Esketamine for the Treatment of Treatment-Resistant Depression: Effectiveness and Value

Response to Public Comments on Draft Evidence Report

May 9, 2019

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Manufacturers		
Janssen		
1.	**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-25 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 USPI6 recommends flexible dosing which is consistent with real world practice. Therefore, we do not consider it appropriate to pool the data from TRANSFORM -17 (fixed doses; 84 mg and 56 mg) and TRANSFORM-25 (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- 25 trial and diminishes the real-world applicability of ICER's cost effectiveness analysis.	The Transform 1 and 2 trials both met the eligibility criteria that were established prospectively in our scoping document. There can be many differences among trials that meet review eligibility criteria. Given that both of these trials were phase III evaluations intended to demonstrate the efficacy of this new medication, included similar study populations, the same drug, the same outcomes and the same follow-up period, we included these two trials in our meta-analysis.
2.	**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-25 and SUSTAIN-14), which are further supported by the FDA advisory committee vote (14 yes, 2 no, 1 abstain) and subsequent FDA approval.	The ICER rating was based upon its review of evidence as laid out in the scoping document and highlighted in the draft evidence report. Given the short-term nature of the phase III trials, the primary endpoint was only achieved in one of the phase III trials, evidence supporting the need for long-term therapy, and the lack of long-term comparative safety data, the ICER rating (promising but inconclusive, P/I) was intended to reflect uncertainty that may remain even after FDA approval. Indeed, the FDA approval included the need to collect long-term data that was not available at the time of approval. As pointed out by Janssen, two members of the FDA advisory committee voted no in terms of recommending for approval.
3.	**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-25, 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-14, ESK + oAD, had a significantly delayed time to relapse versus those treated with placebo (PBO) + oAD after 16 weeks of	The Transform 1 and 2 trials provide comparative evidence of the short-term benefit of esketamine compared to another antidepressant. The Sustain 1 trial provides comparative evidence that stopping esketamine results in a higher rate of relapse than continuing esketamine. The Sustain 2 trial, though assessing outcomes of esketamine over a 48-week period, was not a comparative trial. Thus, it cannot be used to provide evidence

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	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.	that esketamine provides long-term efficacy compared to other available treatments.
4.	In the TRANSFORM-2 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.	The ICER report highlights that there was a statistically significant greater improvement in MADRS score in the esketamine group compared to the placebo group. We have now added a statement regarding the MCID for the MADRS as suggested.
5.	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.	The ICER report highlights these results.
6.	Maintenance of effect was established in a dedicated ESK maintenance of effect study (SUSTAIN-14).	The ICER report highlights the results of the Sustain-1 trial. It supports the role for prolonged use of esketamine for patients initially responding to this therapy.
7.	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.	As highlighted in the ICER report, the results of these studies were carefully reviewed, and the results presented. The ICER rating of P/I reflects these results and the uncertainty pertaining to long-term therapy for this debilitating chronic condition. We recognize that other may interpret these results differently. These results will be presented at a meeting in May 2019 to the Midwest CEPAC and they will have an opportunity to hear from all parties and vote on their interpretation of this data.
8.	**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	We appreciate this comment and recognize that the use of a background antidepressant in all patients is a unique feature of the Transform 1 and 2 trials. In reviewing published data from these trials, treating clinicians in these trials chose among 4 antidepressants (two SSRIs and two SNRIs). Given that these patients had already failed prior therapy during the current episode and many would be expected to have had prior episodes that required treatment, it was unclear if

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	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.	the selected antidepressant was in fact "new". Our expectation would be that many of these individuals would have had prior treatment with either an SSRI or an SNRI and probably exposure to both. So, it is unlikely that these classes of medicines would have been new to study participants. Moreover, it is unclear from the data presented whether the specific SSRI or SNRI had been used previously in a given patient. If one takes into account not just the current episode but also past episodes, we expect many patients may have had prior use of the 4 antidepressants available for use. Thus, for these reasons, we elected to use the term, "background" to describe this additional antidepressant. We would be willing to reconsider this wording if there are data provided to suggest that the antidepressant/class was in fact "new" to the patient.
9.	**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.	We agree that TRD is a complex disease and that there is heterogeneity in patient response. The purpose of economic modeling is to combine data, using the best available data from a variety of sources. As such, every model input has been thoroughly evaluated to produce as unbiased of a model as possible. At the same time, we acknowledged that estimates available in the literature may be biased due to choices made by investigators in their study designs. We have conducted extensive sensitivity analyses to evaluate the potential impact of model inputs on the cost-effectiveness results.
10.	Initial treatment effect: TRANSFORM-25 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 fixed dose study data in the meta-analysis.	Please see the response to the prior comment.
11.	Probability of patients in maintenance treatment with partial response subsequently achieving complete response: We recommend the use of the correct SUSTAIN-1 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.	From the Wajs SUSTAIN 2 poster, the maximal mean effect of treatment (as measured using the MADRS scale) with esketamine was observed by the beginning of the optimization/maintenance phase of the long-term study. These results were not much different from day 28 of the induction phase of the study. Therefore, we believe that extrapolating results from 1 month to 3 months would results in a gross overestimation of the probability of moving from partial response to full response. Unfortunately, we were not provided with the data requested to adequately evaluate the probability of moving from partial response to

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		full response at month 3 or at longer time points. We believe that the estimate of 19.9% for ESK + oAD and 12.4% for oAD alone is an underestimate for this probability in second cycle and an overestimate for each subsequent cycle, and may therefore overestimate the proportion of patients receiving full response to esketamine over the full time horizon of the model. No changes were made to the base-case model.
12.	**Probability of patients in maintenance treatment with partial response subsequently losing response: We recommend the use of the correct SUSTAIN-14 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.	In the poster by Daly et al describing outcomes of the SUSTAIN 1 trial, Figure 2b presents the "Percent of Patients Without Relapse" (y-axis) by "Week" (x-axis) for patients who were stable responders. By our digitized estimates from the poster, at 12 weeks, 21% of the initial cohort of ESK + oAD patients had relapsed while 47.6% of the initial cohort of oAD alone patients had relapsed. It is not clear from where the new estimates of 13% for ESK + oAD and 40.7% for oAD alone were obtained nor how they were analyzed. No changes were made to the base-case model.
13.	**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*D13 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*D2 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-14 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*D2 Step 4 remission for sequential lines of treatment in the model	The remission rates given in the STAR*D trial for each treatment step are 36.8% (step 1), 30.6% (step 2), 13.7% (step 3), and 13.0% (step 4). While there is decline in treatment effects with each step, this effectiveness is likely influenced by selection of the next oral agent. The STAR*D study did not restrict treatment selection, nor did it evaluate a fifth step. We are therefore left with trying to extrapolate results to those starting their fifth therapy and beyond. As noted above, the first and second therapies appear to be very similar in effectiveness. There is a large drop-off in effectiveness when moving to the third step of therapy. A similar reduction in effect is not observed between the third and fourth steps in therapy. Therefore, we believe applying an average reduction between steps is an incorrect approach to estimating steps beyond the second step. Since a functional form could not be fitted to this data, we assumed that subsequent steps (after step 4) would result in effectiveness rates similar to step 4. No changes were made to this input in the base-case model.

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	therefore significantly overestimates the effectiveness of the subsequent treatments in real world, and consequently biased against ESK.	
14.	**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-14 trial and guidelines. After 6-months of treatment in the maintenance phase of SUSTAIN-14 (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 Force14 and the APA9 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-14 trial, as the current value of 40% is derived following acutely remitted patients in the STAR*D2 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	We acknowledge that there is extremely limited evidence regarding treatment discontinuation of effective therapies, which is why we used expert opinion to estimate this model input. In discussions with our clinical experts, we were informed that TRD is not treated in the same manner as first episode depression. The ACNP task force and APA guideline recommend treating patients for 4-9 months for select patients. The guidelines go on to discuss "maintenance phase" to reduce the risk of a recurrent depressive episode in patients who have had three or more prior major depressive episodes, have chronic major depressive disorder, or have additional risk factors for recurrence. In these patients, maintenance therapy, defined as "an antidepressant medication that produced symptom remission during the acute phase and maintained remission during the continuation phase should be considered at a full therapeutic dose. Similar wording g is used in the VA guidelines. However, we heard from our clinical experts that patients with treatment resistant depression are more likely to have more severe depressive episodes and that they frequently recur in a cyclical manner. Therefore, depending on the "degree" of treatment resistance, a small proportion of patients would have an effective treatment discontinued. This was particularly true of patients who are currently receiving ketamine. Based on expert opinion, we estimated that 5% of patients would successfully discontinue treatment each year. Recognizing that there is a high degree of uncertainty in this estimate, we have altered the report to include a broader range of estimates (0-50%) in the one-way sensitivity analysis. The base-case estimate was not changed.

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	have been in remission for much longer (e.g. 9 months) than in the STAR*D trial.	
15.	**Mortality adjustment: A recent study by Bergfeld et al (2018) 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.	Our mortality sources (i.e. USA Human Mortality Database and Reutfors et al 2018) use all-cause mortality as their measure. Adding completed suicide to this number would erroneously double-count mortality in the model. The included analysis compared patients with TRD to those without TRD. While we acknowledge that this may not be the optimal comparison (a comparison of "treated TRD" to "untreated TRD" would be the optimal comparison), our estimates may be biased upward or downward. The suggested adjustment does not properly correct for potential bias in our estimates and may increase any bias in favor of esketamine. No changes were made to the model.
16.	**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," while the CADTH, recommend "restricting access to ketamine to the research setting."	The reasons cited led to ICER not performing a comparison of the cost-effectiveness of esketamine and ketamine. The decision to perform a cost analysis was based upon the similar chemical nature of these drugs and their mode of action, and the widespread use of IV ketamine off label for TRD.
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.	We have extended this analysis to include the full time horizon.
18.	**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.	This is a general table. As noted in its title, it is not specific to any disease or therapy. Other benefits are clarified in the text.

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19.	**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 USPI6). • As noted in the SPRAVATO USPI6, 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.	This is a general table. As noted in its title, it is not specific to any disease or therapy. Contextual considerations are clarified in the text. Though esketamine was approved based upon the studies cited, it is well recognized that a full understanding of the potential benefits and harms of any new drug requires follow-up as the therapy is introduced into clinical practice. There may be specific populations in which a previously approved therapy may be associated with increased harm, as well as other groups that may derive greater benefit. In the example cited, sertraline was approved for use in 1991. Since that time, studies have identified that SSRIs, including sertraline, are associated with increased bleeding risk. This was not recognized in the initial published studies. The FDA label for sertraline first added a precaution about bleeding in 2004.
20.	**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.	See response below.
21.	**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 USPI6, 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.	We have modeled esketamine's treatment duration based on the available trial data. Additionally, based on real-world evidence and clinical expert opinion, we have modeled subsequent lines of therapy and attributed discontinuation rates accordingly to these lines of therapy as well. Finally, it is important to note that total costs represent not just costs of esketamine, but that of the esketamine treatment arm which includes subsequent lines of therapy after esketamine discontinuation.
22.	**Treatment Guidelines:** APA guidelines recommend patients successfully treated with antidepressant medication continue with those agents for 4-9 months for relapse	Our model accommodates for staying on treatment among those successfully treated (no depression) and also includes the possibility of

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	prevention. Those who do not initially respond or who relapse would only decrease the mean length of therapy.	treatment discontinuation upon successful treatment for a small proportion of patients. Similarly, treatment is discontinued among those who do no initially respond to treatment or have loss of response to treatment.
23.	**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. The ICER model overestimates typical treatment durations observed in RWD by at least 2-fold.	We believe that any treatment discontinuation due to adverse events is assumed embedded in the loss of treatment effect in the clinical trials. In the absence of RWE for esketamine, we made this assumption in our model.
24.	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 [See letter].	Thank you.
Patient Groups		
Patients Rising Now		
1.	The draft report states “Depression can increase the risk of suicide.” 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.” However, from a population perspective, depression DOES increase the risk of suicide. 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.”	We have revised this statement to read, "Depression is associated with increased risk of suicide and results in long-term suffering."
2.	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,” but then declares that the benefits are “promising but inconclusive.” Therefore, how can ICER conclude inconclusive results?	Currently available results demonstrate that esketamine appears to provide short-term benefit as reflected in our meta-analysis. However, esketamine is proposed for use in patients with chronic depression, specifically treatment resistant depression. Thus, it is expected that if patients respond to therapy, esketamine may be used for a prolonged period of time. Available data does not permit us to conclude that such use is effective and safe compared to other therapies. For this reason, we conclude that esketamine is a "promising but inconclusive" therapy.
3.	A related concern is that the draft report uses a threshold of at least 50% reduction in symptoms as “Clinical Response.” 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	As noted, "clinical response" is a commonly reported outcome in depression trials. However, the primary outcome of the esketamine trials was change in MADRS score between baseline and follow-up. Clinical experts that we spoke with highlight that clinical remission is a better measure of outcome that reflects a meaningful

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	Montgomery–Åsberg depression rating scales (MADRS) reflects patient-centered benefits of treatment.	change for patients. Clinical remission refers to a level of depression symptoms below a certain threshold.
4.	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," and that "symptoms of depression are more impactful on diminished quality of life than people realize." 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. 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 did seek out input from patients and advocacy groups throughout our review and we believe that our report highlights their insights and concerns. Though it is not possible to include all of these insights into our cost-effectiveness model itself, these quantitative assessments are only one part of our report. We focus considerable attention on the data available and their limitations as well as key insights from all concerned groups including patients and their advocates. Presenting these data, along with insights from patients and other interested parties along with the quantitative results are all necessary to inform policymakers about how best to consider new therapies. The comparative clinical effectiveness, quantitative evaluation, other benefits, and contextual considerations sections of our report all feature prominently in the ICER value framework to inform all decision making by our panels.
5.	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." 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 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.	Thank you for making these points. We agree disparities in coverage and access exist and are problematic. We say so in our report, as you noted.
6.	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	ICER's mission is to ensure that all patients have access to high-value care. We believe we can foster innovation by incentivizing the development of high-value treatments.

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	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.	
7.	**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. 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. [See graph in letter]	Drug and non-drug costs comprise total costs, which along with effectiveness help derive an incremental cost-effectiveness ratio. The ratio of the drug to non-drug costs is key to understanding the linearity of drug price differences to reach specific thresholds. To reach different thresholds, the drug to non-drug ratios will differ since only the drug cost is varied while the non-drug costs are held constant. This results in non-linearity in drug price variation at different thresholds.
8.	**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 have revised our report to reflect the fact that esketamine is now FDA approved.
9.	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. 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	Thank you. We have revised the language.

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	final report and disclosed to the participants at ICER's May 23rd meeting.	
10.	The lead author in the report is not a psychiatrist nor does he seem to have any expertise in mental health. Why does ICER shows a true lack of seriousness when they hire outside consultants who lack expertise in the clinical area for its reports.	We use authors who are expert in evidence-based medicine and in systematically reviewing and synthesizing a body of evidence. While expert input and review is vital to our reports, we believe that experts in evidence-based medicine are best able to provide an unbiased look at the therapies we review.
11.	The draft report states that there is "widespread use of off-label ketamine infusion clinics for patient with TRD," 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," 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.	Thank you for your comment. We have now included a citation that shows evidence of a rapidly growing number of ketamine use.
12.	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."	As part of its review, ICER sought to compare esketamine and ketamine as a way to evaluate the potential difference in efficacy and safety between the S-enantiomer and a mixture of both. Given the lack of comparative data, we were not able to directly or indirectly compare these two drugs. Thus, it is uncertain what differences if any exist between these enantiomers in clinical practice.
13.	The draft report states that "A cost-analysis was conducted evaluating the expected direct treatment costs for treatment with esketamine or ketamine." 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?	The cost-analysis evaluates the expected direct treatment costs for treatment with esketamine or ketamine. This is intended to provide a rough estimate of how much it would cost to receive a year of treatment with esketamine versus a year of treatment with ketamine. Section 4.2 details what this analysis includes. Table 4.8 details the recommended dosage for esketamine and these data inform the estimated annual usage used in the cost-analysis. Annual usage for ketamine was estimated in consultation with clinical experts and is not detailed in Table 4.8. The cost-analysis is separate from the cost-effectiveness analysis in that the latter includes treatment efficacy, while the former is based purely on treatment costs.
14.	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	We discussed using the WAC price with multiple stakeholders and believe this is the most appropriate choice in this case.

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	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.	
15.	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." In the final report please indicate how these comments will be used to improve ICER's modeling for future reports.	Having the manufacturer review the model and submit related feedback for this review informs only this review. ICER is piloting this model transparency program with manufacturers for all future reviews.
16.	**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.	We respectfully disagree. The report highlights these patient concerns and explains the basis for the evidence ratings.
17.	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.	As noted above, we executed a model transparency with manufacturers for this review and will for all future reviews.
National Alliance on Mental Illness		
1.	**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.	Esketamine and ketamine are both thought to exert their anti-depressive effect through similar mechanisms. This led to our interest in comparing these two drugs.
2.	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	ICER did not compare the cost effectiveness of esketamine and ketamine. Instead we performed a cost analysis that sought to estimate the cost of these two drugs. Such analyses are designed to be independent of the payer. It is true that out of pocket costs for patients may differ depending upon the payer. Though ketamine is not currently covered by insurers and patients may have to pay the full cost, it is not clear what patient's out-of-

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	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.	pocket costs for esketamine may be depending upon the payer.
3.	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.	We agree with these comments. Our review of the available evidence for the use of ketamine for TRD identified the deficiencies highlighted here. For that reason, we elected not to perform a direct or indirect comparison of the cost-effectiveness of esketamine and ketamine. Nevertheless, as noted, ketamine is widely used off-label for the treatment of MDD. This led us to perform a cost analysis comparing these therapies.
4.	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.	As noted in other comments, we agree that available evidence does not permit a direct or indirect comparison of the cost effectiveness of esketamine and ketamine. Though short-term comparative data for esketamine are favorable and thus promising, we highlight the lack of long-term efficacy and safety data compared to other therapies. For this reason, we find esketamine to be promising but inconclusive.
5.	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.	We respectfully disagree with this conclusion.
6.	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.	We mention the REMS program and provide citation to its details in various sections in our report. The need for such a program highlights the potential risks of this therapy and will impose a considerable burden on patients and providers who seek to use esketamine. The goal of such a program is to ensure that the benefits and harms from clinical trials are reflected in actual clinical practice. We also acknowledge that the use of REMS program for esketamine potentially provides a higher safety standard for esketamine when compared to ketamine, and this is now

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	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.	mentioned in the other benefits and contextual consideration section of our report.
7.	**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.	The QALY measures both length of life and quality of life improvements. The utilities used in our model are derived from the MADRS and PHQ-9 scales, both of which capture quality of life measures for patients. Additionally, we have included a cost per depression-free day in our analysis. This accounts for symptom improvement, functioning and quality of life. Because many methodologic issues are unresolved, caregiver quality of life is not routinely included in cost-effectiveness analyses, and if included would alter decisions about what threshold ratios should be considered.
8.	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.	QALYs are also only one component of the value assessment, for example, they are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. Additionally, many of the issues your raise are part of the Other Benefits and Contextual Considerations section, which are essential in assessing value.
9.	**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. Of note, the researchers state that 31.7% of patients who had an improvement in depressive symptoms	While there may be evidence that the PHQ9 and GAD2 result in higher responsiveness to depressive and anxiety symptoms, respectively, than the EQ-5D-3L, this does not imply that these components are not adequately captured by the EQ-5D-5L. It is expected that disease-specific measures are more sensitive to changes in domains being measured. However, disease-specific measures generally do not usually provide a comprehensive evaluation of the impact of a

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	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. This suggests that use of the EQ-5D does not capture clinically important changes in the mental health of patients living with TRD.	condition on overall patient quality of life or health utility. Our systematic review of the literature did not identify studies mapping the PHQ9 to utilities. In addition, the EQ-5D-5L has better measurement properties than does the EQ-5D-3L (Buchholz et al, PharmacoEconomics 2018; 36: 645-661).
10.	**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.	See prior comments.
11.	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.	See prior comments.
12.	**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,	In this section, we state, "For patients who have had chronic, treatment-resistant MDD, the burden of this condition can result in a profound impact upon quality of life." We believe this statement reflects the comment raised by NAMI. As noted previously, we have added a sentence highlighting the impact of TRD on work, productivity and disability, as well as the uncertainty about whether esketamine may improve these outcomes or not. We believe that the range of symptoms highlighted in this comment are just those that are captured in quality of life measures.

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	anger, agitation, sexual problems, and unexplained aches and pains.	
13.	**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.	Depression and the therapies to treat it can have impacts on health that go beyond depression-related outcomes. This may include co-morbid conditions such as those listed. Depressive symptoms may directly affect co-morbid conditions through decreased activity, weight gain, and other unhealthy lifestyle changes. Therapies that may help depressive symptoms, such as antipsychotic medications, may have also deleterious effects on these co-morbid conditions. Whether esketamine has a positive or negative effect on these co-morbid conditions remains to be seen. It is possible that the overall effect may be positive, but as noted with its transient increase in blood pressure, esketamine may also increase risk for cardiovascular conditions. We currently state in this section, "For example, use of esketamine is associated with transient side effects with dosing such as dissociation and elevated blood pressure. With longer term use, it is unclear if side effects not seen in short-term studies such as misuse or increased cardiovascular events may be observed." We have added a sentence prior to this one to more broadly address concerns about co-morbid conditions, "Depression and its treatment may impact other health issues such as diabetes and heart disease. It is uncertain whether esketamine may have a net positive or negative effect on these other conditions." With regards to inclusion of comorbid medical conditions in the model, we do attempt to capture the impact of comorbidities on mortality by using all-cause mortality estimates. Unfortunately, we were unable to identify any studies evaluating the costs or benefits of treated depression on economic outcomes of comorbidities in patients with TRD. There is also no evidence, at present, that treatment with esketamine would influence the economic outcomes of these chronic conditions.
Partnership to Improve Patient Care		
1.	**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	The ability of esketamine to provide a quicker response may be an important advantage of this therapy, one that may also be seen with ketamine. However, available data has not yet shown a statistically significant greater response at initial

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	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.	follow-up in the esketamine trials reported to date.
2.	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.	See prior comments.
3.	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.	We evaluated lifetime cost-effectiveness because estimates evaluating short-term cost effectiveness result in very high incremental cost-effectiveness estimates. This is because costs are usually incurred early in treatment and benefits accrue after some time has passed. Importantly, we did attempt to quantify early treatment benefits by applying a utility benefit to patients on esketamine who had remission or response in the first cycle. This difference in benefit was estimated from TRANSFORM-2 (Poster from Popova et al 2018) showing an early improvement in MADRS total score among participants in both the ESK + oAD and oAD only arms of the trial. Although It was not clear from the poster when this difference achieved statistical significance, we chose to include these differences in the model and likely overestimated the early benefits of treatment.
4.	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.	As noted previously, the immediacy of effect has not yet been demonstrated with certainty. It may also be an overstatement to claim that the REMS will lead to a "simplicity of delivery." Though intranasal administration is simpler than IV administration of ketamine, other aspects of the REMS program may represent a considerable burden in terms of time and effort.
5.	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	The QALY measures both length of life and quality of life improvements. The utilities used in our model are derived from the MADRS and PHQ-9 scales, both of which capture quality of life measures for patients. Besides the QALY, we have also included a cost per depression-free day in our

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	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.	analysis. This accounts for symptom improvement, functioning and quality of life.
6.	**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.	We recognize that for newly approved treatments there are often limited data available. However, since these medicines are currently available for use by patients, clinicians and payers, reliable information is needed now. This report uses data that are currently available and highlights the limitations of this data as well as the qualitative input of a range of stakeholders.
7.	**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.	ICER strives to release consistently high-quality work using the best available evidence. The quality of evidence differs between trials and disease states and we consistently state the limitations of the evidence when appropriate. In fact, uncertainties around evidence directly impact our evidence ratings and help to make stakeholders aware of them. This comment specifically mentions SMA. When ICER reviewed SMA, one manufacturer repeatedly objected to an "A" evidence rating for a therapy and felt the rating should be lower.
8.	**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. There is a growing body of evidence that suggests that effectiveness is a dynamic, rather than a static measure. That is, relative	We note that our reports are most up to date at the time of release and we update them if new evidence emerges that would significantly alter our findings.

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	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. 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.	
9.	**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. With this in mind, total economic cost of untreated depression should be taken into consideration, yet is not captured in the draft evidence report.	We conducted a thorough systematic review of the literature to identify the best sources for the economic impact of TRD on patients and the health care system. We identified only a single study that quantified costs in an appropriate way to be included. This study included the costs of hospitalizations, but not caregiver burden or lost labor costs. However, we did develop a scenario analysis in which we included labor gains with treatment. Note that this therapy has been approved for TRD only. Therefore, our model evaluates the cost-effectiveness of treating TRD and not the costs associated with major depressive disorder.
10.	**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 compiled the results from 6 studies published since the study that was used by ICER, suggesting that the cost of TRD was between 30-100% higher on average than treatment responsive depression.	We identified this same review in our systematic review and included these 6 studies in our evaluation. None of these studies met our inclusion criteria. In addition, many of these studies from this review were conducted 15-20 years ago, in the same era as the study used in the model and suffered additional limitations. For example, results involved an inappropriate comparison or were presented in a manner that was not compatible with our model.
11.	**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	We acknowledge that there are limitations in available evidence. However, we do not know how these limitations bias the results. In the last 17 years and in general, medical care has generally become more efficient (e.g., shorter hospital lengths of stay) while rates of prescribing have increased, with a corresponding shift from inpatient to outpatient care. These cultural shifts are not captured in our inflation rate. We encourage researchers to provide updated usable economic evidence on the economic burden of

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	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.	TRD and the potential benefits of TRD treatments. We also evaluated these estimates in one-way sensitivity analyses to evaluate the impact of differing costs, by treatment step, on the model's results.
12.	**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) 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). 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. 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.	See prior comments.