access this new treatment option that offers quicker symptom relief and clinical remission free of the side effects of existing treatments.

It is in this context that NAMI offers comments on this draft ICER evidence report on Esketamine and TRD.

Comparison of Esketamine to Off-Label Prescribing of Intravenous Ketamine

NAMI has a number of concerns with the near exclusive reliance on intravenous (IV) ketamine as the comparator intervention for TRD. First, it is important to note that Esketamine has different chemical properties that are distinct from IV ketamine. It will be administered to patients as a nasal spray and be absorbed in the body differently than IV ketamine.

Second, it is important to note that while IV ketamine clinics can be found across the United States, they operate largely outside of the federal and state regulation and third-party payment systems. Many of these clinics do not accept Medicare, Medicaid or private health insurance. As a result, many patients pay 100% of the costs out of pocket. Unfortunately, this ICER failed to take this patient perspective into account when calculating cost effectiveness. By contrast, as an FDA approved drug, it is expected that private health insurance, Medicare Part D and Medicaid will offer coverage of Esketamine on their Preferred Drug Lists (PDLs) with patients paying co-payments and co-insurance far below the out-of-pocket costs of treatment at an IV ketamine clinic that is not in a health plan's provider network.

Third, while there is significant evidence of the effectiveness of IV ketamine in offering immediate symptom relief for TRD, it is still an off-label treatment that lacks the breadth of evidence required for FDA approval. There are few up-to-date peer-reviewed treatment guidelines for its use in TRD. This means that there is no FDA-approved label regarding dosing, frequency, side effects and other risks. Moreover, IV ketamine clinics are overseen by a variety of physicians across various disciplines – most commonly anesthesiologists. While they may have clinical experience administering IV ketamine, they are not necessarily well versed in treating TRD and lack the expertise in identifying symptom relief and remission.

By contrast, Esketamine has been approved by the FDA as safe and effective. It comes with robust scientific evidence about mechanism of action, dosing, timing, side effect profile and other safety concerns. Further, all of this is based on multiple randomized controlled trials conducted by the product sponsor – the highest standard for medical evidence. None of this exists for IV ketamine. In addition, the FDA has agreed with the sponsor on an extensive REMS (Risk Evaluation Mitigation Strategy) to address a range of safety concerns to ensure proper administration and prevent product diversion.

In summary, NAMI is extremely concerned that this ICER review relies on a comparator (IV ketamine) that lacks reliable guidance on dosing and administration and no patient safety protocols and that could actually result in dramatically higher out-of-pocket costs for patients who access treatment through clinics that do not accept Medicare or private insurance.

Esketamine Approved with FDA REMS

As noted above, the FDA will be imposing an extensive REMS for the prescribing of Esketamine. This will be not only to ensure its safe prescribing and to limit risk for patients prescribed the drug, but also to prevent inappropriate diversion of the product as a street drug. This includes:

- limiting distribution to certified clinics,
- training for prescribers,
- enrolling patients in a registry, and
- requiring monitoring of patients for a minimum of 2 hours after administration.

Unfortunately, these requirements to ensure patient safety and proper administration are barely mentioned in the ICER review. No attempt was made to assess the value of improved outcomes through adherence to a higher safety standard with Esketamine (no REMS exists for IV ketamine as it is off-label). It would have been helpful for ICER to have included an examination of the relative value of this REMS in improving patient outcomes and lowering overall costs.

Use of QALYs to Measure Symptom Improvement in TRD

As NAMI has previously noted to ICER, we have significant concerns about the use of QALYs to measure current and emerging therapies to treat mental illness. Because existing therapies are not disease-modifying in nature and do not cure the underlying condition, QALYs as a measure inherently undervalue improvements in functioning and quality of life that matter to people living with mental illness. Being able to demonstrate extended life expectancy in mental health treatment over a 5-year projection (as ICER does in this review) played a significant role in the low value per QALY gained for all of the comparators in this review. Instead, what is needed is the ability to capture what is meaningful to patients: improvement in individual symptoms, functioning and quality of life—including for caregivers.

In November 2018, NAMI joined with our colleagues at the Depression Bipolar Support Alliance (DBSA) in conducting a "Patient Focused Drug Development" (PFDD) meeting at the FDA where people living with depression shared their personal experiences with TRD and expressed what outcomes really mattered to them. Many of the priorities expressed by patients at this meeting were beyond achievement of single clinical endpoint on a depression scale, such as MADRS, and included side effects of medications and being able to work, spend quality time with family and friends, and enjoy hobbies. NAMI remains very concerned that cost per QALY gained is unable to satisfactorily integrate these important patient priorities into a review of these interventions.

Health-related quality of life assessed by EuroQol-5 Dimension-5 Level (EQ-5D-5L)

NAMI would also note that this evidence review employed a measure of health-related quality of life using the EQ-5D-5L. Recent research concludes that the anxiety/depression (A/D) dimension of the EQ-5D-3L shows limited responsiveness to changes in depressive symptoms measured by PHQ9 and anxiety symptoms measured by GAD2.[iv] Of note, the researchers state that 31.7% of patients who had an improvement in depressive symptoms based on the PHQ9, and 40.0% of those who had deterioration, showed no changes in the A/D dimension of the EQ-5D-3L.[v] This suggests that use of the EQ-5D does not capture clinically important changes in the mental health of patients living with TRD.

Concerns about Differential Measures of Median Time to Remission and Relapse in the Report

NAMI appreciates that ICER attempted to assess the number of patients with TRD that will be successfully treated with Esketamine and reach symptom remission for a sustained period of time. We have known for years that effective treatment can drive individuals living with TRD out of severe depression and into remission. In fact, the American Psychiatric Association's treatment guidelines for depression recommend that after a period of 4 to 9 months of symptom free remission, clinicians consider terminating therapy.

What is concerning is that this ICER report makes assumptions about both the duration of remission and median time to relapse that likely underestimates the number of patients that will be able to achieve long-term remission. This results in findings in the report about the number of patients that are prescribed TRD staying on the medication for as long as 13 years. In NAMI's view, it is simply too early to make such assumptions. Esketamine is a novel breakthrough therapy. NAMI is optimistic that there is a large cohort of patients that have been living with TRD for years that will achieve long-term remission with Esketamine.

Concerns About "Potential Other Benefits and Contextual Considerations"

On page 76, this draft ICER review includes a discussion of Potential Benefits and Contextual Considerations." Given the very debilitating nature of TRD, it is important for other benefits to reflect not just "significantly" improved patient outcomes, caregiver burden, or impact on returning to work (or seeking work) or productivity, but *any* improvement that is meaningful to the patient. It would have been helpful if this review would have included, as important benefits, interventions that result in meaningful reduction of one or more symptoms that are important to a patient that may not be captured by the MADRS depression rating scales. While the report does include some of these "other potential benefits" in a chart on page 77, such as family caregiver burden, improved productivity and employment, reducing racial and ethnic disparities, it excluded a range of other symptoms such as irritability, anger, agitation, sexual problems, and unexplained aches and pains.

Lack of Assessment of the Full Public Health Burden of TRD and Co-Morbid Chronic Medical Conditions

NAMI is concerned that this review lacked any assessment of the overall cost of TRD in general, and in particular, the burden associated with poorly managed co-morbid chronic medical conditions in the TRD population. When these patients are in the grip of a major depressive episode, their ability to engage in adherence to treatment for their diabetes, heart disease, asthma, or other chronic medical condition can be severely compromised. As a result, their risk of an acute episode of a co-occurring medical condition rises significantly. Immediate symptom relief of their depression can allow for the reduction of high cost services to treat co-morbid medical conditions.

With over 4 million adults experiencing the debilitation of TRD, it would have been helpful to have included an assessment this new treatment option in addressing differential responses to treatment and their unique sets of symptoms and side effects.

Conclusion

With the goal of better and expanded treatment options in mind, NAMI appreciates your consideration of our comments and welcome the opportunity to call on us and our community of people living with mental illness as you move forward.

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[i] Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatric services (Washington, DC).* 2014;65(8):977-987.
[ii] *Ibid.*
[iii] World Health Organization. *Depression. Key Facts.* March 22, 2018. Accessed online at http://www.who.int/news-room/fact-sheets/detail/depression.
[iv] Crick K, Al Sayah F, Ohinmaa A, Johnson JA. Responsiveness of the anxiety/depression dimension of the 3- and 5-level versions of the EQ-5D in assessing mental health. March 3, 2018. *Quality of Life Research.* Accessed online at https://www.researchgate.net/publication/323615070_Responsiveness_of_the_anxietydepression_dimension_of_the_3-_and_5-level_versions_of_the_EQ-5D_in_assessing_mental_health.
[v] *Ibid.*

PIPC Partnership to Improve Patient Care

April 17, 2019

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson:

The Partnership to Improve Patient Care (PIPC) is pleased to provide comments on the draft evidence report for *Treatment-Resistant Depression: Effectiveness and Value* from the Institute for Clinical Economic Review (ICER). We continue to urge ICER to move beyond QALYs and similar metrics, and to join others in the field in developing the next generation of value assessment models that are more patient-centered and consistent with our nation's drive toward personalized and precision medicine.

We provide the following concerns and suggestions related to ICER's draft report:

ICER disregards outcomes that matter to patients

As the National Alliance on Mental Illness (NAMI) highlighted in its November comment letter to ICER, individuals with treatment resistant depression (TRD) are in desperate need of treatments that offer fast, effective relief. The ICER model fails to capture the value of the treatment's immediate impact. For patients, the ability to quickly get back to work and their families is invaluable.

In addition to patients, clinicians have attested to the fact that one of the game-changing values of *esketamine* is this instantaneous effect. All other pharmaceutical options for depression are known to have a considerable lag time before their effectiveness kicks in; about 6-8 weeks. We also know the process of finding a 'fit' for a particular pharmaceutical treatment for a patient is largely trial and error and can be time-consuming and frustrating for both clinician and patient.

The ICER Markov model is constructed with each 'cycle' being three months long.
To appropriately evaluate the value of a new drug such as *esketamine*, which addresses a new patient-centered outcome, i.e. the speed of response to a serious and debilitating condition, ICER should move beyond a model limited to longer-term outcomes associated with traditional treatments. ICER should innovate and consider alternative models that are capable of capturing immediate outcomes in addition to longer-term outcomes.

Patients are anticipated to value and appreciate *esketamine*'s simplicity of delivery and immediacy of effect. The immediacy is of huge value to patients but is not captured in the Markov model, which values *esketamine's* immediate impact as equal to something that takes three weeks to work – a finding that is in direct contradiction with patients' preference for fast relief. In addition, *esketamine's* immediacy will have significant impacts on adherence and effectiveness, including for medications not related to a patient's major depressive disorder (MDD). That increased adherence and effectiveness will also decrease overall healthcare utilization.

Patients suffering TRD carry a severe disease burden, and the outcome that matters most to them based on a longitudinal wellness survey conducted by the Depression and Bipolar Support Alliance is, "to function as well as possible, especially in how they function at work, play, and with others." ICER fails to capture this outcome and instead continues to use the QALY, which is unable to capture essential patient preferences. As NAMI noted in its letter to ICER, the use of QALYs to measure treatments for mental illness is not appropriate, as these treatments are not disease-modifying in nature and devalue important outcomes for patients with depression.

ICER continues to produce value reports early - before adequate availability of evidence

We are concerned that this report continues a dangerous trend for ICER of conducting assessments of new drugs prior to the availability of sufficient evidence on their relative effectiveness compared to existing standards of care. We understand that ICER conducts its value assessments for use by payers, not as a tool to help patients make treatment decisions, yet its work has significant implications for patient access to care despite its lack of rigor. ICER's inflexibility on this issue is simplistic and inconsistent with the complex reality that has allowed patients in the U.S. to benefit from innovation early compared to other countries.[1]

- **Lack of consistency:** The information produced by ICER is not of a consistent quality or standard that would allow for a valid comparison to the standard of evidence used to value other treatment options for the same disease or condition.
- **Diminished quality of evidence:** Since 2015, there has been considerable variance in the quality of evidence in ICER assessments since receiving funding to expand its drug program in 2015, as witnessed by its evidence ratings tables. ICER's reviews of treatments in spinal muscular atrophy, multiple sclerosis and now treatment resistant depression rate in the moderate to low categories, including many marked as "promising but insufficient." Yet ICER's studies are often a reference for decisions related to coverage and access to care.

[1] Stevens W, Philipson TJ, Khan ZM, MacEwan JP, Linthicum MT, Goldman DP. Cancer mortality reductions were greatest among countries where cancer care spending rose the most, 1995–2007. Health affairs. 2015 Apr 1;34(4):562-70.

- **ICER does not update its review routinely as evidence improves:** ICER does not systematically update its models when new evidence on the effectiveness or cost of a new drug becomes available. In the one case where ICER did update a report, it was not as comprehensive as its initial report. Yet, there are there numerous examples of the effectiveness and cost-effectiveness of new drugs changing significantly as better evidence becomes available. Over time, real-world effectiveness data becomes more readily available, in particular with respect to longer term outcomes that may take years to generate.[2] There is a growing body of evidence that suggests that effectiveness is a dynamic, rather than a static measure. That is, relative or comparative effectiveness often changes over time as new technologies become embedded into practice; in essence as practitioners learn the best combinations of when, how, and to whom to treat to maximize the health benefit for individual patients.[3] Thankfully, clinicians do not blindly follow any one treatment pathway when they use new drugs. They combine their own experience of treatments with what they know from the existing evidence base. Clinicians also have far more complex patient groups than those seen in the RCTs from which ICER produces its effectiveness estimates for its models. Yet, ICER has not prioritized updates of its models to reflect real-world evidence.

The model does not accurately account for the cost burden of TRD

Depression is a devastating disease, which inflicts significant health and financial burden on our nation. Over 16 million adults experienced a major depressive incident in the past year, and mood disorders, including depression, are the third most common cause of hospitalization in the United States.[4] With this in mind, total economic cost of untreated depression should be taken into consideration, yet is not captured in the draft evidence report.

- **Non-drug cost data is misrepresentative:** The source of all non-drug cost data was from a single study undertaken almost 20 years ago. Although it has been inflated to 2018 prices, it's highly unlikely that the treatment patterns and sources of costs are the same 20 years later. There have been numerous more recent studies looking at U.S. costs in treatment resistant depression. In fact, a recent review of such studies published in 2014[5] compiled the results from 6 studies published since the study that was used by

[2] Grabowski DC, Lakdawalla DN, Goldman DP, Eber M, Liu LZ, Abdelgawad T, Kuznik A, Chernew ME, Philipson T. The large social value resulting from use of statins warrants steps to improve adherence and broaden treatment. Health affairs. 2012 Oct 1;31(10):2276-85.
[3] Incerti, D., et al. "An Empirical Analysis of The Role of Learning by Doing in Dynamic Cost-Effectiveness." *Value in Health* 20.9 (2017): A435-A436.
[4] National Alliance on Mental Illness. Mental Health by the Numbers. Available at: https://www.nami.org/Learn-More/Mental-Health-By-the-Numbers
[5] Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996–2013. Psychiatric services. 2014 Aug;65(8):977-87.

ICER, suggesting that the cost of TRD was between 30-100% higher on average than treatment *responsive* depression.

- **Cost of comorbidities was not captured:** The report did not measure the impact of improved treatment effect on costs beyond those associated with the primary condition. MDD has been strongly associated with opioid abuse over the last decade, a current public health epidemic in the United States which would not be captured in the 2002 study ICER uses. A simple inflation rate cannot account for changes in how diseases are addressed culturally, new emerging trends, or how conditions influence and are influenced by other co-morbid conditions over time.

Reports capturing value to the patient require timely and relevant data related to a holistic set of costs experienced by patients. Additionally, models must recognize the complex nature of conditions that are associated with high sets of comorbidities, such as TRD. At each stage of progression, the burden and cost of treatment of these conditions rises, and models should reflect the burden on patients in particular.

Mortality estimates used are misleading

The mortality multipliers in the draft evidence report may underestimate the true mortality associated with TRD. ICER referenced a particular study to calculate the mortality multipliers for TRD in the model (Ruetfors 2018)[6] that compared the mortality rate of a TRD population to a population suffering treatment-susceptible depression, as opposed to comparing to the mortality rate of the general population. Yet, the ICER model applies the TRD multipliers to general population mortality rates (the US Human mortality database).[7] This makes the assumption that people suffering treatment-susceptible depression have the same mortality rates as the general population, an assumption that runs counter to available evidence.[8] Also, the definition of TRD in this study was more ambiguous, and less severe than the definition of TRD used in the model for triggering the use of *esketamine*, which is another difference that may underestimate the true mortality associated with untreated TRD.

In conclusion

Thank you for your consideration of PIPC's comments. With over 4 million adults suffering from TRD and limited treatment options, it is seminally important that ICER incorporate patient's needs and preferences into its analysis. We again call upon ICER to consider innovating its

[6] Reutfors J, Andersson TM, Brenner P, Brandt L, DiBernardo A, Li G, Hägg D, Wingård L, Bodén R. Mortality in treatment-resistant unipolar depression: A register-based cohort study in Sweden. Journal of Affective Disorders. 2018 Oct 1;238:674-9.

[7] Human Mortality Database. 2016. www.mortality.org. Accessed February 2, 2019

[8] Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA psychiatry. 2015 Apr 1;72(4):334-41.

model to better recognize the considerations that matter most to patients when making treatment decisions instead of using metrics such as QALYs and the evLYG that present an impossible choice between discrimination and inadequate consideration of patient-centered outcomes.

Sincerely,

Tony Coelho
Chairman, Partnership to Improve Patient Care

April 15, 2019

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Evidence Report "Esketamine for the Treatment of Treatment-Resistant Depression"

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with life-threatening conditions and chronic diseases for them to have access to vital therapies and services. Access is a matter of survival and quality of life for those patients, and it spans affordability, insurance coverage, and physical access. To support improved access, we are committed to engaging all stakeholders to foster realistic, patient-centered, solution-oriented discussions for particular conditions and the entire U.S. health care system. That is, our goal is a balanced dialogue that illuminates the truth about health care in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER's March 21st draft report, "Esketamine for the Treatment of Treatment-Resistant Depression: Effectiveness and Value." Our comments about the draft report are organized below into sections concerning: Patient and Family Perspectives and Issues; Technical Issues and Questions; and Additional Points.

Patient and Family Perspectives and Issues

Depression can be a devastating chronic condition that affects individuals, families and communities. And when multiple treatments fail to improve the condition (i.e., it is treatment resistant), then its impact is typically even more overwhelming. As the World Health Organization reported, depression is now the leading cause of disability affecting over 300 million people worldwide, or 4.4 percent of the population.[i] And further, a meta-analysis found that people with depression have about a 50 percent greater mortality risk than people without depression (Relative Risk 95% CI=1.45-1.59).[ii] This article also points out the importance of treating the entire patient rather than specific disease with the observation that "in patients with somatic diseases, depression could have an unfavorable impact on adherence to a prescribed treatment regimen, [that could have] a direct impact on survival."[iii]

The draft report states "Depression can increase the risk of suicide."[iv] From an individual patient perspective, that may be true in the sense that someone either attempts suicide or not, and as the World Health Organization has noted, "[at] its worst, depression can lead to suicide."[v] However, from a population perspective, depression DOES increase the risk of suicide.[vi] This statement in the draft report should be changed to indicated "risk of suicide for the individual patient," or if the intent was to describe population level effects, then "can" should be replaced with "does."

As an introduction to our comments we wanted to recognize those realities because while – as the draft report notes – there are several treatment options for people with depression, (i.e., several types of oral medications, TNS, ECT, psychotherapy, and off-label use of ketamine), there are still many tens of thousands of people with treatment resistant depression (TRD) who have severely decreased quality of life, and are at increased risk of death.[vii]

The burden of depression on families and patients is very significant, so new treatment options are desperately sought and embraced – even if they are not FDA approved, or lack extensive long-term data. Because of the complexity of treating depression, we support shared decision making between a patient and their clinician, which is particularly important for a disease like TRD where many clinical and personal factors that can be important considerations for guiding treatment choices. Hence, we concur with the Canadian Network for Mood and Anxiety Treatments' guidelines, which the draft report notes "emphasize an individualized approach based upon diagnostic reevaluation, consideration of previous medication trials, rational use of adjunctive medications, discontinuation of medications that have not been beneficial and careful monitoring."[viii]

While we appreciate the challenge of evaluating treatment options based upon clinical trials data without real-world information, we are confused by the conflicting statements in the draft report about the benefits of esketamine. Specifically, the draft report found the "Results of the meta-analysis was in favor of esketamine, showing a greater improvement on MADRS score for esketamine plus antidepressant compared to placebo plus antidepressant,"[ix] but then declares that the benefits are "promising but inconclusive."[x] Therefore, how can ICER conclude inconclusive results?

A related concern is that the draft report uses a threshold of at least 50% reduction in symptoms as "Clinical Response."[xi] We recognize that this is the metric used in many clinical trials, but we would urge ICER to discuss if that is a meaningful threshold for patients, and similarly, if determining that response primarily using the Montgomery–Åsberg depression rating scales (MADRS) reflects patient-centered benefits of treatment.

Concerning patient-oriented perspectives, the report notes that patient advocacy groups "highlighted that common outcome measures used in clinical literature may not adequately capture the impact of major depressive disorder on things that affect overall quality of life including relationships, work and family issues," [xii] and that "symptoms of depression are more impactful on diminished quality of life than people realize."[xiii] Those statements raise fundamental questions about the adequacy of ICER's modeling in this draft report and how it accounted for quality of life improvements with treatment.[xiv] We raise this because ICER (again) is noting patients' concerns and perspectives but then does not appear to adequately incorporate them into its analytical processes or conclusions.

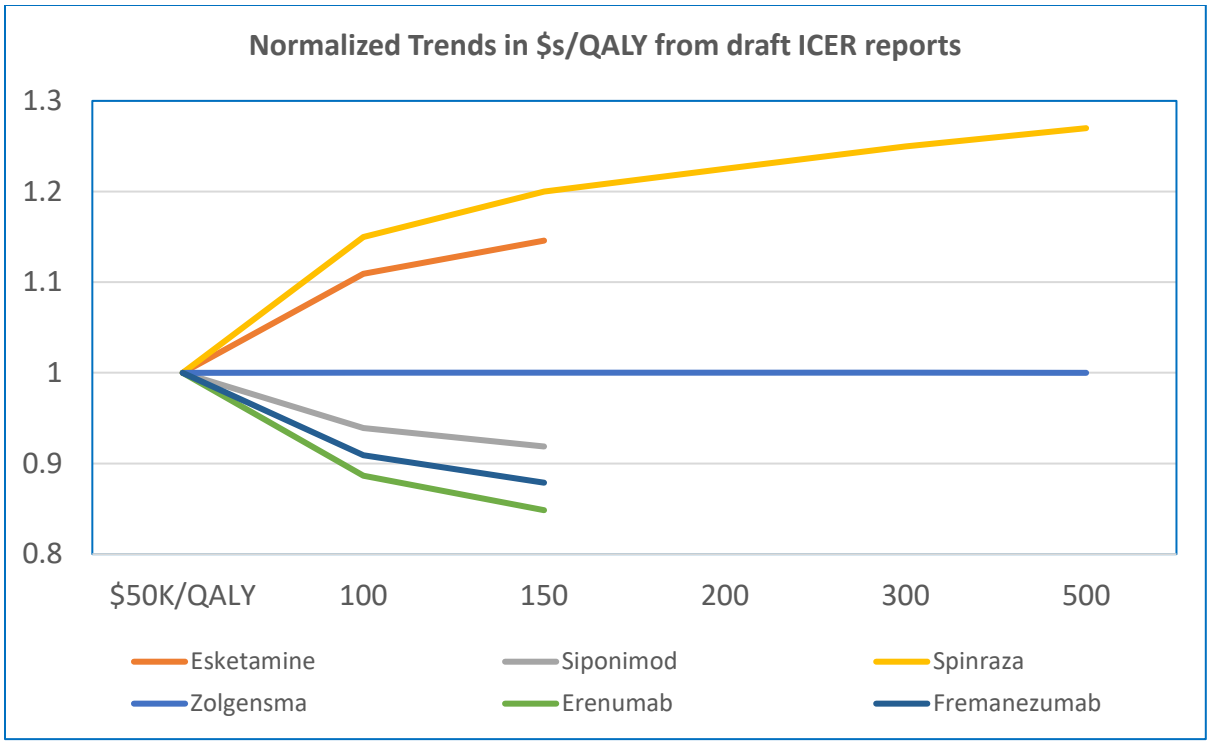
We are also concerned about the heterogeneity of patients with TRD and their ability to access adequate treatments. The draft report notes that "It is unclear how esketamine will affect racial, ethnic, gender, socio-economic, or regional disparities. If the cost of treatment is significant, those with limited financial resources may find it difficult to afford treatment."[xv] This is an important consideration, but it should also be recognized and stated in the report that since the

use of IV ketamine for treating depression is off-label it is considered investigational by insurance companies[xvi] and therefore generally not covered. This means patients have to pay 100% of the costs, which has significant implications for lower-income individuals for whom IV ketamine is then not a treatment option. Similarly, we urge ICER to update the information in the coverage section (Section 2) in the final report to include more accurate information about how different insurance plans are including esketamine in their medical benefit, and also include their requirements for patient cost-sharing. Comparisons to Medicare Part B's 20 percent cost-sharing and $185 deductible would be a good baseline for such a comparison.[xvii]

Similarly, we are concerned that if payers greet this new treatment option with barriers to access, restrict reimbursement to providers, or otherwise undermine its use, that such blocking actions will dissuade other companies and researchers from pursuing new treatment options for depression – and potentially other mental health conditions. And we certainly hope that ICER's analyses and statements do not support such diversion of research resources from finding new treatments for mental health conditions.

Technical Issues and Questions

While we appreciate complexity of modeling to project real-world outcomes, we have a question about ICER's threshold pricing analyses. Specifically, the outputs of models ICER has used in different draft reports has produced different curves of threshold price levels to meet its dollars per QALY targets. As is depicted in the graph below of different threshold levels in draft ICER reports, there is no consistency as to whether a threshold of $100,000/QALY is greater than, the same as, or less than twice the threshold price for $50,000/QALY – with those curve trends extending to the higher dollars per QALY in each draft report.[xviii] We would appreciate ICER describing what are the factors that contribute to those mostly non-linear different results since a surface impression would indicate that if a certain price would yield $50,000 per QALY gained, then twice that price would yield $100,000 per QALY, and three times that price would yield $150,000 per QALY etc., yet that linear progression only seems to be true for zolgensma. ICER's explanation of how its models can result in either increasing and decreasing costs per QALY gained in its threshold analyses would be greatly appreciated.



Additional Points

- On page 9 of the draft report it is stated that esketamine "is being studied as a nasal spray for the treatment of adults with TRD," but since it has been approved by the FDA for that specific indication – which was noted in the preceding sentence in the draft report – the text should be corrected so that it states "was studied." But if the intent was to indicate that there are ongoing trials, then that should be made clear since the current text is self-contradictory. Similarly, on page 18 of the draft report it states, "esketamine is awaiting FDA approval," but the draft report notes that the FDA approved it on March 5th.
- We appreciate ICER consulting with patient groups but conducting a group discussion with three (3) patients is something other than a "focus group." Others have noted that the minimum size of focus group for people with experience in the issue is at least five, and could easily be up 10 or more.[xix] In addition, how the focus group was conducted is not mentioned. This is a critical piece of methodological information that should be included in the final report and disclosed to the participants at ICER's May 23rd meeting.
- The lead author in the report is not a psychiatrist nor does he seem to have any expertise in mental health.[xx] Why does ICER shows a true lack of seriousness when they hire outside consultants who lack expertise in the clinical area for its reports.
- The draft report states that there is "widespread use of off-label ketamine infusion clinics for patient with TRD,"[xxi] but does not cite evidence of this use. Please provide that information. Similarly, the report states that "ketamine is a commonly used alternative treatment for TRD,"[xxii]without citing data. Please either support that statement or qualify it with something like "suspected to be widely used" or "is anecdotical reported to be" widely used.
- Esketamine is the S+ enantiomer, of the racemic compound ketamine. To put the new medicine in context, the physiological differences between the S+ and R- enantiomers should be noted and discussed. One source for those differences would be the 2016 review paper

"Ketamine enantiomers in the rapid and sustained antidepressant effects."[xxiii]

- The draft report states that "A cost-analysis was conducted evaluating the expected direct treatment costs for treatment with esketamine or ketamine."[xxiv] The text indicates that this data is provided in Table 4.8, but we do not see that data in that table, nor in any other table in the report. Please clarify what that sentence means and where that data is provided. Further, we are confused about the reference cost-analyses of treatment with esketamine or ketamine since the "Base-Case Results" seem to indicate comparing treatment with esketamine with no other treatment. So where how does treatment with ketamine (or costs for ketamine) figure into this analysis?
- Undiscounted WAC prices are used because of the belief that esketamine will have no competition, but the draft report states that there are other treatment options for TRD. ICER needs to recognize that competition occurs across all types of treatment options, not just within each type. For example, for treating coronary artery disease, intensive medical therapy competes with angioplasty, which also competes with bypass grafting surgery. The benefits and risks of each of those options has evolved as new variations of each modality have become available and new evidence about their longer-term outcomes – including from comparisons among them – have been documented.
- The draft report states that ICER "will provide the manufacturer of esketamine an opportunity to review and comment on the most recent version of the model base case during the comment period for this report."[xxv]In the final report please indicate how these comments will be used to improve ICER's modeling for future reports.

Conclusions & Recommendations

Patients Rising Now concludes that ICER's Draft Report on treatment resistant depression inadequately reflects patients' perspectives. For example, it doesn't encourage or fully comment on the need for more patient-reported and patient-focused metrics and outcomes. Thus, the draft report's "conclusions" need to be seriously questioned, particularly the statement that the clinical benefits of esketamine are inconclusive.

Patients Rising Now is also concerned that ICER's draft report will undermine patient's access to new treatments for depression, and that it may also delay or deter the creation of new treatments for depression, and potentially other mental health conditions. And further, we also continue to be concerned about ICER's lack of transparency about its modeling, which includes an overly simplified and homogenized construct of the U.S. health care financing, delivery, and innovation systems and organizations.

Sincerely,

Terry M. Wilcox

Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

[i] "Depression and Other Common Mental Disorders: Global Health Estimates," World Health Organization, 2017

[ii] "Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses," Cuijpers P, et al., Am J Psychiatry. 2014 Apr;171(4):453-62
[iii] "Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses," Cuijpers P, et al., Am J Psychiatry. 2014 Apr;171(4): p. 453
[iv] Draft report, p. 8
[v] https://www.who.int/news-room/fact-sheets/detail/depression (March, 2018)
[vi] "[H]aving major depression does increase suicide risk compared to people without depression. The risk of death by suicide may, in part, be related to the severity of the depression." https://www.hhs.gov/answers/mental-health-and-substance-abuse/does-depression-increase-risk-of-suicide/index.html
[vii] The draft report estimates that there are 192,000 people in the U.S. with treatment resistant major depressive disorder (p. 81).
[viii] Draft report p. 20
[ix] Draft report, pp 32-33
[x] Draft report, pp 50
[xi] Draft report, p. 14
[xii] Draft report, p. 16
[xiii] Draft report, p. 16
[xiv] The patient health questionnaire-9 (PHQ-9) is the patient-focused metric discussed in the draft report, but only in a few areas and not directly equated to improvements in quality of life. See Draft report, p. 36
[xv] Draft report, p. 78
[xvi] See UnitedHealthcare Commercial Medical Benefit Drug Policy for Ketamine, (Policy Number: 2019D0069C) Effective 04/01/2019
[xvii] https://www.cms.gov/newsroom/fact-sheets/2019-medicare-parts-b-premiums-and-deductibles
[xviii] The data for this graph was derived from the Threshold prices from different ICER draft reports, e.g., Table 4.14. Threshold Analysis Results in the draft report evaluating esketamine. That is, the "prices" required for each compound to meet different QALY thresholds were normalized by dividing by the threshold level. Specifically, all ICER reports use $50,000/QALY as the lowest threshold level, so that was chosen as the normalized baseline, i.e., 1.0. Each higher QALY threshold was then normalized to that baseline such that if the price for each increment of $50,000/QALY was more than twice the $50,000 it would be greater than 1.0, and if it was less than twice the $50,000/QALY threshold it would be less than 1.0. And of course, if it was an equal multiple of the $50,000/QALY threshold, then it would be equal to 1.0, which is the case for zolgensma.
[xix] "The traditionally recommended size of the focus within marketing research is 10 to 12 people. This is too large for most noncommercial topics. The ideal size of a focus group for most noncommercial topics is five to eight participants." "Participants in a Focus Group," Sage Publications, p. 5. https://www.sagepub.com/sites/default/files/upm-binaries/24056_Chapter4.pdf Also see http://cierp2.utep.edu/development/FocusGroupBasics.pdf and https://irep.olemiss.edu/wp-content/uploads/sites/98/2016/05/Trinity_Duke_How_to_Conduct_a_Focus_Group.pdf
[xx] Steven (Steve) Julius Atlas, MD, Massachusetts General Hospital - https://www.massgeneral.org/doctors/doctor.aspx?id=16325 (Accessed 3/5/19)
[xxi] Draft report, p. 47
[xxii] Draft report, p. 74
[xxiii] "Ketamine enantiomers in the rapid and sustained antidepressant effects," Muller et al., Therapeutic Advances in Psychopharmacology 2016, Vol. 6(3) 185–192 – see Table 1. "Distinct characteristics of S(+) ketamine compared with R(–) ketamine"
[xxiv] Draft report, pp 68-69
[xxv] Draft report, p. 67