INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Digital Therapeutics as an Adjunct to Medication Assisted Treatment for Opioid Use Disorder Response to Public Comments on Draft Evidence Report

November 6, 2020

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Patient Organizations		
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1.	There are some additional points we believe are important, and we ask ICER to consider including them in the final report and as part of ICER's Midwest CEPAC discussion scheduled for November 20th. ● COVID has made it significantly more challenging to access health care services in person, so any auxiliary tools for providing successful MAT for people with OUD should be considered and given higher priority at a time when in-person clinic visits are more problematic or even impossible. ● The draft report noted that there were significantly lower total health care costs observed in people who were adherent to MAT. ● Stigma is a significant barrier for people to receive MAT for many reasons, including personal or family beliefs, insurance coverage, and government actions. Language is an important force for reducing stigma, and we urge ICER to consider expanding its discussion of stigma and how to reduce it in the final report.	Thank you for the suggestions. We encourage you to highlight them at the meeting if you are participating. We will keep them in mind as we prepare for the meeting. They are particularly salient for the discussion of contextual considerations and other benefits and the policy roundtable.

2.	**Terminology and Language** In our comments to ICER in 2018, we noted our disagreement about the meaning of the acronym MAT. We are very glad to see that ICER has adopted the most appropriate, and most people-centered meaning of MAT: Medication Assisted Treatment. Similarly, use of the term "addiction" carries with it a stigma that can create barriers for people with OUD for receiving care. Consistent with this improvement in the report's language – and to promote others from avoiding the use of the term "addiction" we suggest that "addiction" be added to the list of definitions, with language such as: Addiction is a term that had previously been used to refer to people with OUD who were not in recovery or remission, and engaged "in behaviors that become compulsive and often continue despite harmful consequences." However, because OUD is recognized to be a biologically based disease, and the terms "addiction" and "addict" carry societal stigma, they are not preferred and not used in this report. Thus, the preferred terms are "people with OUD," "people with OUD in recovery or treatment," "people with OUD in remission," and "people with OUD who have relapsed." We also suggest that to help reduce stigma from OUD, the report includes some discussion of the biological basis for OUD, and characterize – or define – it as a biologically based chronic condition, and thus it has similarities to diabetes, hypertension, and bipolar disorder, among other conditions.	Thank you. We have added your definition of addiction to the definitions section of the report.
3.	**Research Methodologies and Uncertainties** For the reasons discussed below, it is impractical to perform double-blinded studies on interventions like digital therapeutics, since it would be like doing a double-blinded trial on a knee replacement or LASIK surgery. Applying the same standards to digital therapeutics as those that are used for drugs is not appropriate. Thus, the mere fact that the trial of DynamiCare was observational should not completely discount the validity or utility of its findings.	Randomized trials of surgical techniques using sham surgery have provided invaluable information that spare patients from risky, expensive, and unhelpful surgeries every day. There is an extensive literature on how to provide meaningful control interventions when studying behavioral interventions. We should not lower our standards when the task is challenging. We agree that observational, real-world evidence can be enormously helpful in understanding the true clinical impact of an intervention, but randomized trials remain the gold standard for proving causality.

4.	The research and development processes for health care software, digital therapeutics, and other non-biopharmaceutical interventions that have rapid cycles of updates, upgrades, and improvements, making them generally inappropriate to evaluate using double-blinded controlled trials. Validating the utility of such innovations is complicated because by the time the research is done, new versions may be available and in use. For example, it seems that the primary data source for reSET-O was a clinical trial published in 2014, but like all robust software, there have been significant and frequent updates to the reSET-O digital therapeutic since that time, with six different versions through August 2020. Therefore, while we recognize the uncertainty about the limited length of follow-up for the trials cited, we believe it is important to recognize that performing follow-up or conducting intervention trials that last 12-24 months – as is suggested in the draft report – is simply impractical for digital therapeutics.	Thank you for that perspective, but we respectfully disagree. In fact, several such trials are underway (see section describing ongoing studies).
5.	Because of the inherent paucity of data for each of the three digital therapeutics discussed in the draft report – with only one of them being the subject to ICER's full array of modeling and review – we therefore fundamentally question the utility and validity of the quantitative assessments contained in the draft report. We assume that ICER agrees that better, more accessible MAT for people with OUD is a positive thing with the potential to do tremendous societal good, and particularly since none of the digital therapeutics has been shown to cause any harms, they should be considered an important part of the array of treatment alternatives for people with OUD.	Our prior report highlighted the importance of MAT and the need for greater access. The current report focuses on the potential impact of behavioral interventions delivered via apps. We certainly are not trying to discourage efforts to increase the availability of MAT, which is supported by many randomized trials and years of real-world evidence and experience.

6.	There are a variety of other methodological issues and uncertainties related to the draft report that we believe are important for ICER, policy makers, and others to understand, including: ● We were a bit disappointed that one of the trials evaluating DynamiCare was discounted because it included people who only had other types of substance use disorders beyond OUD. Since it is clear that people with OUD often have other concomitant substance use disorders, the clinical and social utility of addressing all of a person's substance use disorders simultaneously is important, because treating all of a patient's related medical conditions rather than treating each one independently is the basic differentiation between patient-centered care and disease-focused care. ● In assessing the effectiveness of MAT and the serious consequences of OUD, there are many important metrics other than retention, adherence to treatment, being in recovery, and death. While the draft report does discuss rates of HIV and HCV infection, there are also serious non-fatal outcomes of overdoses from opioids – most significantly brain damage from lack of oxygen from severe overdoses, as well as vascular infections that can lead to infections in the heart as well as secondary infection in the kidneys, bones or brain. ● A new NIH-supported clinical trial of reSET-O is preparing to be initiated. Similarly, there is a health system sponsored trial of DynamiCare. (Interestingly, the ClinicialTrials.gov description indicates that DynamiCare is not an FDA-approved device product, while reSET-O is, which illustrates the complex and sometimes nebulous nature of software products intended for improving health or wellness, and the complexity of the FDA regulatory and approval process for innovations in this rapidly evolving realm.) While we recognize that ICER will not wait until the results of those trials are completed before continuing with this review, we strongly suggest that those trials be noted in the report, and that ICER plan on doing an update on this topic in early 2022 – or whenever the results of those trials are available	We agree that polysubstance use is common, and we included trials that enrolled patients with multiple substance use issues as long as OUD was one of the diagnoses for each participant. For instance, this was true for Christensen et al. Thank you for highlighting the ongoing research on this apps. We think that it is essential that high quality research of appropriate duration be done in order to have confidence in the value of these therapies.

7.	Additional Points ● In the first sentence in the last paragraph on page 19, "patient" should be plural. ● We are concerned about the draft report's assumption that because there is a cure for chronic hepatitis C infection (with a 98% effectiveness rate) that only 2% of people with chronic HCV will have "clinical consequences." This is another example of ICER focusing on clinical trials data and results, and ignoring the real world situation where individuals with HCV may not have insurance or have other barriers to accessing treatment, including insurance that has cost-sharing that makes such cures effectively unaffordable for them. In addition, it is known that many people with HCV are undiagnosed, but those people do develop health problems from their HCV and have higher health care costs overall. ● We also note that the draft report's modeling of the risks of contracting HIV or HCV for people with OUD who are not in treatment or recovery focuses on injection drug use. However, it is well known that both HIV and HCV are sexually transmitted infections, and people with OUD who are not in recovery or remission may be trading sex for access to those illicit opioids (as well as other substances), which puts them at increased risk of contracting HIV and HCV. ● We are very concerned that ICER "deviated from the ICER Reference Case lifetime time horizon because of no identified or plausible impacts to costs or outcomes beyond the five-year time horizon and to remain consistent with prior ICER MAT research" without adequate explanation.	We appreciate that there are nuances to some of our assumptions. Because phase 2 illicit use does not differ between the two arms, assumptions around HIV/HCV impact each arm the same; thus, these assumptions do not drive the results. Further, our 5-year time horizon aligns with the time horizon selected and described in the 2018 ICER MAT review. It is quite typical to have even shorter time horizons than 5 years when evaluation MAT and associated interventions. We could have modeled a lifetime time horizon and the results would be nearly identical to the base-case 5-year time horizon due to the miniscule difference in retention (and no difference in abstinence) observed at 5 years between the two arms.

Shatterproof: Stronger than Addiction		
1.	**Innovation in treating OUD** Fortunately, there have been tremendous innovations in treating OUD over recent decades. This includes the remarkable benefit of the rescue medication Naloxone and the several FDA-approved medications for treating OUD, commonly known as Medications for Addiction Treatment (MAT). The acceptance of a medicine as a treatment for OUD was accelerated by the credibility conferred by FDA-approval. Since FDA approval, MAT has been shown to be incredibly effective in treating patients with OUD. Methadone, extended-release injectable naltrexone (XR-NTX), and buprenorphine were each found to be more effective in reducing illicit opioid use than no medication in randomized clinical trials. Methadone and buprenorphine treatment have also been associated with reduced risk of overdose death. We should be encouraged that the promise of digital therapeutics can similarly be guided by following this standard. The effectiveness presumed with FDA-approval enables access for patients that need options and support to assist in their recovery path. We would be very concerned if a premature evaluation of cost-effectiveness for the first FDA-approved digital therapeutic had the unintended consequence of discouraging further innovation and investment in prescription digital therapeutics. We encourage ICER to consider this contextual factor as you make your final report.	Thank you for the input on MAT. If you are interested, you can review our earlier report, which highlighted the benefits of MAT. As for the concern about premature evaluation of digital therapeutics, they are clinically available, so clinicians need to know whether to use them and insurers need to decide whether to cover them, and if so, how much they will pay for them. We are, in fact, somewhat late with our report. Usually we aim to have our report available at the time of FDA approval as it may have the greatest utility at that time. As noted above, we update our reports when important new evidence becomes available.

2.	**Societal costs of addiction** The ICER report details cost inputs associated with its review. As noted, "significantly fewer total costs were observed in the MAT adherent population, although no propensity score matching or pre/post analysis was conducted." We commend ICER for endeavoring to undertake this analysis. However, the societal costs of addiction and frequently co-occurring mental health conditions are of such complexity that we suspect that the inputs of the review model understate the potential value of savings. A recent Milliman Research Report found in a study population of 21 million insured lives that the most expensive 10 percent of individuals accounted for 70 percent of total healthcare costs. Of this cohort of high-cost patients, the annual average healthcare costs were $41,631—which is 21 times higher than the $1,965 for individuals in the remaining 90 percent of the population. Of the population study, only 27 percent were classified as behavioral health. Yet this group accounted for 56.5 percent of total healthcare costs for the entire population. Average annual costs for the behavioral health cohort for medical/surgical (physical) treatment were 2.8 to 6.2 times higher (depending on the BH condition) than such costs for individuals with no behavioral health condition. Changing the trajectory of this population through the higher adherence rates of a digital intervention could redound to system savings. It is not clear that the report model addressed this level of complexity with the inputs adopted. The ICER report cited fewer lost productivity costs and fewer criminal justice and incarceration costs as compared to standard of care due when using the FDA-approved digital therapeutic. However, it is not clear that the report takes into account the benefits that may accrue over a longer time-horizon if the therapy results in sustained and long-term recovery. Further, the criminal justice model neglects the multi-generational cost effects of addiction.	Thank you for providing this report. As part of the ICER reference case, we always include a modified societal perspective to attempt to capture these costs and benefits outside of the healthcare system. We are grateful for the feedback and comments we receive through data requests and public comment periods to help us identify inputs to inform the model. Given no evidence of an impact on abstinence after the 12-week period and no evidence suggesting a difference in continuous abstinence prior to 12 weeks, there is no difference in abstinence and its associated consequences between the intervention and comparator in phase 2 of the model. We do allow for the intervention and comparator to differ based on retention in phase 2. This is an assumption that benefits reSET-O, despite evidence for increased retention after reSET-O use.

3.	**Difficulties evaluating behavioral health treatment** As you know, there are significant challenges in comparing behavioral health clinical trials to the gold standard associated with biomedical interventions approved by the FDA. The ICER report notes that the key study associated with the FDA-cleared application was of fair quality but was neither double-blinded nor were the groups comparable at baseline. The important contextual consideration is that achieving either of these aspirational goals has proved to be very difficult for behavioral treatments in general. One meta-analysis of the research of behavioral treatment for headaches noted that "applying the biomedical research design standards for blinding and placebo control to clinical trials evaluating behavioral and other nonpharmacologic headache treatment nearly always is either infeasible or simply not possible. Only rarely is blinding meaningfully achievable in administration of behavioral or psychological therapies." Analysis of efficacy of cognitive behavioral therapy have also noted the difficulty of having double-blind trials for behavioral treatments. The lack of consistently applied baseline and outcome measures is another emerging area in addiction. It is critical that these standards become more commonly utilized to ensure measurement-based care. However, the lack of comparable groups in a clinical trial is likely a symptom of this need.	Thank you for providing context about the challenges in performing high quality research for behavioral treatments.

4.	**Difficulties evaluating behavioral health treatment** As you know, there are significant challenges in comparing behavioral health clinical trials to the gold standard associated with biomedical interventions approved by the FDA. The ICER report notes that the key study associated with the FDA-cleared application was of fair quality but was neither double-blinded nor were the groups comparable at baseline. The important contextual consideration is that achieving either of these aspirational goals has proved to be very difficult for behavioral treatments in general. One meta-analysis of the research of behavioral treatment for headaches noted that "applying the biomedical research design standards for blinding and placebo control to clinical trials evaluating behavioral and other nonpharmacologic headache treatment nearly always is either infeasible or simply not possible. Only rarely is blinding meaningfully achievable in administration of behavioral or psychological therapies." Analysis of efficacy of cognitive behavioral therapy have also noted the difficulty of having double-blind trials for behavioral treatments. The lack of consistently applied baseline and outcome measures is another emerging area in addiction. It is critical that these standards become more commonly utilized to ensure measurement-based care. However, the lack of comparable groups in a clinical trial is likely a symptom of this need.	Thank you for providing context about the challenges in performing high quality research for behavioral treatments.

#	Comment	Response/Integration
Manufacturers and Industry		
Digital Therapeutics Alliance		
1.	The draft evidence report section titled, "Payer Landscape of Coverage for Digital Therapeutics," (p. 10), states: "…PDTs by definition are products that are approved or cleared by the FDA and have "an approved indication for the prevention, management, or treatment of a mental health or substance use disorder, including Opioid Use Disorder."42 ..." In direct response to this particular section, it is important to refer reviewers to the formal definition of a digital therapeutic: "Digital therapeutics (DTx) deliver evidence-based therapeutic interventions that are driven by high quality software programs to prevent, manage, or treat a medical disorder or disease. They are used independently or in concert with medications, devices, or other therapies to optimize patient care and health outcomes. DTx products incorporate advanced technology best practices relating to design, clinical evaluation, usability, and data security. They are reviewed and cleared or certified by regulatory bodies as required to support product claims regarding risk, efficacy, and intended use."	Thank you for clarifying the specific definition of a digital therapeutic. We have tried to be more rigorous in our use of the terms and have framed the review as one of digital health technologies. In addition, we have highlighted that reSET-O belongs to the subset of digital therapeutics, which have a higher bar of entry, namely FDA approval.
2.	Additionally, it may be helpful to note that while certain DTx products require a prescription from a qualified clinician, other DTx products that may be provided to patients without a prescription. This non-prescription pathway may include a recommendation, referral, or authorization by a clinician, third-party payor, employer, or use of a validated screening tool.	Understood.

3.	Regardless of which pathway a digital therapeutic is provided to a patient, it is critical for policymakers and payors to understand that digital therapeutic products must align with the following criteria: 1. Prevent, manage, or treat a medical disorder or disease 2. Produce a medical intervention that is driven by software 3. Incorporate design, manufacture, and quality best practices 4. Engage end users in product development and usability processes 5. Incorporate patient privacy and security protections 6. Apply product deployment, management, and maintenance best practices 7. Publish trial results inclusive of clinically meaningful outcomes in peer-reviewed journals 8. Be reviewed and cleared or certified by regulatory bodies as required to support product claims of risk, efficacy, and intended use 9. Make claims appropriate to clinical evaluation and regulatory status 10. Collect, analyze, and apply real world evidence and/or product performance data	Thank you for the input.
4.	Digital therapeutics exist at the unique intersection of being classified as a medical device from a regulatory standpoint, while delivering to patients in clinical practice medical interventions alongside – or even in place – of medication-based and in-person therapies. Given the new opportunities and benefits that are presented by this new category of medicine, it may be necessary for groups such as ICER to refine existing health economic evaluation models. First, compared to traditional medications which rely on physical distribution and dispensing processes, DTx products are software-based and are able to be hosted on multi-purpose platforms (e.g., patient-owned smartphone or tablet). This introduces an entirely new degree of product scalability and patient access opportunities. Therefore, instead of having a geographic-dependent delivery model, it is possible to deploy a needs-based delivery model.	Thank you for the input.

5.	As a result of increased product access and scalability, payors and policymakers are now able to ensure that care is delivered to entire populations that have otherwise been unable to secure care – either due to geographic limitations, cultural and language boundaries, well-documented disparities, or health condition severity. Patients who have previously not received care now have the opportunity to receive personalized therapeutic interventions based on their specific needs and abilities, in an engaging way, independent of their work or education schedule, with familiar languages and cultural references, in the privacy and safety of their own environment, and with access to actionable insights that convey their movement toward clinical improvement. It is important that ICER's evaluation frameworks incorporate the patient- and population-impacts of these novel features, especially as individual healthcare payors are increasingly incorporating these considerations into their decision-making models.	Thank you for the input.
6.	Next, in another departure from traditional medications and their inability to provide direct insights related to patient use and clinical impact, digital therapeutics generate a wide variety of real-world data (RWD) outcomes. This includes patient-specific measures (e.g., actionable clinical outcomes, standardized patient assessments, physiologic data via associated sensors), patient and clinician utilization (e.g., patient utilization and engagement, product onboarding metrics, clinician prescribing parameters), and product functionality (e.g., product performance, analytics, quality measures). While RWD is used by patients and clinicians to adjust and optimize critical aspects of therapy, this data may also be translated into fit-for-use, formal real-world evidence (RWE) for healthcare payor and policymaker product evaluation processes. Importantly, it is now possible for decision makers to analyze outcomes related to specific patient cohorts and derive detailed real-world insights on clinical and health economic endpoints. In this case, it is likely that evaluations based on real-world output will eventually replace aspects of evaluations based purely on information derived through secondary sources (e.g., patient registries, EHR systems, claims databases).	Thank you for your input.

7.	Lastly, compared to traditional medications that do not change once FDA approval is granted, DTx products are iterative in nature and continue to evolve throughout their lifecycle. While some of these iterations may require regulatory review if the core algorithm is changed, the majority of iterations by product manufacturers (e.g., product functionality changes, patient engagement optimizations) are delivered to users in real time to ensure immediate benefits. Since DTx products continue to be improved and optimized, it is necessary for groups like ICER and other HTA assessment bodies to determine the best timing and approach to initial and ongoing HEOR evaluations. A one-time evaluation conducted when a DTx product first launches will likely demonstrate very different outcomes and value a year or two later. Based on these key differences between traditional drugs and digital therapeutics – including product scalability/accessibility, generation of RWD/RWE, and their iterative evolution – it is important for bodies conducting HEOR assessments to make appropriate adjustments within currently existing models or develop new models that appropriately account for DTx product features and opportunities.	ICER's Value Assessment Framework includes a 12-month check up for each report. One year after issuing its final report and meeting summary, ICER will initiate a process to determine whether new evidence has emerged that warrants an update and if necessary, incorporate new evidence into an update of the report. In addition, ICER may determine that an ad hoc New Evidence Update may be needed at any time after the release of a final report if new evidence becomes available.

Pear Therapeutics		
1.	New peer-reviewed evidence on the cost and clinical effectiveness of reSET-O A. Real-world reduction in healthcare resource utilization following treatment of opioid use disorder with reSET-O, a novel prescription digital therapeutic. Expert Review of Pharmacoeconomics and Outcomes Research. October 2020. This retrospective study evaluated healthcare resource utilization up to 6 months before/after reSET-O initiation (index) in 351 commercial patients with OUD with available claims. No exclusion criteria were applied to this real-world population. In patients prescribed reSET-O, there were 45 fewer inpatient stays and 27 fewer emergency room (ER) visits post-index vs pre-index. Clinical encounters with largest changes were drug testing, psychiatry, case management, other pathology/laboratory, office/other outpatient, behavioral rehabilitation, alcohol/substance rehabilitation, other rehabilitation, mental health rehabilitation, and surgery. Improvements resulted in a reduction in high-cost service utilization including facility/clinical encounters saving $2,150/patient (Appendix Table 1). Such cost savings with reSET-O, coupled with a QALY benefit attributed to it, resulted in reSET-O dominating current standard of care.	We first want to thank Pear Therapeutics for sharing this publication with us. Due to the design of the study mentioned in this public comment, we are not able to include it in the economic model. The pre period rates of health care resource use reported in the publication are higher than the average healthcare resource utilization of the OUD population. A 2019 publication by Peterson and colleagues reported the annual rate of opioid-related US hospital discharges. We compared the rates from Peterson and colleagues to the number of patients in the US with OUD, and these were more representative of the rates reported in the post period of the study discussed in this comment (not the baseline pre period). Therefore, we have concerns whether the patients included in the study mentioned in this comment are representative of the general US OUD population. Further, there was no description of how the study sample was identified. For example, did the patients in the study receive reSET-O due to prior high health care utilization or some inpatient trigger? If that was the case, then regression to the mean could explain the reduction over time. If an external comparator group was included in the study that did not receive reSET-O, that would help alleviate this concern; however, no comparator group was included which prohibited the ability to assess for difference in differences and attribute the observed reduction in health care resource use to reSET-O.

2.	**B. Real-world evidence for a prescription digital therapeutic to treat opioid use disorder. Current Medical Research and Opinion. Provisionally Accepted. 2020.** An observational study of an all-comer population of patients with OUD (n=3,114) who accessed a 12-week prescription for reSET-O evaluated retention in treatment as well as abstinence from substance use. Individuals prescribed reSET-O engaged with therapeutic content across a 12-week duration (Appendix Figure 1). Exponential declines in app use, as reported in real-world data of health and wellness apps (Baumel, 2019), was not observed (Appendix Figures 2 & 3). reSET-O adherence and engagement rates were superior to adherence rates of buprenorphine in observational studies (Baumel, 2019; Ronquest, 2018; Mark, 2020). Results were consistent with the pivotal RCT (Appendix Figures 4, 5 & 6), suggesting generalizability of clinical trial data and positive real-world impact of reSET-O.	Thank you for letting us know about the new data. We have added a description to the report.
3.	**C. Safety and efficacy of a prescription digital therapeutic as an adjunct to buprenorphine for treatment of opioid use disorder. Current Medical Research & Opinion. Provisionally Accepted. 2020.** This manuscript summarizes the pivotal RCT analysis supporting reSET-O FDA clearance, which utilizes the generalized-estimating equations (GEE) analysis of abstinence in weeks 9-12, analysis of additional timepoints (last 6, 8 weeks), and safety from the RCT Christensen, 2014 (Appendix Table 2).	Thank you for letting us know about the new data. We have added a description to the report.

4.	**D. Cost-Effectiveness Analysis of a Prescription Digital Therapeutic for the Treatment of Opioid Use Disorder. Journal of Market Access & Health Policy. October 2020.** This manuscript provides a third-party payer perspective decision analytic model evaluating the cost-effectiveness of reSET-O + TAU relative to TAU (i.e., oral buprenorphine, face-to-face counseling [F2F], and contingency management) over 12 weeks. Clinical effectiveness data (retention and health state utilities) were obtained from published clinical trial, and resource utilization and cost data obtained from claims data analyses. A reduction in medical costs after initiation of reSET-O observed in a real-world claims analysis drove reSET-O + TAU's economic dominance ($954 less costly, more effective) vs. TAU alone over 12 weeks. These new data directly inform ICER's clinical and cost-effectiveness analyses as they demonstrate successful real-world use of the reSET-O commercial product, driving enhancements in treatment along with cost savings stemming from reduced inpatient stays and emergency department visits.	As mentioned in a prior response, we have concerns with the generalizability of the reduction in medical costs, which as mentioned in this comment, were a key driver of the findings reported in this economic evaluation. This highlights the sensitivity of the model to potential savings due to averted healthcare utilization. More robust and rigorous research examining this is necessary to reduce these uncertainties.
5.	**We provide multiple recommendations on updating ICER's economic evaluation of reSET-O.** **A. ICER's model inadequately attributes abstinence to patients utilizing reSET-O. We recommend increasing the proportion of patients in the reSET-O arm entering health state M2 in phase 2 of the model by 25% to align with the standard GEE model.** ICER's current approach does not account for the increased likelihood of abstinence with reSET-O in weeks 9-12 (75.9% vs 60.6%) as shown in the reSET-O GEE model that is standard in the field (NIDA/NIH) and utilized by FDA (Clinical Trials Network, 2010; FDA, 2020; FDA, 2016; Campbell, 2014). Instead, ICER's model assumes the same proportion of abstinence for patients in both treatment arms. The GEE model estimates population-averaged outcomes, consistent with ICER's approach to cohort modeling, and showed a 1.25x increased likelihood of abstinence with reSET-O vs. comparator (assessed repeatedly over time weeks 9-12 using urine drug screen) (Appendix Table 2). Consistent results were observed in weeks 7-12 and 5-12. We recommend ICER increase the cohort proportion in the 'On MAT without Illicit Use of Opioids' (M2) health state in phase 2 by 25%, to accurately reflect reSET-O's likelihood of inducing abstinence.	Our model does assign a difference in abstinence between reSET-O and standard of care for the first 12 weeks of the model, which represent the time using reSET-O. This improvement in abstinence while using reSET-O (first 12 weeks) has been documented in the literature and is used in our modeling efforts. Therefore, our model does account for the increased number of abstinent days with reSET-O from weeks 0 through 12. However, neither the GEE model, nor any other evidence, shows that this increase in abstinence days continues after reSET-O use has stopped (after week 12) or that there is a significant difference in continuous abstinence between reSET-O and its comparator while using the digital therapeutic. The proportion of the cohort that enters phase 2 of the model in the On MAT without Illicit Use of Opioids health state is defined based on a pattern of continuous abstinence, not abstinence at a single point in time like the GEE reports.

6.	**B. Clinical benefit of MAT retention should be reflected in the model's health state utilities for both injection and non-injection users.** SAMHSA guidelines list retention in treatment as one of three key outcomes in OUD alongside abstinence and reduced mortality (FDA, 2020). ICER's current approach to assigning health state utilities for patients in the 'On MAT with Illicit Use of Opioids' (M1) health state does not reflect the clinical benefit of MAT when compared to illicit off treatment ('Off MAT with Illicit Use of Opioids' [M3]). The model currently attributes a minimal utility gain of 0.006 among non-injection users and 0.044 among injection users in M1 vs. M3. ICER previously used the Wittenberg 2016 study to estimate utility values for all other health states in the model, but not for the M1 health state. The utility value used by ICER for the M1 health state is from a study (Connock 2007) that represents societal preferences from a non-US (UK) population. The Wittenberg study is relevant to all health states in ICER's US model as the study was conducted after the third wave of the opioid epidemic started (Appendix Figure 7), which saw marked increase in deaths due to illicit fentanyl use. We recommend that ICER use the Wittenberg 2016 study to estimate US utility values more accurately for the M1 health state (0.761 for non-injection users and 0.689 for injection users) (Appendix Table 3).	We appreciate this explanation and have changed the utilities in the model to align with this public comment.

7.	**C. Contingency Management included in the comparator arm should be used as the base case analysis, reflecting reSET-O's pivotal trial conditions and real-world indications for use**. ICER is currently not including CM in the base case analysis since it believes CM isn't widely used in OUD treatment. However, a 2017 SAMHSA survey showed that 56% of 13,500 facilities providing addiction treatment used CM. Including CM in the base case analysis most accurately reflects conditions in the Christensen study which evaluated the efficacy of the neurobehavioral therapy component (digital community reinforcement approach [CRA] + CM) vs. a comparator that did not contain CRA, but only CM. This approach is consistent with reSET-O's FDA label as its intended use includes transmucosal buprenorphine and CM. Federal agencies NIDA/NIH and SAMHSA find that CM is an effective treatment, and the American Society of Addiction Medicine (ASAM) strongly recommends CM as a component of psychosocial treatment for OUD in their National Practice Guideline for the Treatment of Opioid Use Disorder. Appendix Table 4 lists studies showing efficacy with vs. without CM. We recommend that ICER include CM and its costs in the comparator arm of the base-case analysis and make efficacy adjustments for a comparator without CM in a scenario analysis.	The SAMHSA survey reports the use of contingency management as 56% of substance use disorder facilities that reported using contingency management at least sometimes. This does not suggest the majority of the SUD patients at these facilities are being treated with contingency management, let alone the majority of the OUD patients specifically. A 2019 study by Becker and colleagues suggests contingency management is not widely used (used by less than 10% of OUD treatment providers). Because contingency management is currently not standard of care, it will not be included in the base case. However, we continue to present a scenario analysis that includes contingency management in the comparator.
8.	**D. Cognitive Behavioral Therapy (CBT) should be included in the base case and all scenario analyses in the comparator arm since it is an essential component of OUD treatment and what reSET-O is providing.** While the ICER model currently includes six counseling visits in each treatment arm in phase 1, these visits do not pertain to CBT, an essential component of OUD treatment which reSET-O delivers. In the 2017 SAMHSA survey, 94% of all 13,500 surveyed facilities offered CBT. CBT outperforms usual care or nonspecific counseling (Ray, 2020). reSET-O offers digital, asynchronous CBT, enabling clinician substitution and higher completion of CBT modules versus F2F CBT as shown in RWE. Given ICER's commitment to use RWE when available, we recommend that ICER include CBT in the comparator arm of the model across all analyses using our RWE. More details on recommended approach to include CBT and its associated cost per session are found in Appendix Table 5.	Based on the health care resource utilization presented in the pivotal trial, o which our effectiveness estimates are based on, both arms of the study received the same counseling (biweekly counseling). CBT was not provided/mentioned in the pivotal trial.

9.	**E. Provider interactions with reSET-O's clinician platform (pear.md) should not double-count costs.** ICER's model already counts six counseling visits and double-counts costs of clinician interactions by adding a dashboard charge of $65 each (using CPT 99212; Refer to Appendix Table 6 criteria to bill 99212) for the reSET-O arm in phase 1 of the model. Clinicians use pear.md to inform interactions with patients as part of standard follow-up outpatient visits already billed. There are no incremental reimbursable billing codes for pear.md sessions. We recommend that ICER eliminate duplicate costs associated with pear.md in the base case and any scenario analyses.	We have updated the price to reflect the price now provided in this public comment.
10.	**G. Health care resource use costs in the ICER model should be updated to reflect real-world practice.** The health system and societal costs associated with an abstinent health state should be lower when compared to an illicit-use health state. ICER's model currently applies the same health system costs for patients in the M1 and M2 health states (Table 5.14 in report) without accounting for the economic benefit associated with abstinence. In response to ICER's model analysis plan, we provided references supporting lower health system costs when abstinent vs. non-abstinent. A third study, Budilovsky-Kelley, 2019, found OUD patients with evidence of a relapse (illicit use) had 2.9x higher health care resource use costs vs. those without evidence of a relapse (abstinent). ICER should assume a reduction in health care resource use costs in M2 vs. M1. Similarly, ICER's model assumes the same criminal justice/incarceration costs for patients in health states M1 and M2 (Table 5.16 in report), which does not represent the benefits of abstinence to society. ICER should assume the same 2.9x reduction in costs of criminal justice and incarceration when abstinent (M2) vs. non-abstinent (M1). In addition, it is also being assumed that patients off MAT without illicit use (M4) cost the same as patients who are off MAT with illicit use of opioids (M3), when in actuality the former group of patients represents the lowest costing health state. We recommend that ICER update its cost assumptions to represent the economic benefit of abstinence. Incorporating all the above recommended changes in the model results in reSET-O being the dominant treatment strategy: cost-savings (approximately -$16,500) with a QALY gain of 0.009 with reSET-O vs. comparator over the modeled five-year time horizon. These results are directionally similar to the results of our cost-effectiveness analysis that used real-world utilization and cost data (see section 1D).	The table in the draft report that included the health care costs by health state was not well labeled and caused confusion. We apologize for this confusion. We have updated the table headers to be more clear. Now it is more clearly labeled that patients off MAT without illicit use do not cost the same as patients who are off MAT with illicit use of opioids. Patients who are off MAT without illicit use of opioids are only assigned general age-adjusted health care costs, and are not assigned any OUD-specific costs like those who are off MAT with illicit use of opioids. Last, there is no difference in abstinence after 12 weeks between the intervention and comparator arm (due to no evidence suggesting a difference in abstinence after reSET-O use and the available evidence suggesting no difference in continuous abstinence between reSET-O and comparator). Thus, the cost savings associated with abstinence are not a key driver of the model.

11.	**We provide multiple recommendations on Updating ICER's Clinical Evidence Assessment of reSET-O** **A. ICER's report inaccurately states that there were no clinical trials of reSET-O.** It is incorrect for ICER to state that there are no direct, peer-reviewed studies with evidence of safety and effectiveness of reSET-O and its clinical content. There have been multiple RCTs (Christensen, 2014, Bickel, 2008; Marsch, 2014) evaluating the research version of reSET-O (called TES) (and an additional clinical study evaluated a related product, reSET, for treating substance use disorders, which was reSET-O's regulatory precedent and the first software to receive FDA market authorization and a label to treat disease, [Campbell, 2014, FDA, 2016]). Real-world performance of the commercial version of reSET-O has been examined across >3,000 patients. ICER's distinction between research and commercial versions of reSET-O is inconsistent with precedent. FDA-cleared PDTs, like reSET-O, are evaluated for effectiveness, safety, and GMP/Quality manufacturing. FDA evaluated and confirmed equivalence of TES and reSET-O, as well as safety and effectiveness of the clinical data. US Pharmacopeia (USP), the global quality standards organization, establishes a similar conclusion as FDA, that reSET-O's clinical content is validated in multiple randomized clinical trials (Ambrose, 2020). ICER has utilized similar precedent of evaluating clinical content, whether delivered on browser, mobile or other device formats in the ICER 2016 Diabetes Prevention Program (DPP) review where ICER did not differentiate between delivery format or location while assigning B+ clinical effectiveness ratings. We are not aware of any prior instances in which ICER concluded there were "no clinical trials" whatsoever for an FDA-authorized product. Based on content equivalence validated independently by FDA and USP, as well as ICER precedent, it is inaccurate to conclude reSET-O has no clinical studies examining its effectiveness.	We summarized all three of the cited trials in the text and abstracted their data, but they are not reSET-O. The CM used in the studies is fundamentally different than that of reSET-O and the patient experience is different (app on phone outside of clinic versus internet version on a computer in the clinic).

12.	**B. reSET-O's clinical evidence is high quality.** All three reSET-O studies included randomization, comparison to standard-of-care (or better) control, pre-specified standard, objective endpoints, safety, and guideline-based follow-up (Appendix Table 7). Based on systematic and objective criteria evaluating study design, quality, outcomes evaluation (Oxford Centre for Evidence-Based Medicine, 2009; U.S. Preventive Services Task Force, 2012: Appendix Table 8), the clinical evidence rating of reSET-O is 1a and 'Good' respectively. These data are reinforced by RWE of >3,000 individuals prescribed reSET-O demonstrating that patients engage with reSET-O across the 12-week prescription and have outcomes consistent with studies (Appendix Figures 1,2 & 4-6). Given positive homogeneity of these studies in demonstrating safety and effectiveness, there is a totality of evidence supporting effectiveness of reSET-O in trials and generalizability by real-world evidence. ICER specifically highlights several critiques on clinical rating addressed specifically below: Blinding: While the gold standard for studies evaluating pharmacotherapies are double-blind, placebo-controlled (RCTs), there is no equivalent for studies evaluating behavioral and/or digital interventions. Unlike in pharmaceutical studies, blinding is difficult to impossible because there are inherently visible differences between control and active digital therapeutics. This is particularly true with treatment modalities that utilize neurobehavioral and/or psychosocial techniques like CBT, in which the behavioral intervention is visible and knowable by the participant (Castelnuovo, 2010; Berger, 2015). The concept that blinding is not possible is well-known in clinical studies evaluating face to face delivery of neurobehavioral therapies. As noted in Appendix Table 9, prior ICER reviews have given B+ ratings to DPPs supported by evidence from clinical studies that were not blinded, or in some cases, did not randomize participants or include controls. We note that in ICER's CAR-T review, CAR-T therapies were given B+ ratings when their studies were not blinded.	As noted above, the intervention is different, so the data from these three trials do not directly apply. The FDA would never approve a drug given orally at 10 mg once a day based on a trial of the same drug given IV 1 mg once every 2 weeks. As for blinding, sham trials are done all the time and are the basis for findings that several surgical techniques for knee arthritis are 100% placebo effect. There are a myriad of examples in the surgical treatment of angina, Parkinson's disease, multiple sclerosis, and spinal compression fractures that find large effects when no sham is used, but find no effect when a sham procedure is the control group. There was controversy about the quality rating within ICER. Some argued that the Christensen study was poor quality rather than fair. It is clearly not a good quality RCT. Finally, in the DPP review, there were a number of high-quality randomized trials that backed up the evidence rating.

13.	Safety: An essential component of any therapeutic includes an evaluation of safety. FDA review of a PDT centers on establishing the safety profile of a therapeutic, as was done for other PDTs including reSET®, Somryst(™), Freespira®, EndeavorRx™. FDA evaluates not only manufacturing quality, but safety as well as effectiveness (which it verifies through evaluation and replication of analysis of the raw data). As noted in the FDA 510k summary for reSET-O (FDA, 2019) and its predicate reSET (FDA, 2016), AEs were evaluated throughout the study, and no differences in AE rates were detected between treatment arms (Appendix Table 9).	We agree and that is why we gave it a C+ rating and not a P/I. We specifically note this in the review.
14.	Contingency Management: CM is highlighted above as an evidence-based treatment that should be included in the base case analysis. CM is considered in the literature and guidelines as one of the most efficacious addiction interventions, with moderate-to-large, clinical effect size (Appendix Table 4). While debate may exist as to its specific benefits in populations with OUD populations and how those benefits accrue, CM is included in reSET-O's indication statement. FDA recognized clinical practices may already use their own algorithm and that algorithms vary, thus FDA didn't specify a particular algorithm. It is inconsistent for ICER to conclude that CM is not effective but then include the outcomes of using CM in the comparator base case without including CM costs.	We compare reSET-O to standard of care, and contingency management is not standard of care in the OUD population. The effect of contingency management in the OUD population is uncertain, with some studies suggesting a benefit as you note. However, there are also many studies that show no significant effect of contingency management on abstinence or retention, and some studies that suggest a negative effect. Further, the delivery of contingency management varies dramatically. There are different ways to receive incentives, and different values of incentives to name a few. Further, there are notable differences in the delivery and incentive structure of contingency management between what was delivered in the pivotal trial to what is delivered in the reSET-O app.

15.	Duration: NIDA/NIH, which funded reSET-O pivotal has recommended behavioral treatments, such as CBT, in SUD and OUD be delivered over 12 weeks. 12 week studies are standard, having supported safety and efficacy studies in New Drug Applications (NDA) for tobacco and opioid addictions (FDA, 2006; FDA, 2010). Patients with OUD are difficult to retain in treatment with outpatient dropout rates ranging from 40-80%, and ~30% of patients discontinue treatment in the first month alone (Stark, 1992; Hser, 2014; Soeffing, 2009; Stein, 2005; Bickel, 2008; Marsch, 2014; SAMHSA, 2006). Short-term studies have been predictive of long-term outcomes. High discontinuation rates and frequency of treatment restarts were cited by ICER in its OUD review as a reason to deviate from its reference case of modeling a lifetime time horizon to a shorter 5-year time horizon. Studies of additional durations (Bickel, 2008; Marsch, 2014) and health economic outcomes in the real-world demonstrate persistence of benefit.	As noted above, we respectfully disagree. An oral therapy is never approved on the basis of a study of IV therapy.
16.	Generalizability: Multiple RCTs demonstrate safety and effectiveness of reSET-O therapeutic content in OUD patients reinforced by RWE from more than 3,000 commercial patients (Appendix Figures 1,2 & 4-6). Based on comprehensive evidence and its positive homogeneity across multiple studies, real-world evidence and health-economic studies, results from reSET-O's pivotal study are generalizable. reSET-O should be given a B+ clinical effectiveness rating, consistent with past ICER reviews and consensus evidence ratings	We reviewed the RCTs of TES and again disagree about the generalizability to reSET-O. We are primarily concerned about the fundamentally different form of CM used by reSET-O, but the difference in delivery method is also of concern.
17.	Coverage Policies: We urge ICER to cite in its revised report the multiple coverage policies for reSET-O (Appendix Table 12) that are in effect.	We have added these plans to our description of available coverage policies for reSET-O.

#	Comment	Response/Integration
Payers/Providers		
Alicia Bell, RN-SN, MA		
1.	Buprenorphine, is 60% effective allowing for periods of relapse and recovery versus abstinence which is only 30% effective. The real key to long term recovery is keeping patients engaged in treatment. A great tool I have recently discovered is reSet and reSet-O. Patients enjoy the ease of using it; the reinforcement of the Cognitive Behavioral Therapy, (CBT); and for the contingency management (CM), "the money's not bad either." I know from research dating back to the 1960's that CM works. It's currently the best treatment with behavioral therapy for methamphetamine use disorder. So I was excited to learn about this APP. CBT is well researched as an effective therapy. And for people to be able to work through the exercises on their own is so important. My population in particular is very sensitive to stigma and to have a tool they can use in the privacy of their own home, in their own time frame, is invaluable to them. I have one patient who wants to keep doing the exercises over and over. She told me, "They keep me grounded. I don't want to go back to counseling. Counseling never helped me in the way this does." However, during her second time through the exercises, she went back to counseling and joined a support group. I have heard similar comments from patients.	Thank you for the testimonial. We agree that the key to long-term recovery is keeping people engaged in treatment. Studies suggest that engagement for at least one to two years translates into better long-term outcomes. Unfortunately, we only have 12-week data on a precursor for reSET-O and no data on the long-term benefits of reSET-O. It may be effective, but there are no high-quality data to support its effectiveness.
2.	I like them to use the APP because I can encourage them in their progress. One of my patients has been an IV drug user for decades is beginning to have insight into her drug use and connecting her thoughts to her behavior. Another patient stated that he never realized that being hungry was a trigger for him.	These are great testimonials, but again, we require a higher level of evidence to have high certainty of a net clinical benefit.
3.	Whether patients become fully abstinent or not is not the mark of success I look for. I want them to live. I want them to be more functional. 8 people die of drug overdose in this country every hour. Opioid overdose has become the number one cause of injury related death. And since Covid 19, illicit drug use is up 45%. Thanks again to Covid 19, the drug supply on the Western US is changing and heroin and other drugs laced with fentanyl and car-fentanyl increasing and the number of deaths are likely to increase again.	We agree. The 12-week study provided no data on increased patient function or a reduction in death from overdose.

4.	You found that negative Urine Drug Screens are not statistically different than positive ones which seems illogical to me. Now, if you say that what that means is that UDS's are not a statistically valid deterrent I might agree with you. But they are a deterrent for some of my patients; especially those who have a good relationship with the provider.	No, the company provided us data showing that there was no difference in abstinence, as judged by urine drug screens, between patients randomized to reSET-O and those treated with usual care. We certainly agree that regular urine drug screens are an integral part of MAT and contribute to the long-term success of treatment.
5.	Ultimately your study found that the APP didn't reduce costs related to the patient's treatment. I doubt that you have fully considered ER visits, or death by overdose due to relapse. My response is that you need to do more research over a longer period of time. I am motivated to write to you because I want insurances to continue to pay for this treatment. While it may not be conventional; neither are my patients.	We account for differences in health care resource utilization and mortality based on health state status (on MAT/off MAT/no illicit use/illicit use).
Dr. Adam Rubinstein		
1.	I did not see your deep consideration of the costs to patients, insurers, and society when patients are not retained in treatment as long as possible. Patients experience infections and abscess formation, even infective endocarditis from returning to heroin injection. They end up in jail or prison, which is costly. They are likely to eventually be hospitalized in an expensive inpatient or PHP program, or even become homeless and turn to crime to support their need for their opioid of choice. Your interpretation of the Christensen study raises questions for me. First, if the hypothesis was that no difference in retention in treatment would be found, why is that a valid concern when a statistically significant difference was identified? Lack of a sham group does not affect the power of the study. Since both arms received TAU and CM, the study was specifically evaluating the effect of the TES and Clinician Dashboard.	The fundamental statistical underpinning of randomized clinical trials is that the only p value that is meaningful is that of the pre-specified primary outcome of the trial. In Christensen 2014, the primary outcome was not statistically significant. Any other findings are hypothesis generating and not "significant." Respecting this fundamental scientific principle is the grounding that has moved medicine from killing patients with blood letting to the remarkable improvements in length and quality of life that we enjoy today. We also present a modified societal perspective as a scenario analysis to capture some of these costs outside of the health care system.

2.	A single site may not seem preferrable to a multi-center trial, but in some cases it is preferrable. I am a typical provider and know my patients well. Many multi-center trials involve large group practices with providers participating who are not able to fill their schedule. Or the administrators desire extra revenue. Thus, patients may see different providers at each visit. The therapeutic alliance, the relationship between provider and patient, the ability to model and teach patients what comprises a trusting relationship can not be over-emphasized. Why dilute the real-world benefit based on a faulty notion that many centers are more real-life than one center? According to the logic you present, the utilization of a single center might have risked findings consistent with no difference between treatment and controls groups. However, in the FDA-reviewed study 82.4% vs 68.4 % retention is impressive.	Indeed, the retention is impressive - the retention in the control group is greater than is typically reported at three months (<50% per Pear in their public comments). This site certainly does not seem to be representative of the sites treating patients with OUD, so its results are likely not generalizable. In addition, since it was a single site and continued to treat the patients, there is no reason that they could not report retention beyond 12 weeks. The paper was published years after the end of the trial. We can only assume that one- and two-year retention rates were similar in the two arms of the trial.
3.	Certainly a 12-week trial is not equal to a 6 or 12 month trial. However, 12-week trials for medications and other interventions are common. Those medications are then stopped. In this case the value of the internalized and implemented skills from the CBT modules can persist for months or years – much more likely due to the training of the patient. That would, in my opinion, lower costs on many levels related to physical illness, interpersonal, financial, employment and anger-aggression problems that the modules address.	Short trials are appropriate for diseases of limited duration, like UTIs or URIs. However, the opposite is true for life long chronic illness like OUD, CVD, diabetes, hypertension, cancer, and the like. Typically, we look trials of five to 10 years duration to provide convincing clinical evidence of benefit.
4.	On page 21 you mention no evaluation of serious adverse events related to the apps. What possible adverse events were you considering? Patients are already using their smart phones. They are not at increased risk based on using the same device as prior to the study.	As we state, we did not think that there were likely any important adverse events. If we thought that they were plausible our evidence rating would have been P/I or I, not C+. Unfortunately, none of the clinical trials of TES (much less reSET-O) reported on adverse events.

5.	It is surprising that you looked at UK health status models when comparing health status of patients retained in treatment vs those who dropped out. I assure you – as a practicing clinician I see a huge difference in health status of any patient who drops out. And, if there really was no difference why are we treating patients at all? The wide range of conditions we see in the drop-out group (many see me later, when returning to treatment after an expensive inpatient stay) are more expensive than your considerations consider. Further, I have lectured overseas and was struck by the immense differences I noted between patients, caregivers, health-systems and cultural beliefs in Europe compared to the US. UK data seems to be more of a confounding variable than the minor differences between treatment and controls participants or lack of a sham intervention.	We have updated the health utilities used in this report based on feedback provided in these public comments.
6.	Finally, numerous studies demonstrate the efficacy of CM. The FDA evaluated the data and authorized reSET-O based on CM-inclusive studies. Since CM was present in both arms, and you even point out the treatment group reaped smaller average rewards, it seems this is worth another look.	Rather than cherry picking individual studies, here are seven reviews/systematic reviews published in the past three to four years highlighting the controversy about the added benefits of CM. From our discussion with experts, treating clinicians, and providers, CM is not standard of care. 1. Ainscough TS, McNeill A, Strang J, Calder R, Brose LS. Contingency Management interventions for non-prescribed drug use during treatment for opiate addiction: A systematic review and meta-analysis. Drug Alcohol Depend. 2017;178:318-339. 2. Carroll KM, Weiss RD. The Role of Behavioral Interventions in Buprenorphine Maintenance Treatment: A Review. Am J Psychiatry. 2017;174(8):738-747. 3. Davis DR, Kurti AN, Skelly JM, Redner R, White TJ, Higgins ST. A review of the literature on contingency management in the treatment of substance use disorders, 2009-2014. Prev Med. 2016;92:36-46. 4. Dugosh K, Abraham A, Seymour B, McLoyd K, Chalk M, Festinger D. A Systematic Review on the Use of Psychosocial Interventions in Conjunction With Medications for the Treatment of Opioid Addiction. Journal of addiction medicine. 2016;10(2):93-103.

		5. Korownyk C, Perry D, Ton J, et al. Opioid use disorder in primary care: PEER umbrella systematic review of systematic reviews. Can Fam Physician. 2019;65(5):e194-e206. 6. Ray LA, Meredith LR, Kiluk BD, Walthers J, Carroll KM, Magill M. Combined Pharmacotherapy and Cognitive Behavioral Therapy for Adults With Alcohol or Substance Use Disorders: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3(6):e208279. 7. Sheridan Rains L, Steare T, Mason O, Johnson S. Improving substance misuse outcomes in contingency management treatment with adjunctive formal psychotherapy: a systematic review and meta-analysis. BMJ Open. 2020;10(10):e034735.
Dr. Michael Genovese, Acadia Healthcare		
1.	One such example of an erroneous assumption is that ICER did not consider the improved cost profile of abstinent patients. Instead, abstinent are assumed to cost the health care system just as much as patients in therapy who are not abstinent. ICER should use lower cost estimates for abstinent patients in its model in order to not adversely affect the economic value of reSET-O, which is retaining a greater proportion of patients after 3 months. A greater proportion of these retained patients with reSET-O will go on to enter the abstinent state in subsequent cycles of the model, and this value should be captured by the model.	The table in the draft report that included the health care costs by health state was not well labeled and caused confusion. We apologize for this confusion. We have updated the table headers to be more clear. Now it is more clearly labeled that patients off MAT without illicit use do not cost the same as patients who are off MAT with illicit use of opioids. Patients who are off MAT without illicit use of opioids are only assigned general age-adjusted health care costs and are not assigned any OUD-specific costs like those who are off MAT with illicit use of opioids. Lastly, there is no difference in abstinence after 12 weeks between the intervention and comparator arm (due to no evidence suggesting a difference in abstinence after reSET-O use and existing evidence suggesting no difference in continuous abstinence between reSET-O and comparator). Thus, the cost savings associated with abstinence are not a key driver of the model.

2.	Another value that should be captured by the model is the higher health utility value of being retained in treatment vs dropping out of treatment. In the current model ICER assumes that patients who drop out of treatment and have illicit use of opioids have similar health utilities as patients who remain in treatment. Again, this works against reSET-O which has been shown to significantly increase retention in treatment. Retention in treatment is important because it reduces exposure to illicit opioids (when patients are not in treatment it is much more difficult to prevent cravings and withdrawal symptoms which lead to accidental poisonings). As evidenced by the previous two examples, unfavorable assumptions are present both on the numerator and on the denominator, further amplifying the unfavourability of the model towards reSET-O.	We have updated the health utilities used in this report based on feedback provided in these public comments.
3.	Thirdly, ICER assumes that patients who are off treatment and not using illicit opioids are just as costly as patients off treatment and using illicit opioids. ICER should correct this assumption in order to maintain the internal validity of the model.	The table in the draft report that included the health care costs by health state was not well labeled and caused confusion. We apologize for this confusion. We have updated the table headers to be more clear. Now it is more clearly labeled that patients off MAT without illicit use do not cost the same as patients who are off MAT with illicit use of opioids. Patients who are off MAT without illicit use of opioids are only assigned general age-adjusted health care costs and are not assigned any OUD-specific costs like those who are off MAT with illicit use of opioids.

4.	It also caught my attention that ICER is using a single publication to support the position that there is no clinical benefit to contingency management. Other publications (See, for example, Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: Efficacy of contingency management and significant other involvement Kathleen M Carroll, Samuel A Ball, Charla Nich, Patrick G O'Connor, Dorothy A Eagan, Tami L Frankforter, Elisa G Triffleman, Julia Shi, Bruce J Rounsaville; Archives of General psychiatry 58 (8), 755-761, 2001, See also: Contingency management for treatment of substance abuse, Maxine Stitzer, Nancy Petry, Annu. Rev. Clin. Psychol. 2, 411-434, 2006; See also: Lessons Learned from a Randomized Trial of Fixed and Escalating Contingency Management Schedules in Opioid-Dependent Pregnant Women, Michelle Tuten, Dace S. Svikis, Lori Keyser-Marcus, Kevin E. O'Grady & Hendrée E. Jones (2012) The American Journal of Drug and Alcohol Abuse, 38:4, 286-292, 2012.) have shown the benefit of CM. Furthermore, CM in reSET-O is different, as it rewards the act of completing lessons and fluency training (a relatively easier task to achieve), in addition to negative urine drug screens (a more difficult and slightly more longer-term task to achieve). In the Campbell trial, the control arm (which also included CM) had a retention rate of almost 70% after 3 months. By comparison, treatment with buprenorphine sees similar retention after one month, and it continues to decrease over time. It is problematic to portray CM in this way as it actually increases the bias towards the adoption of neurobehavioral therapies in recovery and prevents the field from helping more patients.	Thank you. Your concern is identical to that raised by another commenter. Rather than cherry picking individual studies, here are seven reviews/systematic reviews published in the past three to four years highlighting the controversy about the added benefits of CM. From our discussion with experts, treating clinicians, and providers, CM is not standard of care. 1. Ainscough TS, McNeill A, Strang J, Calder R, Brose LS. Contingency Management interventions for non-prescribed drug use during treatment for opiate addiction: A systematic review and meta-analysis. Drug Alcohol Depend. 2017;178:318-339. 2. Carroll KM, Weiss RD. The Role of Behavioral Interventions in Buprenorphine Maintenance Treatment: A Review. Am J Psychiatry. 2017;174(8):738-747. 3. Davis DR, Kurti AN, Skelly JM, Redner R, White TJ, Higgins ST. A review of the literature on contingency management in the treatment of substance use disorders, 2009-2014. Prev Med. 2016;92:36-46. 4. Dugosh K, Abraham A, Seymour B, McLoyd K, Chalk M, Festinger D. A Systematic Review on the Use of Psychosocial Interventions in Conjunction With Medications for the Treatment of Opioid Addiction. Journal of addiction medicine. 2016;10(2):93-103. 5. Korownyk C, Perry D, Ton J, et al. Opioid use disorder in primary care: PEER umbrella systematic review of systematic reviews. Can Fam Physician. 2019;65(5):e194-e206. 6. Ray LA, Meredith LR, Kiluk BD, Walthers J, Carroll KM, Magill M. Combined Pharmacotherapy and Cognitive Behavioral Therapy for Adults With Alcohol or Substance Use Disorders: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3(6):e208279. 7. Sheridan Rains L, Steare T, Mason O,

		Johnson S. Improving substance misuse outcomes in contingency management treatment with adjunctive formal psychotherapy: a systematic review and meta-analysis. BMJ Open. 2020;10(10):e034735.
5.	Lastly, although the use of a value framework is useful and of value to overall decision-making, ICER should make equally prominent statements in its final report around the absolute cost difference between the interventions. In the case of the draft report, ICER should note the impact on total cost alongside the cost/QALY conclusion, to minimize the risk of the audience reaching the wrong conclusion. In the draft report the total cost difference between the two treatments over five years was $1,400. This is less than $300 per year, a small cost for an evidence-based treatment which I have seen work in the clinic, and which delivers a suite of neurobehavioral therapies that would be cost-prohibitive for the health care system to reliably implement.	We present the magnitude of the costs for each arm in our result tables.
New York Association of Alcoholism and Substance Abuse Providers, Inc.		
1.	The ICER model incorrectly assumes abstinent patients cost the healthcare system the same as patients who are in treatment and not abstinent. This could not be further from the truth. ICER would have to go no further than recent outcomes from New York State's DSRIP projects to discover that, once engaged in medication assisted treatment, people no longer using opioids drive significant decreases in unnecessary hospitalization; most of which were associated with health issues unrelated to their addiction. The ICER model must consider lowering cost estimates for abstinent patients in order to accurately represent the true economic value of reSET-O, which has a demonstrated impact at patient retention in care after 3 months. A large number of these patients utilizing reSET-O will go on to become abstinent in succeeding cycles of the model, thereby demonstrating its cost effectiveness in both the short-term and, even more so, in the longer term.	The table in the draft report that included the health care costs by health state was not well labeled and caused confusion. We apologize for this confusion. We have updated the table headers to be more clear. Now it is more clearly labeled that patients off MAT without illicit use do not cost the same as patients who are off MAT with illicit use of opioids. Patients who are off MAT without illicit use of opioids are only assigned general age-adjusted health care costs and are not assigned any OUD-specific costs like those who are off MAT with illicit use of opioids. Lastly, there is no difference in abstinence after 12 weeks between the intervention and comparator arm (due to no evidence suggesting a difference in abstinence after reSET-O use and existing evidence suggesting no difference in continuous abstinence between reSET-O and comparator). Thus, the cost savings associated with abstinence are not a key driver of the model.

2.	The model's assumption that patients who are not in treatment and not using opioids are as expensive as patients who are not in treatment and using opioids is also far from the truth. Patients who begin using illicit opioids again, more likely without access to reSET-O, frequently require expensive health care, such as increased use of the emergency room and inpatient hospitalization for their substance use disorder; and, even more likely, to need expensive care for other health related issues - both are costly to the health system as documented by NYSDOH in recent reports.	The table in the draft report that included the health care costs by health state was not well labeled and caused confusion. We apologize for this confusion. We have updated the table headers to be more clear. Now it is more clearly labeled that patients off MAT without illicit use do not cost the same as patients who are off MAT with illicit use of opioids. Patients who are off MAT without illicit use of opioids are only assigned general age-adjusted health care costs and are not assigned any OUD-specific costs like those who are off MAT with illicit use of opioids. Lastly, there is no difference in abstinence after 12 weeks between the intervention and comparator arm (due to no evidence suggesting a difference in abstinence after reSET-O use and existing evidence suggesting no difference in continuous abstinence between reSET-O and comparator). Thus, the cost savings associated with abstinence are not a key driver of the model.
3.	ICER is, apparently, using only one publication to support their claim that there is no clinical benefit to contingency management. ICER should also consider volumes of peer reviewed research (see NIDA, NIAAA, etc.) that refutes that claim. Contingency management in reSET-O is used to reward an individual when they have completed a cognitive behavioral therapy lesson and fluency training (short term, easy tasks), in addition to negative urine drug screens (long term and more difficult task), because it is strongly supported in the research and seen in the field as a best practice ICER's negative portrayal of contingency management denies the value of successful neurobehavioral therapies and will serve to obstruct patient access to innovative treatments like reSET-O if it is left unchallenged.	Thank you. Your concern is identical to that raised by another commenter. Rather than cherry picking individual studies, here are seven reviews/systematic reviews published in the past three to four years highlighting the controversy about the added benefits of CM. From our discussion with experts, treating clinicians, and providers, CM is not standard of care. 1. Ainscough TS, McNeill A, Strang J, Calder R, Brose LS. Contingency Management interventions for non-prescribed drug use during treatment for opiate addiction: A systematic review and meta-analysis. Drug Alcohol Depend. 2017;178:318-339. 2. Carroll KM, Weiss RD. The Role of Behavioral Interventions in Buprenorphine Maintenance Treatment: A Review. Am J Psychiatry. 2017;174(8):738-747. 3. Davis DR, Kurti AN, Skelly JM, Redner R,

		White TJ, Higgins ST. A review of the literature on contingency management in the treatment of substance use disorders, 2009-2014. Prev Med. 2016;92:36-46. 4. Dugosh K, Abraham A, Seymour B, McLoyd K, Chalk M, Festinger D. A Systematic Review on the Use of Psychosocial Interventions in Conjunction With Medications for the Treatment of Opioid Addiction. Journal of addiction medicine. 2016;10(2):93-103. 5. Korownyk C, Perry D, Ton J, et al. Opioid use disorder in primary care: PEER umbrella systematic review of systematic reviews. Can Fam Physician. 2019;65(5):e194-e206. 6. Ray LA, Meredith LR, Kiluk BD, Walthers J, Carroll KM, Magill M. Combined Pharmacotherapy and Cognitive Behavioral Therapy for Adults With Alcohol or Substance Use Disorders: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3(6):e208279. 7. Sheridan Rains L, Steare T, Mason O, Johnson S. Improving substance misuse outcomes in contingency management treatment with adjunctive formal psychotherapy: a systematic review and meta-analysis. BMJ Open. 2020;10(10):e034735.

#	Comment	Response/Integration
Researchers		
David Epstein		
1.	Your report correctly notes that the Christenson (2014) study of OUD treatment was actually a study of desktop-based software, not a mobile app. But you don't seem to mention the problems with the evidence base for the original reSET app, the app that appears to give reSET-O its legitimacy. I described those problems in this peer review of a manuscript recently submitted by the reSET group. I said, in part: This manuscript describes a reanalysis of a randomized clinical trial comparing contingency management (CM) plus cognitive behavioral therapy (CBT), delivered via smartphone app [reSET], versus in-person treatment as usual (TAU) for patients with substance use disorders. The reanalysis focused on participants without opioid use disorder. The study found that the experimental intervention (plus a reduced version of TAU) was more effective than TAU.	Yes, there is additional uncertainty in the value of reSET-O because the value of reSET is questionable despite the FDA approval. The 510(k) process has been roundly criticized and clearly OUD cannot be treated in the same way as SUD or there would not be separate applications and a long history or separate research.
2.	The paper has major issues. 1. This appears to be the third paper reporting the outcome of this trial, […] 2. The paper characterizes reSET as a "novel SUD treatment modality," the novelty apparently being that it is an app-based version of "the Therapeutic Education System (TES), an evidence-based digital intervention." That claim is rife with problems.	We agree.
3.	First, reSET appears to be simply TES ported to a smartphone interface. TES was Web/desktop software that was based on CBT and the community reinforcement approach (CRA) (Bickel et al., 2008). That was novel in 2008. I see no sign that the developers of reSET did any formative work to adapt the content of TES for mobile delivery. reSET seems to be the same old content on a smaller screen, and the content itself is based on treatment modalities that go back to the 1970s (CRA) and 1960s (CBT). That's fine, and it might be effective, but it's no more "novel" than using a smartphone app to display the full text of a self-help book.	We agree.

4.	Second, the study design completely confounds the CRA/CBT elements of reSET with the delivery of prize-based contingency management (CM). In a prior publication, the investigators say that they made that design decision to reduce the cost and duration of the study (Campbell et al., 2012, doi 10.1016/j.cct.2011.11.001). Now the authors need to accept the consequences. CM is the most effective treatment for each of the SUDs in the sample, so, on its own, it can easily account for all the benefits the authors observed (less drug use, better retention). It is impossible to conclude that reSET was more effective than CM alone. reSET might even be less effective than CM alone, at least in the short run, because prior studies suggest that CBT can delay the benefits of CM for people with cocaine use disorder. The most supportable conclusion is that the well-established benefits of CM continue to be observable when CM is delivered through an app. That's not a novel finding, either.	We agree.
5.	Third, software for prize-based CM is already freely available to community clinics. NIDA began distributing it in 2012 under the name Motivational Incentives Package. It requires no prescription and imposes no cost beyond that of the reinforcers. The authors do not mention it, and certainly do not provide any evidence that their "novel" proprietary app is as effective as the free, no-prescription alternative. This omission, along with the other issues I've mentioned, gives me a sense that this manuscript is effectively a long-form version of an ad more than it is a contribution to the scientific literature. I cannot speak to the FDA's reasoning in approving reSET for prescription; I can only evaluate the evidence the authors present.	We agree.
6.	The choice of statistical analyses needs better justification. I would expect these data to be analyzed with generalized linear mixed models, not generalized estimating equations (GEEs). GEEs require fixed intercepts (rarely a good choice in a heterogeneous sample) and make stringent assumptions about the completely random nature of missing data.	We agree with these limitations of generalized estimating equations. We do not use any estimates from the GEE. Our primary concern with the GEE estimates is that they produced likelihoods at a single point in time, and we were interested in a measure suggesting more continuous abstinence metrics.

Health Analytics		
1.	I was honored when ICER included our 2017 American Journal of Managed Care paper which reported on the result of a collaborative effort with Aetna. Of course, in that paper, we identified the incremental cost associated with different levels of patient adherence with buprenorphine medication assisted treatment (B-MAT). Those with higher levels of adherence (>60%) showed higher pharmacy costs, but much lower medical costs mostly due to lower use of hospital-based services (i.e., outpatient hospital and inpatient hospital). Upon reviewing the model, it was not clear to me how the reduction in medical costs were handled among the cases that stayed on MAT in Phase 2. I see the incremental increase in cost associated with continuing B-MAT, that is likely mostly medication. Further, the assumption that most cases will discontinue B-MAT in Phase 2 may not be evenly supported with evidence. Nor is it easily defensible to assume that attrition would occur at about the same rate for the two arms. Such an assumption means that CBT and similar interventions have no residual effect on adherence with B-MAT.	Thank you for your work. Because we did not have any evidence of a residual effect on adherence or abstinence (after completion of the modules), there is no difference in abstinence after 12 weeks and no significant difference in continuous abstinence prior to 12 weeks. This aligns with no significant difference in continuous abstinence reported in the pivotal trial for reSET-O. The addition of reSET-O to outpatient MAT alone resulted in extra costs to download the digital therapeutic and additional MAT costs; however, health care utilization costs were marginally lower due to the higher percentage of individuals retained on MAT.
2.	The model could be more highly specified to account for the many effects that have been detailed in the literature during the past 15 years. I suggest the following: • Specify the effect that CBT and similar interventions has on attrition from B-MAT and apply a correction factor accounting for the digital medium; • Specify the cost difference between abstinent and non-abstinent individuals regardless of B-MAT status in Phase 2 • Specify the cost avoidance associated with continuing on B-MAT (80.4%) compared to those whose adherence is low or who have discontinued B-MAT (64.1%).	Based on the healthcare resource utilization presented in the pivotal trial, of which our effectiveness estimates are based on, both arms of the study received the same counseling (biweekly counseling). There was no mention of CBT delivery. The table in the draft report that included the health care costs by health state has been relabeled and described to state these cost differences more clearly.

Warren Bickel, Fralin Biomedical Research Institute at VTC		
1.	I am writing to you as an addiction scientist with considerable experience. My expert opinion is that contingency management is one of the most effective treatments in substance use disorders and has demonstrated its efficacy in opioid use disorder. In my view, any statement that it is not efficacious is not consistent with the extant literature. Moreover, contingency management provides the underlying science in support of Conditional Cash Transfers that are making a tremendous impact throughout the world.	As noted above, there is considerable controversy about this as described in these 7 recent systematic reviews. From our discussion with experts, treating clinicians, and providers, CM is not standard of care. 1. Ainscough TS, McNeill A, Strang J, Calder R, Brose LS. Contingency Management interventions for non-prescribed drug use during treatment for opiate addiction: A systematic review and meta-analysis. Drug Alcohol Depend. 2017;178:318-339. 2. Carroll KM, Weiss RD. The Role of Behavioral Interventions in Buprenorphine Maintenance Treatment: A Review. Am J Psychiatry. 2017;174(8):738-747. 3. Davis DR, Kurti AN, Skelly JM, Redner R, White TJ, Higgins ST. A review of the literature on contingency management in the treatment of substance use disorders, 2009-2014. Prev Med. 2016;92:36-46. 4. Dugosh K, Abraham A, Seymour B, McLoyd K, Chalk M, Festinger D. A Systematic Review on the Use of Psychosocial Interventions in Conjunction With Medications for the Treatment of Opioid Addiction. Journal of addiction medicine. 2016;10(2):93-103. 5. Korownyk C, Perry D, Ton J, et al. Opioid use disorder in primary care: PEER umbrella systematic review of systematic reviews. Can Fam Physician. 2019;65(5):e194-e206. 6. Ray LA, Meredith LR, Kiluk BD, Walthers J, Carroll KM, Magill M. Combined Pharmacotherapy and Cognitive Behavioral Therapy for Adults With Alcohol or Substance Use Disorders: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3(6):e208279. 7. Sheridan Rains L, Steare T, Mason O, Johnson S. Improving substance misuse outcomes in contingency management treatment with adjunctive formal psychotherapy: a systematic review and meta-analysis. BMJ Open. 2020;10(10):e034735.