publiccomments@icer-review.org

Drs. Tice, Whittington, Fluetsch, Zapata, Mendola, Chapman, Campbell, Pearson, and Brandt

October 9, 2020

Dear Dr. Tice, Dr. Whittington, and concerned parties at ICER

I am writing to you, as a public respondent, regarding your Draft Evidence Report on Digital Therapeutics as an Adjunct to Medication Assisted Therapy for Opioid Use Disorder. I want to tell you why I don't agree with your findings.

While your 54 page document appears very thorough, there are some areas you seemed to have ignored or not paid enough attention to. I want you to understand how passionate I am about this product and why that is true. I am a Population Health Nurse and RN Navigator for the MOUD program at Newport Health Center. I have 20 years of experience as an RN and have worked for a year in my current position. I am a member of the APNA, the Harms Reduction Coalition, and the International Society for Substance Use Prevention, the National Prevention of Overdose Network, the Tri-County Opioid Treatment Coalition, and sit on 3 School Coalitions for the prevention of substance use in young people; as well as other organizations. But above all else, I am a nurse who works with people who use drugs.

We use buprenorphine to treat opioid use disorder. 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.

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.

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.

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.

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.

Sincerely,

Alicia Bell RN-BSN, MA Newport Health Center/Newport Hospital and Health Services W 714 Pine St Newport WA 99156 509-447-3139

Alicia.bell@nhhsqualitycare.org

Hi, Dr. Tice. I saw the ICER's draft report the other day, and I was pleased that it showed the gap between the app vendors' claims and the actual evidence base.

I want to add some information for your final report. It's about the reSET-O app, or, actually, the original reSET app on which it was based. Your draft report says:

There were no clinical trials of reSET-O....The FDA clearance of reSET-O was based on its similarity to the reSET app.

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.

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.

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 selfhelp book.

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.

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.

(3) 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.

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

Submitted electronically: publiccomments@icer-review.org

Dear ICER Review Team:

We appreciate the opportunity to respond to the draft evidence report, "Digital Therapeutics as an Adjunct to Medication Assisted Therapy for Opioid Use Disorder," published on September 17, 2020.

As the leading international organization on digital therapeutic (DTx) thought leadership and education, the Digital Therapeutics Alliance (DTA) is dedicated to providing policymakers, payors, clinicians, and patients with the necessary tools to evaluate and utilize DTx products. DTA's 40 members – including organizations dedicated to manufacturing, evaluating, supporting, and utilizing DTx products in clinical practice – are based in 15 countries, across four continents.

Targeted Comments

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:¹

"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."

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

¹ https://dtxalliance.org/wp-content/uploads/2019/11/DTA_DTx-Definition-and-Core-Principles.pdf

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.

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

Overarching Commentary

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.

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 populationimpacts of these novel features, especially as individual healthcare payors are increasingly incorporating these considerations into their decision-making models.

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).

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.

HTA Evaluation Process

If ICER is going to take a nationalized approach to evaluating DTx products, it is may be helpful to consider other HTA processes that are developing internationally. The Appendix contains references to efforts underway in the United Kingdom and Germany. Both of these models are being developed to ensure that the evaluation process matches the type of products being evaluated.

On behalf of the Digital Therapeutics Alliance, I welcome the opportunity to become further involved in this critical process.

Sincerely,

Megan Coder, PharmD, MBA Executive Director Digital Therapeutics Alliance

<u>Appendix</u>

Diagram 1. United Kingdom's National Institute for Health and Care Excellence (NICE) "Evidence Standards Framework for Digital Health Technologies" (March 2019): Functional classification of DHTs.

The NICE framework describes standards for the evidence that should be available or developed for digital health technologies (DHT) to demonstrate their value in the UK health and care system. This includes evidence of effectiveness relevant to the intended use(s) of the technology and evidence of economic impact relative to the financial risk. The evidence standards framework is intended to be used by technology developers to inform their evidence development plans, and by decision makers who are considering whether to commission a DHT.

Figure 1 DHTs classified by function and stratified into evidence tiers



Further information related to corresponding clinical and health economic studies provided here: <u>https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/evidence-standards-framework/digital-evidence-standards-framework.pdf</u>

Diagram 2. Germany's BfArM Fast-Track Process for Digital Health Applications (DiGA).

In Germany, BfArM (Federal Institute for Drugs and Medical Devices) established in December 2019 a fast-track process for digital health applications (DiGA). BfArM assesses each DiGA product within a three-month period to examine the manufacturer's statements about the product qualities and evidence of the positive healthcare effect of the DiGA. This review serves as a prerequisite for the DiGA to be included in the official directory of reimbursable digital health applications (DiGA Directory).



Further information related to BfArM's evaluation process is provided here: <u>https://www.bfarm.de/SharedDocs/Downloads/EN/MedicalDevices/DiGA_Guide.pdf?_blob=p</u> <u>ublicationFile&v=2</u>



October 15, 2020

ICER Staff and Consultants Institute for clinical and economic review (ICER)

publiccomments@icer-review.org

Dear respected ICER staff and consultants,

As a Physician Board Certified in Internal Medicine and Addiction Medicine, I am submitting my comments on your Draft Evidence Report titled: Digital Therapeutics as an Adjunct to Medication Assisted Therapy for Opioid Use Disorder prepared for Midwest CEPAC.

Your thorough review of the data you selected and thoughtful approach to a wide range of considerations regarding the cost effectiveness of reSET-O is quite impressive. My concern is that the conclusions you reached are not consistent with my clinical experience, nor are they consistent with published data not mentioned in your draft report. I have practiced Internal Medicine for 27 years and have been treating patients with Transmucosal Buprenorphine for 12 years. I have a mature practice made up of patients who consider me their Primary Care Physician, and a mature (smaller yet still quite busy) consultation practice treating patients for primarily Substance Use Disorder for Opioids, most of whom have co-existing mood disorders. Via my skills in psychopharmacology and referrals to counselors I offer dual-diagnosis treatment.

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As an Internist, I treat a wide array of medical problems. I can see the affect of various illness on my patients' lives, those of their family, friends and employers. 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. A single site may not seem preferrable to a multicenter 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

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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. 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.

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.

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

Adam M. Rubinstein, MD Patient Focused Medicine

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.

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.

Please consider revisions of your draft document. Include a wider range of economic impacts. Each additional tool we have for patient care is potentially preventing serious morbidity or mortality. This has been authorized, and ongoing studies may show the differences you seek over longer duration. Why jump to conclusions now? This epidemic is taking 130 lives per day. This product was not rushed to market like the Coronavirus vaccines in progress. Both are meant to save lives.



Respectfully submitted,

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Adam Rubinstein MD FASAM Internal Medicine and Addiction Medicine 250 Center Dr. Vernon Hills, IL 60061 847 922-4550 (m) 847 247-0300 (o) 847 247-8011 (f) dr@adamrubinstein.com www.adamrubinstein.com



October 13, 2020

Steven D. Pearson, MD, MSc Institute for Clinical and Economic Review

Dear Dr. Pearson:

I am the chief medical officer of Acadia Healthcare. At Acadia, we operate a network of behavioral health facilities across the country. Substance use disorders are a large focus of the care we provide. I am a psychiatrist by training with a focus on treating addiction.

ICER's evaluation of digital apps for the treatment of opioid use disorders helps policymakers and health care decision makers pay increased attention to one of the most important issues in US healthcare. Currently the opioid epidemic continues to affect our society and overwhelm the health care system with increasing costs, and patients are at even greater risk due to the health and economic uncertainty brought about by the current Covid-19 crisis. The majority of patients do not receive evidence-based treatments (i.e., medication assisted treatment), face significant barriers and stigma, with and continue to struggle to achieve a full long-term recovery.

The reSET-O therapeutic is one of these evidence-based treatments. It was good to see that it was the only app with sufficient evidence to support its economic evaluation. We have utilized reSET-O with our patients and have been impressed with the results and positive feedback we have received from patients. As such, my hope is to make this important treatment modality available to more patients.

In its evaluation of the clinical and economic value of reSET-O ICER makes several assumptions that are likely having a significant impact on the output of the model. Incorrect assumptions will cause the model to deviate from its stated goal of simulating the potential impact of clinically relevant evidence-based treatments on the health care system. It would be a shame to see access to reSET-O made more difficult by unfair projections from a poorly supported model assumption.

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.



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.

Thirdly, ICER assumes that patients who are off treatment and not using illicit opioids are just as costly as patients off treatment <u>and</u> using illicit opioids. ICER should correct this assumption in order to maintain the internal validity of the model.

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 longerterm 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.

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 <u>absolute</u> 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.

In closing, ICER should ensure the integrity of its model and its ability to reflect changes in utilities and costs with retention and abstinence. ICER should also enhance its transparency in reporting the incremental cost over five years to avoid inadvertently increasing barriers to a much-needed treatment. Finally, ICER should consult with addiction specialists on the front lines who have direct experience with the use and implementation of these therapeutics, as its assumptions as not all of the relevant information will be explicitly available in the literature.

Thank you for your consideration in this matter. As we continue to deal with the deadly opioid epidemic, we need more effective, evidence based tools in our toolbox.

Sincerely,

Michael V. Genovese, M.D., J.D.



October 15, 2020

To: Steven D. Pearson, MD, MSc, FRCP President, Institute for Clinical and Economic Review (ICER) Two Liberty Square, 9th Floor Boston, MA 02109

From: Charles Ruetsch, PhD President and CEO Health Analytics, LLC 9200 Rumsey Rd. Suite 215 Columbia, MD 21045

RE: ICER's Review of Digital Therapeutics with Medication Assisted Treatment for Opioid Use Disorder (OUD): Effectiveness and Value

Dear Dr. Pearson, I was pleased to see that the Institute for Clinical and Economic Review (ICER) reviewed the clinical and economic value of digital therapeutics that are indicated for use with medication treatment for opioid use disorder (OUD). As more digital therapeutics become available, it occurs to me that we may need a more substantial method for evaluating their likely cost-effectiveness in market. They are neither medications nor devices. This report will likely be both lauded and criticized as it attempts to establish precedence in this topical area. Nevertheless, the community review and commentary period offers the opportunity to make the report even more representative of real-world experience, through the fine-tuning. I am writing to provide observations and recommendations regarding some of the model assumptions.

I am the owner and Principle Investigator for Health Analytics, LLC a small medical research and outcomes firm that specializes in embedding health economics and outcomes research projects within payers, provider groups, and health systems. It has been my pleasure to conduct no fewer than 15 health outcomes and health economics studies within national (i.e., Aetna, Optum/UHC) and regional (i.e., Horizon BCBS, TennCare) payers focusing on outcomes and economic burden of OUD and the potential for cost-offset associated with treatment of the same. 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 (\geq 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.

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%).

Thank you for the opportunity to comment on the ICER's Review of Digital Therapeutics with Medication Assisted Treatment for Opioid Use Disorder (OUD): Effectiveness and Value. I hope that you find my comments helpful. Please feel free to contact me with any questions or concerns.

Sincerely,

Charles Ruetsch, PhD President and Chief Scientific Officer Health Analytics, LLC <u>c.ruetsch@healthanalytics.com</u> 410-997-3314 x 501



October 15, 2020

To Whom it May Concern:

As Executive Director for the New York Association of Alcoholism and Substance Abuse Providers, Inc (ASAP) and as a clinician, administrator, and advocate in the substance use disorders field for almost 40 years, I strongly encourage ICER to conduct a more in depth study of research, studies, and data from federal (NIDA, NIAAA, SAMHSA), state (NYSDOH, OASAS), and local (NYCDOH-MH) SourceSafe and correct some of the erroneous conclusions reached in your report.

I have spent my career working with those suffering from substance use disorders and in my current role I represent alcoholism and substance abuse treatment, prevention, recovery, research, and training providers throughout New York State. I am in a unique position to request that you reconsider some of your assumptions, do some additional research, and refine your recommendations.

During the COVID 19 pandemic, we have seen rising rates of substance and opioid abuse, overdoses and related deaths and had the opportunity to see how efficacious the use of technology could be in the treatment of addiction. Pandemic-related social distancing, funding cuts, limited access to in-person treatment and suspension of inperson support groups have all conspired to erode recovery supports and contribute to relapse, increased drug/alcoholuse, overdose, and deaths related to alcohol and other drugs. We needed innovative technologies to address an abrupt interruption in access to treatment services and widening gaps in the service delivery system,, particularly in-person services.

When the FDA approved reSET-O it was given "breakthrough" designation. Were it more widely available when COVID-19 hit our communities, we would have seen much better supports for people suffering with opioid use disorders. It is imperative that tools like reSET-O are more widely understood and incorporated into treatment tool boxes to help stem the tide of escalating opioid addiction and overdose. Used in conjunction with medication assisted treatment and addiction counseling/treatment, issues related to retention in treatment would be significantly remediated.

It is important that ICER understand the implications its' draft report relative to public perception about addiction and treatment, stigma, and progress in addressing the pandemic of opioid addiction and overdose. Inaccurate assumptions on the impact reSET-O will have on the healthcare system predispose the ICER model and its report to reach inaccurate conclusions leading to ill-advised recommendations. This breakthrough therapy has the ability to positively impact many individuals in recovery and an incorrectly designed model has the potential to limit patient access.

New York Association of Alcoholism and Substance Abuse Providers, Inc.

11 North Pearl Street Suite 801 Albany, New York 12207

> (P) (518) 426-3122 (F) (518) 426-1046

www.asapnys.org



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 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.

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.

It is my hope that ICER will regroup and examine the incorrect assumptions included in their model. ICER's research and modeling would benefit from a more in-depth review of scientific literature and research and by more thorough consultation with substance use disorder providers who have first-hand knowledge of the benefit of utilizing prescription digital therapeutics.

Thank you for your consideration of this important matter.

Sincerely yours,

John Coppet

John J. Coppola Executive Director New York Association of Alcoholism And Substance Abuse Providers



October 15, 2020

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

RE: Draft Evidence Report "Digital Therapeutics as an Adjunct to Medication Assisted Therapy for Opioid Use Disorder"

Dear Dr. Pearson:

Patients Rising Now welcomes the opportunity to comment on ICER's September 17th draft evidence report about digital therapeutics used in conjunction with Medication Assisted Therapy (MAT) for Opioid Use Disorder (OUD). As you know, we advocate on behalf of patients with serious conditions and chronic diseases for them to have access to vital therapies and services. Access to such treatments can result in significant improvement in quality of life and productivity, as well as survival.

As has become alarmingly clear over the past several years, opioid-related deaths are truly a national emergency.¹ The opioid crisis in the U.S. has been eclipsed in 2020 by the COVID-19 pandemic, which has also raised challenges for monitoring the opioid epidemic and for people with OUD to receive treatment. Our concerns about "access equaling survival" are exceptionally and unquestionably true for people with OUD, and the consequences for those people either receiving treatment or dying from their disease also extends to their families, their communities, and the country overall.²

Our comments about the draft report are organized into sections about Patient and Family Perspectives; Terminology and Language; Research Methodologies and Uncertainties; and Additional Points.

Patient and Family Perspectives

The draft report does a reasonably good job of describing the effects that OUD can have on people with the disease and their family members. Those personal and societal consequences have been widely documented in academic literature and in the media. However, we appreciate ICER continuing to include those patient and family perspectives in the draft report, as they are important to keep in mind and can help reduce stigma.

¹ <u>https://www.whitehouse.gov/opioids/</u>

² "Where have all the workers gone? An inquiry into the decline of the U.S. labor force participation rate," Brookings Institution, Krueger, Thursday, September 7, 2017"; "The Economic Burden of Opioid Abuse: Updated Findings," JMCP, Vol. 23, No. 4 April 2017; "HEALING MICHIGAN An Examination of State-Level Responses to the Opioid Epidemic in Michigan," Greenberg, University of Michigan Gerald R. Ford School of Public Policy, December 2016.

We are also gratified to see that ICER has reiterated from its 2018 report the clinically responsible concept that the goal of MAT is stable recovery that can involve long-term use of MAT, and that seeking complete withdrawal from opioids, or detoxification – including MAT – can be dangerous and is often not successful: "[L]ong-term maintenance treatment approaches using methadone or buprenorphine to reduce cravings for opioids have been found to be more effective than short-term managed withdrawal methods that seek to discontinue all opioid use and detoxify patients."³

It is generally recognized that people with OUD may often relapse after success with some treatment modalities, and thus repeated – and sometimes different – approaches and types of MAT or clinical settings may be needed, and that subsequent attempts at recovery are more likely to be successful. Thus, it is not surprising that the data the draft report discusses for reSET-O found that "in treatment naïve participants, treatment completion rates were 51.0% in the CBT group and 53.5% in the CM-only group. However, in treatment experienced participants, treatment retention rates were 91.9% in the CBT group and 46.0% in the CM-only group. There were similar findings for the longest period of continuous abstinence and total abstinence."⁴

We are also gratified that the draft report concluded that "the use of reSET-O in addition to outpatient MAT may provide clinical benefit in terms of increased MAT retention, which may have implications for cost offsets and clinical gains compared to outpatient MAT alone for adults with OUD."⁵

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.⁶
- 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.

Terminology and Language

³ Draft report, p. 1.

⁴ Draft report, p. 17.

⁵ Draft report, p. 48.

⁶ Draft report, p. 38.

In our comments to ICER in 2018, we noted our disagreement about the meaning of the acronym MAT.⁷ We are very glad to see that ICER has adopted the most appropriate, and most peoplecentered 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.⁸ 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."⁹ 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.

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.¹⁰

The research and development processes for health care software, digital therapeutics, and other non-biopharmaceutical interventions that have rapid cycles of updates, upgrades, and

⁷ <u>http://icerwatch.org/wp-content/uploads/2018/10/100418-Patients-Rising-Now-Comments-to-ICER-RE-Treatments-for-OUD-draft-v6.pdf</u>

⁸ "We recommend that ICER not use the term "Medications for Addiction Treatment" when referring to MAT. That term is used only rarely in the literature and is not used in SAMSHA's "Medications for Opioid Use Disorder" nor in other major documents and recommendations. In addition, we note in the draft report that MAT can be used by a person in recovery, i.e., in a state of dependence and not addiction: "A person in recovery refers to an individual who abstains from further use, reduces their substance use to a safer level, or takes steps to mitigate the potential physical and emotional harm resulting from continued use. A person can be considered in recovery while on MAT." Therefore, we urge ICER to use "Medication Assisted Treatment" as a definition for MAT because it is much more commonly used and a much less controversial – although we do recognize that this term also has problems related to whether the medication is the treatment or is assisting the treatment. That is, for other chronic diseases pharmacological therapies are also part of overall optimal treatment programs, e.g., diabetes, (where nutritional and exercise counseling are important), depression (where cognitive therapy can be important), and for other substance use disorders, such a nicotine dependence (where combining non-pharmaceutical therapies with a pharmacological agent can leader to better outcomes)." Patients Rising Now Comment Letter to ICER, October 8, 2018, pp 2-3

⁹ ASAM Definition of "Addiction," https://www.asam.org/Quality-Science/definition-of-addiction

¹⁰ Draft report, p. 16.

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 2020.¹¹

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 report¹² – is simply impractical for digital therapeutics.

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.

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 heart¹³ as well as secondary infection in the kidneys, bones or brain.¹⁴
- A new NIH-supported clinical trial of reSET-O is preparing to be initiated.¹⁵ Similarly, there is a health system sponsored trial of DynamiCare.¹⁶ (Interestingly, the ClinicialTrials.gov description indicates that DynamiCare is not an FDA-approved device product, while reSET-

¹¹ <u>https://apkpure.com/pear-reset-o%C2%AE/md.reset.reSETO/versions</u>

¹² Draft report, p. 21.

¹³ <u>https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2769232</u>

¹⁴ <u>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4953807/</u>

¹⁵ <u>https://clinicaltrials.gov/ct2/show/NCT04129580</u>

¹⁶ <u>https://clinicaltrials.gov/ct2/show/NCT04235582</u>

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.

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."¹⁷ 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.¹⁸

Conclusions & Recommendations

Patients Rising Now believes that ICER's draft report about digital therapeutics for OUD fails to recognize the important differences between digital and biochemical therapeutics in terms of the development and validation processes – particularly concerning the timeframes for updates and revisions. We strongly recommend that this facet of digital therapeutics be discussed in the final report and at the Midwest CEPAC's meeting. In addition, although ICER has improved its language to describe MAT for OUD, we would recommend additional discussion about the biological basis for OUD as a chronic disease as well as other factors noted above that will help reduce stigma by all stakeholders. After many years of an increasing opioid crisis in the U.S., and many, many years of evidence of the effectiveness of MAT, it is clear that stigma must be reduced to significantly improve care for people with OUD. ICER should do its part to help reduce that stigma – or at the very least, not continue to perpetuate it.

Sincerely,

¹⁷ Draft report, p. 33.

¹⁸ Draft report, p. 23.

Tenny M. Wilcon

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



October 15, 2020 - Submitted electronically via: publiccomments@icer-review.org

RE: ICER's Draft Evidence Report on Review of Digital Therapeutics with Medication Assisted Treatment for Opioid Use Disorder (OUD)

Dear Dr. Pearson:

Pear Therapeutics, Inc. ('Pear" or "we") thanks ICER for considering prescription digital therapeutics (PDTs) in this review and appreciate the opportunity to provide comments on ICER's draft evidence report, published on September 17, 2020. Upon review and discussion with external experts, we believe ICER's current assessment understates the clinical and economic benefit associated with reSET-O[®] and by extension, addiction treatment as a whole. At this moment in history, people in the United States are suffering from an epidemic of addiction, with insufficient access to treatment and poor outcomes. Novel therapies that expand patient access and safely improve outcomes are desperately needed for this underserved population that suffers from stigma and inequity.

In the response below, we provide information on the most recent peer-reviewed clinical and economic evidence pertaining to real-world use of reSET-O¹. We then provide recommendations for ICER to consider in updating its economic and clinical effectiveness evaluation for reSET-O in this review.

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.

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.

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 <u>Christensen, 2014</u> (Appendix Table 2).

¹The contents of this letter include real world evidence and health care economic information. The information is in no way intended to imply or suggest any claims regarding reSET-O® beyond its cleared indications and uses and FDA-required labeling.

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 realworld use of the reSET-O commercial product, driving enhancements in treatment along with cost savings stemming from reduced inpatient stays and emergency department visits.

2. 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.

B. Clinical benefit of MAT retention should be reflected in the model's health state utilities for both injection and non-injection users. <u>SAMHSA guidelines</u> 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 more accurately estimate US utility values for the M1 health state (0.761 for non-injection users and 0.689 for injection users) (Appendix Table 3).

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.

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.

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.

F. ICER's model overestimates the commercial cost associated with reSET-O. The current WAC used in the model does not reflect the real-world negotiated price paid for reSET-O. We recommend ICER use the price of \$1,218.78 for a 12-week prescription of reSET-O. This price is net of rebates, discounts, allowances and warranty payments where applicable. For example, Pear offers a warranty model that typically includes a refund to the payer, employer, or insurance company on the cost of purchasing the product (minus any applicable third-party fees) when the parties agree that the product was not effective for a patient.

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, <u>Budilovsky-Kelley, 2019</u>, 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).

3. 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 (<u>Christensen, 2014</u>, <u>Bickel, 2008</u>; <u>Marsch, 2014</u>) 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, [<u>Campbell, 2014</u>, 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. FDAcleared 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 <u>ICER</u> <u>2016 Diabetes Prevention Program (DPP)</u> 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.

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 (<u>Oxford Centre for Evidence-Based Medicine, 2009; U.S. Preventive Services Task Force, 2012</u>: 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 (<u>Castelnuovo</u>, 2010; <u>Berger</u>, 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 <u>DPPs</u> 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 <u>CAR-T</u> review, CAR-T therapies were given B+ ratings when their studies were not blinded.

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 <u>reSET®</u>, <u>Somryst(TM</u>), <u>Freespira®</u>, <u>EndeavorRxTM</u>. 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).

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 <u>reSET-O's indication</u> 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.

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.

Delivery Location and Method of Use: FDA clearance of reSET-O demonstrates applicability of the Christensen study data to reSET-O, despite differences in delivery platform (browser vs mobile-application and location). The difference in computing platform (mobile device vs. browser) is analogous to different drug delivery methods, where the same active pharmaceutical ingredient is delivered using different technology, e.g. auto injector vs. syringe. Likewise, differences observed between clinical trials where a drug may be administered in clinic and labeling, where the same drug is intended to be self-administered at home by the patient. Prior ICER reports have given stronger clinical ratings despite differences in delivery method and location, as summarized in Appendix Tables 9 & 11. reSET-O's real-world data demonstrate that positive engagement as well as outcomes occur regardless of in-clinic versus remote.

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 (Appendix Table 8: Oxford Centre for Evidence-Based Medicine, 2009; U.S. Preventive Services Task Force, 2012).

Coverage Policies: We urge ICER to cite in its revised report the <u>multiple coverage policies for reSET-O</u> (Appendix Table 12) that are in effect.

In closing, we respectfully request ICER revises its current modeling approaches by: (1) updating the cohort proportions for the reSET-O arm in phase 2, (2) updating the utility estimates to accurately represent the utility benefit of MAT, (3) including CM and CBT in all its analyses, (4) using costs that accurately represent the disease trajectory and resource use, and (5) reconsider its clinical evidence and study quality rating pertaining to reSET-O using the fully available evidence.

The ICER assessment, as is, can have far reaching adverse consequences on patients' access to treatment, which we believe can be avoided after careful reconsideration of the evidence and updating the report to reflect the value of reSET-O. We look forward to continuing our collaboration with ICER with the goal of improving the OUD treatment paradigm and enabling access to care through PDTs such as reSET-O.

Respectfully,

Michael Pace

Appendix

Table 1: Analysis of Health Care Resource Use Reductions and Associated Cost Savings with reSET-O versus without reSET-O in a Real-World Setting

	Pre	Pre-index period (N=351)			st-index period ((N=351)			
	Patients n (%)	Incidence rate (95% CI)	Encounters ^a n	Patients n (%)	Incidence rate (95% CI)	Encounters ^a n	Difference ^a n	IRR ^b (95% CI)	p-value
Facility Enco	unters	<u> </u>	<u> </u>	1	L				.L
All settings	104 (29.6%)	0.651 (0.481, 0.881)	229	48 (13.7%)	0.437 (0.318, 0.600)	153	-76	0.67 (0.45, 0.99)	0.047
Inpatient	29 (8.3%)	0.204 (0.106, 0.392)	72	13 (3.7%)	0.077 (0.042, 0.140)	27	-45	0.38 (0.16, 0.88)	0.024
Intensive care unit	3 (0.9%)	0.011 (0.004, 0.030) ^c	4	0 (0.0%)	0.000 (0.000, 0.009) ^c	0	-4	NA	NA
Emergency department	84 (23.9%)	0.388 (0.293, 0.514)	136	38 (10.8%)	0.310 (0.220, 0.437)	109	-27	0.80 (0.55, 1.17)	0.247
HOPD surgical	5 (1.4%)	0.014 (0.006, 0.034) ^c	5	0 (0.0%)	0.000 (0.000, 0.009) ^c	0	-5	NA	NA
Partial hospitalizati on	3 (0.9%)	0.046 (0.012, 0.172)	16	3 (0.9%)	0.057 (0.017, 0.191)	20	4	1.24 (0.20, 7.55)	0.813
Clinical Services ^d									

Pathology and laboratory: Drug testing	281 (80.1%)	9.470 (8.493, 10.560)	3324	239 (68.1%)	7.652 (6.775, 8.642)	2686	-638	0.81 (0.73, 0.89)	<0.001
Medicine: psychiatry	198 (56.4%)	7.595 (6.579, 8.767)	2666	189 (53.8%)	6.6 (5.697, 7.646)	2317	-349	0.87 (0.76, 0.99)	0.036
E&M: Case management services	122 (34.8%)	6.087 (4.236, 8.746)	2137	109 (31.1%)	6.589 (4.597, 9.443)	2313	176	1.08 (0.81, 1.44)	0.588
Pathology and laboratory: Other	224 (63.8%)	3.421 (2.841, 4.118)	1201	151 (43.0%)	2.948 (2.402, 3.619)	1035	-166	0.86 (0.75, 0.99)	0.039
E&M: Office/other outpatient services	310 (88.3%)	11.779 (10.652, 13.025)	4134	289 (82.3%)	11.34 (10.338, 12.439)	3980	-154	0.96 (0.90, 1.03)	0.302
Rehabilitati ve services: Behavioral health	54 (15.4%)	0.538 (0.304, 0.952)	189	20 (5.7%)	0.854 (0.455, 1.604)	300	111	1.59 (0.88, 2.87)	0.124
Rehabilitati ve services: Alcohol & substance	86 (24.5%)	1.288 (0.783, 2.120)	452	38 (10.8%)	1.015 (0.533, 1.932)	356	-96	0.79 (0.48, 1.30)	0.348
Rehabilitati ve services: Other	92 (26.2%)	3.255 (2.577, 4.112)	1143	70 (19.9%)	3.068 (2.399, 3.924)	1077	-66	0.94 (0.82, 1.08)	0.387

Rehabilitati ve services: Mental health	43 (12.3%)	0.247 (0.173, 0.354)	87	18 (5.1%)	0.42 (0.213, 0.828)	147	61	1.7 (0.91, 3.18)	0.097
Surgery	139 (39.6%)	0.78 (0.647, 0.940)	274	75 (21.4%)	0.608 (0.481, 0.769)	213	-60	0.78 (0.60, 1.02)	0.07
Medicine: physical medicine and rehabilitatio n	31 (8.8%)	0.469 (0.244, 0.901)	165	13 (3.7%)	0.622 (0.270, 1.435)	218	54	1.33 (0.56, 3.14)	0.521
Medicine: cardiovascul ar	58 (16.5%)	0.326 (0.228, 0.465)	114	24 (6.8%)	0.177 (0.117, 0.269)	62	-52	0.54 (0.36, 0.82)	0.004
E&M: Domiciliary rest home	31 (8.8%)	0.334 (0.224, 0.496)	117	26 (7.4%)	0.445 (0.304, 0.650)	156	39	1.33 (0.99, 1.79)	0.058
Medicine: chiropractic manipulativ e treatment	9 (2.6%)	0.124 (0.037, 0.418)	44	8 (2.3%)	0.227 (0.071, 0.727)	80	36	1.82 (0.34, 9.74)	0.481
Radiology	108 (30.8%)	0.594 (0.484, 0.730)	208	60 (17.1%)	0.493 (0.380, 0.640)	173	-35	0.83 (0.63, 1.09)	0.182
Transport services	26 (7.4%)	0.212 (0.120, 0.375)	74	10 (2.8%)	0.313 (0.125, 0.783)	110	35	1.48 (0.63, 3.46)	0.371

E&M: Emergency department services	93 (26.5%)	0.446 (0.339, 0.588)	157	43 (12.3%)	0.368 (0.266, 0.509)	129	-27	0.82 (0.57, 1.20)	0.310
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CI, confidence interval; E&M, evaluation and management; IRR, incidence rate ratio; n, number of patients; NA, not applicable.

a The number of encounters are estimated from the incidence rates (i.e., rate x 351). Encounters difference is the estimated encounters in the post-index period minus the estimated encounters in the pre-index period. Hospital encounters (inpatient, emergency department, HOPD surgical, and partial hospitalization) are mutually exclusive.

b IRR is the incidence in the post index period relative to the incidence in the pre index period (e.g., an IRR < 1 indicates lower healthcare resource use in the post index period). Incidence and IRR are evaluated from a repeated-measures (i.e. pre and post for each patient) negative binomial model of count of encounters, with an offset for the number of days in each period.

c Based on the crude estimate and Poisson 95% CIs. Where incidence is 0 (i.e., no events), the upper 95% CI is based on the rule of 3 (i.e., $3\div351 = 0.009$).

d Clinical encounters represent groups of procedures (e.g.Current Procedure Terminology categories).

Note: The mean number of days in the pre-index and post-index periods was 180.0 and 104.0 days, respectively. The number and percent of patients are provided for description only and should not be compared given the difference in the number of days between the pre-index and post-index periods. Index dates: 01 January 2019 through 04 October 2019.

Variable	TAUTAU+ digital(n=79)therapeutic (n=91)		Odds Ratio (95% CI)	P Value
Primary endpoint (weeks 9-12)				
Abstinence from opioids and cocaine	60.6%	75.9%	2.05 (1.07, 3.90)	.03
Abstinence from opioids only	62.1%	77.3%	2.08 (1.10, 3.95)	.02
Abstinence from cocaine only	64.5%	82.4%	2.58 (1.37, 4.86)	.003
Secondary endpoint (weeks 0-12)				

Table 2: Abstinence from substance use with reSET-O (digital therapeutic) vs. TAU.

Total one-third weeks abstinent	24.06 (11.89)	27.97 (8.17)		.02
Exploratory endpoint (weeks 5-12)				
Abstinence from opioids (weeks 7-12)	63.9%	78.2%	2.03 (1.09, 3.80)	.03
Abstinence from opioids (weeks 5-12)	68.5%	82.4%	2.16 (1.16, 4.01)	.01

Data are proportion of participants (%) or mean (SD).

Abstinence was assessed by UDS throughout the 12-week study (3x per week). The primary endpoint evaluated abstinence during the last four weeks of treatment (weeks 9-12) using a repeated measures logistic generalized estimating equations model with factors for treatment, time, and treatment x time (FDA, 2016; Clinical Trials Network, 2010). Each UDS assessment was used to determine a participant's abstinence from opioids, cocaine or both. Participants were considered non-abstinent (i.e., positive) if the UDS indicated cocaine or opioid use for a given third-week time point, or if the sample was missing/not provided, which is a standard, and conservative, approach in the field of addiction research (National Institute on Drug Abuse, 2012).

Health State	Value
Off MAT without Illicit Use of Opioids (M4)	0.852
On MAT without Illicit Use of Opioids (M2)	0.766
On MAT with Illicit Use of Opioids – Not Injected (M1)	0.761*
Off MAT with Illicit Use of Opioids – Not Injected (M3)	0.694
On MAT with Illicit Use of Opioids – Injected (M1)	0.689 [‡]
Off MAT with Illicit Use of Opioids – Injected (M3)	0.574

Table 3: Health State-Specific Utility Values, Wittenberg, 2016

*Replace existing value of 0.7 sourced from Connock 2007. This will result in a 0.067 improvement in utility benefit in M1 vs. M3 among non-injection users. In Wittenberg, 2016, 0.761 is the utility of being initiated on buprenorphine among illicit users.

[‡]Replace existing value of 0.618 sourced from Connock 2007. This will result in a 0.115 improvement in utility benefit in M1 vs. M3 among injection users. In Wittenberg, 2016, while 0.689 is the utility of being initiated on methadone among illicit users, it is more representative of the utility benefit of MAT vs. illicit users not on treatment.

Table 4. Studies Demonstrating Positive Effect of Contingency Management for Individuals with OUD on Medications for Opioid Use Disorder (buprenorphine or methadone)*

Intervention	Outcomes	References
	Improved retention in treatment	<u>Hser et al., 2011</u> Chen et al., 2013
CM (vouchers with monetary prizes) + medication for OUD (methadone or buprenorphine)	Improved opioid abstinence	Preston et al., 2000 Bickel et al., 2008 Hser et al., 2011 Chen et al., 2013
	Increased therapy attendance or adherence	<u>Chutuape et al., 1999</u> <u>Neufeld et al., 2005</u> <u>Chen et al., 2013</u>

*Contingencies varied across studies.

Table 5: CBT Use and Costs to be Included in the Comparator Arm in Phase 1 of the Model (as recommended for reimbursement eligibility by ASAM levels of care 1 (outpatient) or 2 (intensive outpatient)

Number of hours/week (<u>required minimum</u>)	Cost per 30- minute visit	Payer covered, %	Payer Cost/week	Number of weeks	Total Payer Cost Over 12 weeks
9 (18 half-hour visits)	\$110 (2020 CPT code 99214 [25 minutes])	70%	\$1,386	12	\$16,632

Table 6: 99212 Billing Criteria

Number	Criteria
1	Clinician records patient's medical history
2	Clinician conducts a physical examination on patient
3	Clinician and patient make a treatment decision

2/3 of the following criteria should be satisfied DURING an OP patient visit to a physician's office.

Study	Medication	Randomization	Study Design	Study	Number of	Objective	Outcomes
Study	Used	Kundonnization	Study Design	Duration	Participants	Endpoints	
Bickel et al, 2008	Buprenorphine	Yes	 TAU: 1:1 biweekly counseling 30 minutes Human-delivered CRA: 1:1 biweekly counseling 1.5 hours/week, weeks 1- 12; 50 min/week,weeks 13- 23 + CM Computer delivered CRA: 1:1 biweekly counseling 30 minutes + TES + CM 	23 weeks	135	Abstinence and treatment retention	 Statistically significant improvement in objective abstinence was observed in both arms in which patients received CRA (either human delivered or TES-delivered) compared to TAU Mean weeks continuous abstinence were comparable for human delivered CRA and TES - no significant difference from each other, but both significantly higher than TAU Retention rates were high for all study arms, but highest in the TES arm - rates at week 23 were as follows: 58% (TAU), 53% (Human CRA), 62% (TES)
<u>Christensen</u> et al, 2014	Buprenorphine	Yes	 CM: 1:1 biweekly counseling (30 minutes) + CM CRA+: 1:1 biweekly counseling + CM + TES 	12 weeks	170	Abstinence and treatment retention	 Significantly higher rate of retention in treatment for CRA+ (80%) vs CM (64%) Significant improvements in number of days abstinent: mean of 67.1 days for the CRA+ arm vs 57.3 days for CM arm, t(133.4) = 2.59, p = 0.011
Maricich et al, (provisionall y accepted	Buprenorphine	Yes	 TAU: 1:1 biweekly counseling (30 minutes) + CM TAU + digital 	12 weeks	170	Abstinence and treatment retention	1. Significantly higher rate of retention in treatment for TAU+ digital therapeutic (82.4%) vs TAU (68.4%)

Table 7. Clinical Evidence Supporting reSET-O Therapeutic Content

2020)			therapeutic: 1:1				2. Increased likelihood of
			biweekly counseling				abstinence from opioids and
			+ CM + TES				cocaine during weeks 9-12: 75.9%
							(TAU+ digital therapeutic) vs
							60.6% (TAU), OR 2.05, 95% CI
							1.07-3.90; P=0.03)and retention
			1. TAU: 1:1				
			counseling (1hr)				
			weekly for 4 weeks,				1. Statistically significant
Marsch at al			biweekly after week 4			Abstinence	improvement in objectively
<u>2014</u>	methadone	Yes	2. TES: 1: 1	52 weeks	160	and treatment	measured abstinence: 48% (TES)
2014			counseling (30			retention	vs. 37% (TAU) abstinence across
			minutes) weekly for				all study weeks
			4 weeks, biweekly				
			after week 4 + TES				

Table 8. Quality of Studies Evaluating reSET-O Therapeutic Content

	OUD	Randomization &	Pre-Specified +				
	population	TAU (or better)	Gold Standard		Effectiveness (UDS	Robust Data	
Study	with MAT	Control	Endpoints	Safety	&/or retention)	Collection	Duration
Bickel et al, 2008	Yes	Yes	Yes	Yes	Yes	Yes	23 weeks
Christensen et al, 2014	Yes	Yes	Yes	Yes	Yes	Yes	12 weeks
Marsch et al, 2014	Yes	Yes	Yes		Yes	Yes	52 weeks

Based on <u>Oxford Classification of Evidence</u>, reSET-O achieves **1a** rating. Based on <u>USPSTF</u>, reSET-O clinical evidence receives the highest rating of 'Good'.

Diabetes Prevention Program (DPP) Delivery Format	Name	Study	Study Design	Blinding	Study Interventions	Comparator	Delivery Mode (Route of Administration) - 16 Weekly Core Lessons	Delivery Mode (Route of Administration) - Monthly Maintenance Sessions	Note
Reference Study: In- person, individual coaching	DPP	DPP Researc h group 2002	Multi-site RCT	Assignment to metformin and placebo were double- blinded	1) standard lifestyle recommendati ons plus metformin, 2) standard lifestyle recommendati ons plus placebo, 3) intensive program of lifestyle modification	Usual care	In-person, one-on- one	In-person, one-on-one	The original DPP Trial data were summarized to serve as a standard for comparison with implementation trials
In-person, group coaching	DEPLO Y	Ackerm an 2008	Multi-site, cluster RCT	Not blinded.	 DPP intervention, standard advice alone 	Brief coaching	Group	Group	
In-person, group coaching	RAPID	Ackerm an 2015	Multi-site RCT	Research staff were blinded to intervention assignments Participants	 DPP lifestyle intervention, usual care plus brief counseling and information about existing 	Brief coaching	Group	Group	

Table 9. Studies Implementing Diabetes Prevention Programs (DPP) (ICER, 2016)

			were not blinded.	community resources for lifestyle modification				
In-person, group coaching	<u>Vojta</u> 2013	Pre-post study	Not blinded.	YMCA DPP program	N/A	Group	Group	
In-person, group coaching	<u>Boznac</u> <u>k 2014</u>	Pre-post study	Not blinded.	YMCA DPP program	N/A	Group	Group	
In-person, group coaching	<u>Brokaw</u> 2015	Pre-post study	Not blinded.	DPP program	N/A	Group	Group	
In-person, group coaching	<u>Marrero</u> 2015	RCT	Participants were informed of their treatment assignment.	1) Weight Watchers lifestyle modification program (covers same behavioral topics as DPP), 2) Your Game Plan to Prevent Type 2 Diabetes educational materials by National Diabetes Education program	NDEP Your Game Plan	Group (weight watchers curriculum contains core content)	Weekly weight watchers meetings	

In-person, group coaching	HELP PD	<u>Katula</u> 2011	Single site RCT		1) DPP program, 2) usual care consisting of 2 individual sessions with a nutritionist and a monthly newsletter about community resources	Two individual sessions with nutritionist plus monthly newsletter	Group (24 weekly groups)	Group (18 monthly groups)	
Digital, human coaching	VLM	<u>McTigu</u> <u>e 2009</u>	Pre-post study	Not blinded.	DPP lifestyle intervention	N/A	Online	Online	Web-based (Microsoft Internet Explorer 6.0)
Digital, human coaching	Omada	<u>Sepah</u> 2014	Pre-post study	Not blinded.	Prevent program	N/A	Online	Online (9)	Participants could access the Prevent program online via home computer or web-enabled mobile devices
Digital, fully- automated Coaching	Alive- PD	<u>Block</u> 2015	RCT, multi- speciality practice	Participants were informed of their treatment assignment.	 Alive-PD intervention, wait-list usual care 	Usual care	Weekly tailored goal setting mapped to DPP curriculum	Every 2 weeks after first 6 months	Alive-PD delivered via the web, internet, mobile phone, automated phone calls

 Table 10. Safety Data Supporting reSET-O Clearance (Maricich et al, provisionally accepted 2020)

Variable	TAU (n=79)	TAU+digital therapeutic (n=91)	Total (n=170)	P Value
Participants reporting at least one adverse event	55 (69.6%)	57 (62.6%)	112 (65.9%)	.42
Adverse events ^a				
Gastrointestinal disorders	23 (29.1%)	23 (25.3%)	46 (27.1%)	
Musculoskeletal and connective tissue disorders	18 (22.8%)	18 (19.8%)	36 (21.2%)	
Psychiatric disorders	19 (24.1%)	17 (18.7%)	36 (21.2%)	
Nervous system disorders	13 (16.5%)	21 (23.1%)	34 (20.0%)	
General disorders and administration site conditions	11 (13.9%)	17 (18.7%)	28 (16.5%)	
Skin and subcutaneous tissue disorders	9 (11.4%)	8 (8.8%)	17 (10.0%)	
Infections and infestations	5 (6.3%)	8 (8.8%)	13 (7.6%)	
Investigations	3 (3.8%)	10 (11.0%)	13 (7.6%)	
Respiratory, thoracic and mediastinal disorders	5 (6.3%)	7 (7.7%)	12 (7.1%)	
Injury, poisoning and procedural complications	3 (3.8%)	4 (4.4%)	7 (4.1%)	
Eye disorders	1 (1.3%)	5 (5.5%)	6 (3.5%)	
Metabolism and nutrition disorders	1 (1.3%)	2 (2.2%)	3 (1.8%)	
Reproductive system and breast disorders	0	3 (3.3%)	3 (1.8%)	
Renal and urinary disorders	0	2 (2.2%)	2 (1.2%)	
Hepatobiliary disorders	0	1 (1.1%)	1 (0.6%)	
Pregnancy, puerperium and perinatal conditions	1 (1.3%)	0	1 (0.6%)	

Surgical and medical procedures	1 (1.3%)	0	1 (0.6%)	
Vascular disorders	0	1 (1.1%)	1 (0.6%)	

Data are n (%).

^a Adverse events coded using preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA) system organ classifications. Observed adverse events were of the type and frequency anticipated in a population of patients with OUD (e.g., gastrointestinal, musculoskeletal, and psychiatric events). The proportion of participants reporting adverse events in each treatment group did not differ significantly (P=.42). No suicide-related events were reported. None of the adverse events observed were adjudicated to be device related.

Table 11. Summary of Studies of Disease-Modifying Therapies (DMTs) for Relapsing-Remitting Multiple Sclerosis (RRMS) (ICER, 2017)

Reference	Clinical Trial	Double blind?	Administration Type	Delivery Technology (in study) syringe type, autoinjector, etc	Name of Drug, indicated dosage and route of administration	Indicated route of administration	Delivery Technology (per label) syringe type, autoinjector, etc
<u>Jacobs</u> <u>1996</u>	Interferon β-1a 30 mcg (Avonex), IM Placebo, IM	Yes	in-clinic, clinician- administered	Injection - syringe type not specified	Interferon β-1a 30 mcg (Avonex), IM	Intramuscular injection; self- administered. Perform first injection under HCP supervision	 Vial with freeze-dried (lyophilized) powder Prefilled syringe Single-Use Prefilled Autoinjector Pen
<u>Calabrese</u> 2012	Interferon β-1a 30 mcg (Avonex), IM IFN β-1a 44 mcg, SC Glatiramer 20 mg, SC	No	information unavailable/uncle ar	Injection - syringe type not specified	Interferon β-1a 30 mcg (Avonex), IM	Intramuscular injection; self- administered. Perform first injection under HCP supervision	 Vial with freeze-dried (lyophilized) powder Prefilled syringe Single-Use Prefilled Autoinjector Pen

<u>Lublin</u> 2013	Interferon β-1a 30 mcg (Avonex), IM Glatiramer 20 mg, SC	No	information unavailable/uncle ar	Injection - syringe type not specified	Interferon β-1a 30 mcg (Avonex), IM	Intramuscular injection; self- administered. Perform first injection under HCP supervision	 Vial with freeze-dried (lyophilized) powder Prefilled syringe Single-Use Prefilled Autoinjector Pen
<u>Vollmer</u> 2014	Interferon β-1a 30 mcg (Avonex), IM Placebo, oral	No	information unavailable/uncle ar	Injection - syringe type not specified. Full text unavailable	Interferon β-1a 30 mcg (Avonex), IM	Subcutaneous injection; self- administered. Perform first injection under HCP supervision	 Vial with freeze-dried (lyophilized) powder Prefilled syringe Single-Use Prefilled Autoinjector Pen
<u>IFNβ</u> <u>Multiple</u> <u>Sclerosis</u> <u>Study</u> <u>Group</u> <u>1993</u>	Interferon β-1b 250 mcg (Betaseron), SC Placebo	Yes	"usually" patient self-administered	Injection - syringe type not specified.	Interferon β-1b 250 mcg (Betaseron), SC	Subcutaneous injection; self- administered. Perform first injection under HCP supervision	vial of BETASERON and pre- filled diluent syringe for each injection.
<u>Durelli</u> 2002	Interferon β-1b 250 mcg (Betaseron), SC Interferon β-1a 30 mcg	No	patient self- administered	Injection - syringe type not specified.	Interferon β-1b 250 mcg (Betaseron), SC	Subcutaneous injection; self- administered. Perform first injection under HCP supervision	vial of BETASERON and pre- filled diluent syringe

	(Avonex), IM						
<u>Etemadifar</u> 2006	Interferon β -1b 250 mcg (Betaseron), SC Interferon β -1a 30 mcg (Avonex), IM IFN β -1a 44 mcg, SC	No	patient self- administered	Injection - syringe type not specified	Interferon β-1b 250 mcg (Betaseron), SC	Subcutaneous injection; self- administered. Perform first injection under HCP supervision	vial of BETASERON and pre- filled diluent syringe
<u>Cadavid</u> 2009	Interferon β-1b 250 mcg (Betaseron), SC Glatiramer 20 mg, SC	No	information unavailable/uncle ar	Injection - syringe type not specified	Interferon β-1b 250 mcg (Betaseron), SC	Subcutaneous injection; self- administered. Perform first injection under HCP supervision	vial of BETASERON and pre- filled diluent syringe
<u>O'Connor</u> <u>2009</u>	Interferon β-1b 250 mcg (Betaseron), SC Glatiramer 20 mg, SC	No	information unavailable/uncle ar	Autoinjector	Interferon β-1b 250 mcg (Betaseron), SC	Subcutaneous injection; self- administered. Perform first injection under HCP supervision	vial of BETASERON and pre- filled diluent syringe

Bornstein 1987	Glatiramer Acetate 20mg (Copaxone), SC Placebo, SC	No	patient self- administered	Injection - syringe type not specified. Full text unavailable	Glatiramer Acetate 20mg (Copaxone), SC	Subcutaneous injection; self- administered. Perform first injection under HCP supervision	single-dose prefilled syringe
Panitch 2002	Interferon β-1a 44 mcg (Rebif), SC IFN β-1a 30 mcg, IM	No	information unavailable/uncle ar	Injection - prefilled syringes	Interferon β-1a 44 mcg (Rebif), SC	Subcutaneous injection; self- administered. Perform first injection under HCP supervision	 single-dose prefilled syringe single-dose autoinjector
<u>Mikol</u> 2008	Interferon β-1a 44 mcg (Rebif), SC Glatiramer Acetate 20mg (Copaxone) , SC	No	information unavailable/uncle ar	Injection - syringe type not specified	Interferon β-1a 44 mcg (Rebif), SC	Subcutaneous injection; self- administered. Perform first injection under HCP supervision	 single-dose prefilled syringe single-dose autoinjector
<u>Vermersch</u> 2014	Teriflunom ide 7mg (Aubagio), PO Teriflunom ide 14mg (Aubagio), PO	No	patient self- administered	oral administration - type not specified	Teriflunomide 7mg (Aubagio), PO Teriflunomide 14mg (Aubagio), PO	Oral administration	Film-coated tablet

	Interferon β -1a 44 mcg (Rebif), SC						
<u>Fox 2012</u>	Dimethyl fumarate 240 mg (Tecfidera) , PO Glatiramer Acetate 20mg (Copaxone) , SC Placebo	No	patient self- administered	oral administration - type not specified	Dimethyl fumarate 240 mg (Tecfidera), PO	Oral administration	Delayed-release capsule
<u>Cohen</u> 2012	Alemtuzu mab 12 mg (Lemtrada), IV Interferon β-1a 44 mcg (Rebif), SC	No	information unavailable/uncle ar*	IV infusion	Alemtuzumab 12 mg (Lemtrada), IV	Intravenous infusion; administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reaction	information unavailable/unclear
<u>Coles</u> 2012	Alemtuzu mab 12 mg (Lemtrada), IV	No	information unavailable/uncle ar*	IV infusion	Alemtuzumab 12 mg (Lemtrada), IV	Intravenous infusion; administered in a setting with appropriate equipment and	information unavailable/unclear

Interferon β-1a 44 mcg (Rebif) SC		personnel to manage anaphylaxis or serious infusion reaction	
(Rebif), SC			

*Drug presumed to be administered in-clinic by HCP

Table 12: reSET-O Coverage Policies Not Noted in Draft Report Section 3.1

Payer Name	Coverage Policy Description
Wellpath	Wellpath community care patients can get access to reSET-O through outpatient care
PreferredOne (Health Plan in MN)	reSET-O is covered as a standard medical benefit for all PreferredOne medical members
Serve You Rx (PBM)	reSET-O has been added to Serve You Rx's standard formulary and PDL as a Tier 2 Preferred Product and is being administered as a pharmacy benefit
The Hartford (Employee Health Plan)	reSET-O has been added to The Hartford's Employee Health Plan formulary and is being administered as a pharmacy benefit by The Hartford's pharmacy benefit manager
ChristianaCare (Employee Health Plan)	reSET-O has been added to ChristianaCare's Employee Plan formulary and is being administered as a pharmacy benefit by ChristianaCare's pharmacy benefit manager
RemedyOne	reSET-O is available as a covered pharmacy benefit benefit to RemedyOne's covered population

Figure 1. Real world engagement with the reSET-O PDT. Core lessons comprise the key CBT content delivered by reSET-O (n = 3,114).



Engagement and therapeutic use data were collected and analyzed on a population level, with engagement/use defined as active therapeutic use in a given week.

Figure 2. Engagement by prescription week from an observational analysis of real world individuals (n=3,114) prescribed reSET-O.





Figure 3. Real World Engagement with Mental Health Apps Other Than reSET-O

Gradual reduction in use is observed (Figure 2) rather than exponential declines in use reported for real world use of mental health apps (Figure 3, <u>Baumel, 2019</u>), as well as real world use of buprenorphine (47.5% adherence at 6 months and 37% adherence after 12 months) (<u>Mark, 2020; Ronquest, 2018</u>).



Figure 4. Abstinence in weeks 9-12 under different imputation methods.

Substance use was evaluated as a composite of patient self-reports recorded in the reSET-O app as well as with urine drug screens recorded by clinicians. Consistent with prior real-world and observational studies, 33 missing abstinence data for any given week was imputed in two different ways: the first approach was missing data excluded, where weeks with no outcomes were excluded, and the second approach was missing data removed, where patients without any self-reports or negative urine drug screens during the last 4 weeks were dropped from

the analysis population. Note: Although GEE analysis is the preferred method of evaluating likelihood of abstinence, it assumes data are missing at random, a situation not applicable to the real-world data set.

Figure 5. Comparison of treatment retention (defined as last face-to-face contact) in the reSET-O pivotal study (FDA, 2019) with reSET-O retention (defined as active therapeutic use) from a real world dataset.



Figure 6. Responder analysis.



Comparison of responders from the reSET-O pivotal study and reSET-O real world data set. Responders are defined as individuals with $\ge 80\%$ negative UDS or self-report. This definition of responder is a standard for the field and is consistent with FDA guidance for evaluating the efficacy of treatments for OUD (<u>Haight, 2019;</u> Lofwall, 2018; FDA)





3 Waves of the Rise in Opioid Overdose Deaths



October 15, 2020

Steven D. Pearson, MD, MSc President Institute for Clinical and Economic Review Two Liberty Square, Ninth Floor Boston, MA 02109 *Via e-mail: <u>publiccomments@icer-review.org</u>*

RE: Public Comment for Opioids: Digital Therapeutics

Dear Dr. Pearson:

I am writing in response to the public comment period for ICER's Draft Evidence Report "Digital Therapeutics as an Adjunct to Medication Assisted Therapy for Opioid Use Disorder."ⁱ As the report cites, the addiction crisis continues to kill Americans at alarming rates, reaching approximately 70,000 deaths in 2017 of which approximately 50,000 were from opioids. There is strong evidence that COVID-19 is exacerbating this already dire situation as suspected drug overdoses nationally rose 18 percent in March, 29 percent in April and 42 percent in May.ⁱⁱ Amidst this crisis, we welcome the evaluation ICER has given of the effectiveness of digital therapeutics for Opioid Use Disorder (OUD). This letter aims to assist you in this effort by providing comment on substantive and contextual issues relating to this crisis.

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.^{iiiiv} Methadone and buprenorphine treatment have also been associated with reduced risk of overdose death.^v

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.

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."^{vi} 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.^{vii} 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.^{viii} 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.^{ix}

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."^x Analysis of efficacy of cognitive behavioral therapy have also noted the difficulty of having double-blind trials for behavioral treatments.^{xi}

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.

Conclusion

The ICER report is an important contribution to addressing the addiction crisis. Rigorous evaluation enables investment and alignment of coverage for effective treatments. However, in the complex and dire circumstances that encompass the addiction crisis, we hope that you will consider these comments as additional



context for your work. It is important to recognize the unique challenges to developing effective behavioral treatments. Doing so will help preserve the incentives for innovation and avoid additional costs and health care expenses.

Thank you for your kind attention to these comments. Please let me know if we can be of further assistance.

Kevin Roy

Chief Public Policy Officer

¹ Tice JA, Whittington M, Fluetsch N, Zapata LV, Mendola N, Chapman R, Campbell J, Pearson SD, Bradt P. Digital Therapeutics as an Adjunct to Medication Assisted Therapy for Opioid Use Disorder; Draft Evidence Report. Institute for Clinical and Economic Review, September 17, 2020.

ⁱⁱ Shaw, Gina. Special Report: COVID-19 Reignites Substance Use Epidemic. *Emergency Medicine News*: <u>September 2020 - Volume</u> <u>42 - Issue 9 - p 26-27</u>.

ⁱⁱⁱ Krupitsky, E., Nunes, E. V., Ling, W., Illeperuma, A., Gastfriend, D. R., & Silverman, B. L. (2011, April 30). Injectable extendedrelease naltrexone for opioid dependence: A double-blind, placebo-controlled, multicentre randomised trial. Lancet, 377(9776), 1506– 1513.

 ^{iv} Lee, J. D., Friedmann, P. D., Kinlock, T. W., Nunes, E. V., Boney, T. Y., Hoskinson, R. A., Jr., ... O'Brien, C. P. (2016). Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. New England Journal of Medicine, 374(13), 1232–1242.
 ^v Degenhardt, L., Randall, D., Hall, W., Law, M., Butler, T., & Burns, L. (2009). Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: Risk factors and lives saved. Drug and Alcohol Dependence, 105(1–2), 9–15.

^{vi} Tice JA, Whittington M, Fluetsch N, Zapata LV, Mendola N, Chapman R, Campbell J, Pearson SD, Bradt P. Digital Therapeutics as an Adjunct to Medication Assisted Therapy for Opioid Use Disorder; Draft Evidence Report. Institute for Clinical and Economic Review, September 17, 2020, p. 38.

vii Stoddard Davenport, MPH, T.J. Gray, FSA, MAAA, Steve Melek, FSA, MAAA. How do individuals with behavioral health conditions contribute to physical and total healthcare spending? Milliman Research Report. Commissioned on behalf of The Path Forward for Mental Health and Substance Use, August 13, 2020, p. 1.

^{ix} Tice JA, Whittington M, Fluetsch N, Zapata LV, Mendola N, Chapman R, Campbell J, Pearson SD, Bradt P. Digital Therapeutics as an Adjunct to Medication Assisted Therapy for Opioid Use Disorder; Draft Evidence Report. Institute for Clinical and Economic Review, September 17, 2020, p. 43.

^x Jeanetta C Rains 1, Donald B Penzien. Behavioral research and the double-blind placebo-controlled methodology: challenges in applying the biomedical standard to behavioral headache research. Headache. 2005 May;45(5):479-86.

^{xi} <u>https://www.psychiatrictimes.com/view/cognitive-behavioral-therapy-escape-binds-tight-methodology</u>



October 15, 2020

Institute for Clinical and Economic Review Email: <u>publiccomments@icer-review.org</u>

To Whom It May Concern:

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.

Please contact me if you require any additional information.

Sincerely,

Warren K. Bickel, Ph.D.

Virginia Tech Carilion Professor of Behavioral Health Research Director, Center for Transformative Research on Health Behaviors Director, Addiction Recovery Research Center Fralin Biomedical Research Institute at VTC Professor of Psychology, Neuroscience, and Health Sciences, Virginia Tech Professor of Psychiatry, Virginia Tech Carilion School of Medicine