ICER Review of Digital Therapeutics for OUD

Blue Shield of California comments:

We would recommend adding elements that address benefits to the physician experience to your review. Provider adoption and connection/disconnection to office workflow seems to be a challenge area.

Table 1.1 Potential Other Benefits or Disadvantages and Contextual Considerations

(Adding to the table in the document)

1 (suggests lower value)	2 (intermediate)	3 (Suggests higher value)
The intervention offers no special benefits to improving provider well-being (catch-all for professional fulfillment, work-life integration, burnout, stress, fatigue)		The intervention offers special benefits to improving provider well-being (catch-all for professional fulfillment, work-life integration, burnout, stress, fatigue)
The intervention offers little to no reduction in provider workload and job demands		The intervention offers substantial reduction in provider workload and job demands
The intervention offers little to no subjective improvement in provider experience in caring for their patients.		The intervention offers substantial subjective improvement in provider experience in caring for their patients.

*Drawn from the paper by Shanafelt and Noseworthy 2017
https://pubmed.ncbi.nlm.nih.gov/27871627/

Public Comment on ICER Review of Digital Therapeutics for OUD

In the draft scoping document, a number of smartphone apps/interventions are listed for evaluation, such as reSET-O and WeConnect. CHESS' Connections App was not listed, perhaps because the project team didn't learn of the app and CHESS Health until after the draft scoping document was published.

We're hopeful the committee has already elected to add the Connections App/eRecovery to the list of interventions to be studied. Nevertheless, we're using this public comment to reiterate some details of our relevant background and extensive experience to make the case for the inclusion of the Connections App in your review:

- The Connections App/eRecovery solution is the commercial version of the ACHESS smartphone app developed by Dave Gustafson, PhD, of the University of Wisconsin (Dr. Gustafson is a co-founder of CHESS Health). With the support of the NIH, ACHESS was the first evidence-based smartphone app for substance use disorder and has been the subject of multiple clinical trials with demonstrated efficacy in increasing sobriety, reducing re-hospitalization, increasing treatment adherence, and other positive outcomes.

- Most recently, a 2018 study measured the impact on treatment adherence among impoverished women with opioid use disorder in Southeastern Kentucky. Compared to a cohort that didn't have the app, the women with the app stayed in treatment 56% longer and benefitted from twice as many treatment/recovery services. Here's a link to the article.

- In 2019, CHESS dramatically enhanced the base app functionality (the original ACHESS functionality) by integrating into the app the CBT4CBT programs developed by Kathleen Carroll, PhD, of Yale University. She's an expert in cognitive behavioral therapy (CBT) and, over the course of ten years, developed, refined and studied a set of online programs for patients to learn/practice recovery skills which she named CBT4CBT (stands for computer-based training for cognitive behavioral therapy).

- The CBT4CBT program is a 'digital therapeutic' similar to reSET-O (both teach recovery skills using CBT). CBT4CBT has demonstrated more durable benefits (measured in reduced substance use), even without contingency management. See www.chess.health/evidence or http://www.cbt4cbt.com/evidence/ for published evidence of the effectiveness of the CBT4CBT programs.

- While CBT4CBT was first tested for individuals with alcohol use disorder (AUD), Dr. Carroll has developed and tested a version specifically for patients with OUD being treated with buprenorphine. A preliminary clinical trial of this version, conducted in a

primary care setting, demonstrated a significant difference in effectiveness (measured in negative urine screens). Here's a link to the results of the preliminary clinical trial. Dr. Carroll is now conducting a larger trial of this same version, also in a primary care setting.

- **Thus, the Connections App from CHESS Health is the combination of TWO evidence-based programs, ACHESS and CBT4CBT**. We don't believe there's another digital solution with the breadth of functionality (treatment and recovery support + digital therapy) as the Connections App. We'll soon be adding telehealth/video chat and gamification/rewards into the app functionality.

- Other experts and researchers in the treatment of opioid use disorder (OUD) have also recognized the unique (and proven) features of the Connections App. Recently, the Connections App was selected for inclusion in a four year, 20-site, 1600 patient clinical trial conducted via the Clinical Trails Network, led by researchers from NYU, Columbia, and Harvard (due to COVID, the trial has been delayed until October). In this study, the Connections App will be given to OUD patients who have stabilized on medication-assisted treatment (MAT) and whose use of MAT will be tapered down during the trial. We were selected for this important trial based on our outcomes history and real-world deployment experience.

- While we have a lot of experience with clinical trials, most of our implementations are, in fact, 'real-world'. Most recently, the State of West Virginia contracted with CHESS to offer the Connections App with eTherapy/CBT4CBT to all West Virginians with substance use disorder, both directly to individuals and through as many as 90 providers. CHESS has the eRecovery solution and Connections App live within 6 days after the contract was signed and, eight weeks later, have 20 providers either live, using the Connections App with their patients, or in various stages of implementation. We have a similar, large, multi-provider implementation in Oklahoma where thousands of patients have used the Connections App, across a variety of levels of care including intensive OP, medication-assisted treatment (MAT), and drug treatment court programs.

In closing, we believe the inclusion of the Connections App in ICER's review of digital therapeutics for opioid use disorder (OUD) is critical. Among evidence-based apps for substance use disorder (SUD), it is the most widely-utilized. The conclusions of the review will be more complete and more useful with the inclusion of the Connections App.

Thank you,

Hans P. Morefield
CEO
CHESS Health

Dartmouth
GEISEL SCHOOL OF MEDICINE

June 1, 2020

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

Submitted via email: publiccomments@icer-review.org

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) is conducting a review of the clinical and economic value of digital therapeutics provided along with medication treatment for opioid use disorder (OUD). This is a significant and timely topic, and ICER's report based on a fair and balanced assessment of the relevant scientific evidence on this topic promises to be highly impactful. I am writing to provide recommendations regarding this planned ICER review.

I am the Director of the Center for Technology and Behavioral Health [www.c4tbh.org] within the Geisel School of Medicine at Dartmouth College. This research center is focused on using science to inform the development, evaluation, and implementation of digital therapeutics in the treatment of substance use disorders (SUDs). Our Center is the only "Center of Excellence" funded by the U.S. National Institute on Drug Abuse (NIDA) focused on digital therapeutics for SUDs. And, I have personally led a line of research for over two decades developing and evaluating digital therapeutics for SUDs, including several NIDA-funded randomized, clinical trials focused on evaluating the research version of the digital therapeutic that is now reSET-O® in adults receiving medication treatment for OUD. I am also the Director of the NIDA-funded Northeast Node of the National Drug Abuse Treatment Clinical Trials Network which leads national multi-site, rigorous clinical trials evaluating a wide variety of treatments for SUDs, with a large focus on the treatment of OUD. My comments thus reflect my career-long experience seeking to identify the most scientifically-validated treatments for SUDs as well as optimal strategies to scale-up access to effective SUD treatments to the large population suffering from SUDs. Note that I am a consultant with Pear Therapeutics which has commercialized reSET-O®, but I am not receiving any compensation from Pear Therapeutics for preparing this letter to ICER.

I provide my comments within the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework ICER plans to use in its review.

1. **Population:** I support ICER's draft plan to focus on adults who are seeking treatment from an OUD. Given that it is well-documented that medications are an essential and life-saving component of treatment for OUD and that OUD is a chronic, relapsing disorder, I recommend ICER focus on outcomes observed while adults with OUD are receiving ongoing maintenance medication treatment for OUD (not a medication taper protocol) with an FDA-approved medication for the treatment of OUD.

   Additionally, given that digital therapeutics refer to software programs to prevent, manage or treat a medical disorder or disease, I recommend focusing on a population that has access to a device on which they can use such software (such as a smartphone or tablet). These results would be highly generalizable, given that all over the world, many individuals either have, or are rapidly getting access to, smartphones

(including populations with SUDs). Additionally, a key benefit of digital therapeutics is that they provide therapeutic support as individuals live their daily lives (like a "clinician in your pocket"). Thus, individuals need mobile devices to benefit from these digital treatments.

2. **Intervention:** I recommend that ICER is precise in how it defines a digital therapeutic. As noted above, digital therapeutics refer to software programs to prevent, manage or treat a medical disorder or disease. They are not wellness apps. And they are not telehealth which provides remote access to a clinician. Rather, they provide clinical-grade, software-delivered therapeutic interventions.

   Additionally, I recommend that ICER focus on digital therapeutics that have been cleared by the FDA as "prescription digital therapeutics". The launch of "prescription digital therapeutics" as a new therapeutic class that receives FDA clearance was transformative for the field of digital health. In the two decades that I have worked in this field, I have seen an enormous surge in interest of clinicians and healthcare systems that want to provide digital therapeutics to their patients to extend the reach and impact of the therapeutic resources they can offer to their patients. This demand is now greater than ever given the need to expand the reach of effective treatments for OUD as a result of the U.S. opioid epidemic, which is further compounded by a marked increase in demand for remote treatments as a result of the COVID-19 global pandemic. However, many have historically found it very difficult to navigate the mobile app space to know which are clinically-validated digital treatments. Now, with the introduction of "prescription digital therapeutics", healthcare providers can be assured that those that have been vetted by the FDA reflect clinically-validated treatments that are effective in the prevention, management, or treatment of a medical disorder or disease. Additionally and importantly, a digital therapeutic that receives a designation of a "prescription digital therapeutic" has been required to demonstrate considerable rigor in software development, including compliance with good manufacturing practices and state-of-the-science privacy and security practices. These issues are particularly important when offering treatment for the highly sensitive topic of SUDs.

3. **Comparators:** I recommend that ICER's evaluation include only rigorous randomized, clinical trials that compare a digital therapeutic to a "treatment as usual" condition and/or an additional active intervention control condition. Such experimental research designs are essential to allow for causal inference about the effectiveness of the intervention under study, thus providing greater confidence in conclusions that are drawn from the research. And, in ICER's interpretation of results, it is important to recognize that in many controlled trials, "treatment as usual" conditions often do not reflect the standard of treatment offered in real-world treatment settings but rather often exceed that level of care. This is due to many factors, including that treatment sites that agree to participate in research trials may have a different level of commitment to best practices or reflect academic medical settings with a higher level of resources and capacity than some community-based systems of care. Additionally, the very process of measuring "treatment as usual" may enhance the quality and scope of care that is offered. Thus, the magnitude of the differences in outcomes observed across experimental conditions in a randomized trial may actually underestimate the magnitude of the benefit that would be observed when digital therapeutics are offered in real world systems of care.

4. **Outcomes:** I recommend that ICER's evaluation focus on outcomes of greatest value to patients and clinicians with a clear recognition of the chronic, relapsing nature of OUD. Specifically, it is well-documented that retention in treatment for OUD is a strong predictor on long-term outcomes (with greater retention predictive of better outcomes, including reduced levels of mortality and morbidity and enhanced patient functional outcomes). Thus, I recommend that retention is one of the key outcomes assessed in ICER's evaluation.

   Additionally, there is strong consensus in the scientific, clinical and funding communities that abstinence is a critical outcome to assess (as increasing drug abstinence is also strongly associated with marked reductions in mortality and morbidity and improvement in functional outcomes).

I further recommend that total abstinence data in a clinical trial are considered as well as abstinence at the end of a trial. Although we know OUD is highly treatable, it is not rapidly resolved with brief interventions. Rather, effective medications are needed to stabilize the brain neurochemistry of an individual with an OUD while intensive behavioral treatments are needed to help individuals learn new skills to understand and disrupt their self-defeating patterns of drug-taking behavior. This behavioral repertoire is not established overnight but requires intensive treatment. Thus, examining outcomes after at least a couple of months of treatment is critical.

Additionally, although patient self-report of drug use provides valuable data in clinical trials, I recommend ICER ensure that objective measurement of drug use is included (as evidenced by state-of-the-science urinalysis testing) to enhance confidence in conclusions and reduce response bias that may result from reliance on self-report data alone.

Finally, when evaluating economic outcomes, I strongly suggest that ICER consider that a prescription digital therapeutic is not a simple mobile app. Rather, it packages an entire model of care – that is delivered with fidelity and in accordance with state-of-the-science practices –into a unified, seamless digital delivery system. Indeed, the best practices that are offered by the reSET-O® FDA-cleared prescription digital therapeutic for OUD (e.g., gold-standard community-reinforcement approach to behavior therapy delivered to patients; motivational incentives to promote the initiation and maintenance of behavior change) are often not provided by most OUD systems of care in the U.S. And further, the clinician workforce for treating OUD has been insufficient to meet the population-level need. Thus, prescription digital therapeutics for OUD can offer gold-standard treatment that can complement the work of our clinician workforce and can scale to a population level.

5. **Timing:** I support ICER's draft plan to evaluate evidence from studies of varying follow-up durations as long as the studies meet the criteria outlined above.

6. **Settings:** I support ICER's draft plan to primarily evaluate data in outpatient and office-based settings. As noted above, it is important to evaluate data in populations that have access to devices on which they can engage with a digital therapeutic and this is unlikely or impossible in some inpatient settings and most (if not all) prisons/jails.

In closing, I thank ICER for the leadership role it is taking in conducting this important evaluation, and I appreciate the opportunity to share my perspective as ICER embarks on this important review.

Please feel free to contact me should you need any additional information (lisa.a.marsch@dartmouth.edu; 603-646-7000).

Sincerely,

Lisa A. Marsch, PhD
Andrew G. Wallace Professor
Department of Psychiatry
Director, Center for Technology and Behavioral Health [www.c4tbh.org]
Director, Northeast Node National Drug Abuse Treatment Clinical Trials Network
Dartmouth College

The Frost Medical Group LLC
10 East 6th Ave, Ste 200
Conshohocken, PA 19428
Phone: 610-567-0088
Fax: 610-567-0881

June 1, 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: Michael P. Frost, MD, FACP, FASAM
President/Medical Director, The Frost Medical Group, LLC
10 East 6th Ave, Suite 200
Conshohocken, PA 19428

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

Dear Dr. Pearson,

As a practicing addiction medicine specialist with considerable experience in the use of digital therapeutics, I am pleased to have the opportunity to comment on ICER's review of digital therapeutics, specifically reSET-O developed by Pear Therapeutics.

When making comparisons of digital therapeutic platforms it is important to separate prescription digital therapeutics (PDT's) from Health and Wellness apps or other less rigorous, non-healthcare provider managed platforms. Since reSET-O is the only such FDA-authorized device for the treatment of OUD, which offers validated, evidence-based cognitive behavioral therapy (CBT) modules using a Community Reinforcement Approach (CRA) along with Contingency Management, the only suitable comparison is to live, in-person addiction counseling/therapy.

Since reSET-O has undergone scrutiny and validation via an FDA-authorization pathway, an adequate body of evidence showing therapeutic effectiveness and safety has been established and reviewed. This cannot be said for any other non-FDA authorization apps or platforms. Outcomes data for determining efficacy, namely treatment retention and abstinence from opioids at weeks 9-12 should be used for comparison as these endpoints were established as part of the FDA-

authorization process. Other apps and platforms lack the rigor of data to appropriately determine efficacy and in most cases have not undergone a process to confirm that they do not pose a risk to the end user.

Another point of consideration needs to be the total cost and capacity to provide Contingency Management (CI) as part of reSET-O. CI is a validated, evidence-based therapeutic approach for the treatment of substance use disorders. In a live clinical setting, the cost of staffing to oversee the program as well as the cost of rewards are incurred by the practitioner, whereas those operational costs are incorporated into the total cost of reSET-O. Additionally, despite CI being considered a standard of care intervention, there are not enough trained practitioners to be able to provide CI to all the patients currently in need of treatment. reSET-O allows for such evidence-based treatment to be accessed by large numbers of patients anytime and anywhere it is needed.

Since reSET-O gives the opportunity for portability, convenience and anytime access based programs not equivalent.

A final point for consideration is that reSET-O offers the opportunity and encourages provider/clinician management of the user's interaction with the platform. It has been demonstrated that the ability of the provider/clinician to observe and interact with the program through the clinician dashboard, supports user engagement and retention with the treatment. Devices or apps that do not have the capability for the same level of provider interaction should not be compared with reSET-O.

Having used reSET-O extensively with my patients for more than a year, the response from users has been decidedly positive. Many patients report that through the interaction with the modules, they are able to obtain a helpful perspective on their illness and develop tools for managing the behavioral and thought components of OUD. Being able to track cravings, opioid use and medication adherence has given several patients a way to recognize patterns of use and to prevent relapse through better insight.

reSET-O, as a unique therapeutic tool in the treatment of OUD, deserves to have its value assessed as the stand-alone, first of its kind platform that it is.

Thank you for the opportunity to provide comment.

Sincerely,

Michael P. Frost, MD, FACP, FASAM
President, The Frost Medical Group, LLC.

May 27, 2020

Institute for Clinical and Economic Review

Joe Glass, PhD, MSW, LICSW
Kaiser Permanente Washington Health Research Institute
1730 Minor Avenue, Suite 1600, Seattle, WA 98101

Re: Digital Therapeutics with Medication Assisted Treatment for Opioid Use Disorder: Effectiveness and Value

Dear Institute for Clinical and Economic Review Committee,

I am writing to submit a public comment for your forthcoming review "Digital Therapeutics with Medication Assisted Treatment for Opioid Use Disorder: Effectiveness and Value." Your review will undoubtably serve as an excellent resource for the field.

By way of introduction, I am an addiction health services researcher who studies the integration of addiction care into healthcare systems. Most of my research focuses on the use of digital therapeutics and other substance use disorders interventions in healthcare. I am the Principle Investigator of two grants from the National Institutes of Health to study the integration of digital therapeutics for substance use disorders in real-world healthcare. One of these grants is a career award from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to study digital therapeutics for alcohol use disorders. The other is a large research project grant from National Institute on Drug Abuse (NIDA) to study the implementation and effectiveness of reSET and reSET-O in primary care. I have been involved in the direct study of three digital therapeutics, including reSET/reSET-O, A-CHESS, and Square2 Laddr. I would like to acknowledge that Pear Therapeutics plans to provide reSET/reSET-O for free to Kaiser Permanente during a small quality improvement study that precedes the NIDA-funded trial. The views in this letter are my own opinion and do not represent the official views of National Institutes of Health or Kaiser Permanente.

Your review has clear implications for the field, and I appreciate the opportunity to provide input. I would like to provide several brief observations and comments about the scoping document.

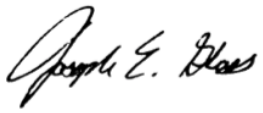
1) The review should carefully assess the scientific literature on each product. Here are several questions to consider: To what extent have the products been subjected to rigorous independent (arms-length) scientific evaluations? By rigor, the level of evidence would include an adequately powered randomized controlled trial beyond the pilot stage. It is also critical to consider the type of outcomes that have been studied and whether they are viewed by the scientific community as clinically important endpoints.
2) The review should consider that the products being evaluated are extremely diverse. To my knowledge, many of the products address different healthcare gaps. Some products will be designed for recovery support among people who are currently engaged in

evidence-based treatment programs. Other products are designed as evidence-based treatments themselves. This has important implications because health systems will need to select a product that matches the care gap or a care need that they current face. In this regard, I think it is excellent that your review will consider therapeutics that can be used in “various treatment settings”. However, please note that I do not think that a review of digital therapeutics can ultimately compare products head-to-head. The value of a digital therapeutic is highly dependent on a health system’s current resources and needs.

3) Regarding the domain of “timing” set forth in the review, the scoping document states that “Evidence on intervention effectiveness and harms will be derived from studies of any follow-up Duration.” It is important to note that patients often stop using app-based digital therapeutics within just a few weeks. Assessment of outcomes too early in the treatment process could potentially yield findings that do not persist.
4) I would also recommend that the committee consider evidence on patients’ engagement in the digital apps. Do patients tend to use the apps over time, or do they stop using them early? How engaged are they?

Thank you for taking the time to lead this important project. It has utmost relevance to society. Please do not hesitate to contact me if you find that you need input on this review.

Sincerely,



Joe Glass, PhD, MSW, LICSW
Associate Investigator
Kaiser Permanente Washington Health Research Institute

Kaiser Permanente
Phone: 206-287-4266
*E-mail: joseph.e.glass@kp.org FAX 206-287-2871
Metropolitan Park East, 1730 Minor Ave, Suite 1600, Seattle, WA 98101-1466

Memo 6/1/20

To: ICER

From: Edward Nunes MD and Aimee Campbell PhD

Re: Comment on ICER's Review of Digital Therapeutics with Medication Assisted Treatment for Opioid Use Disorder (OUD)

Dear Colleagues at ICER,

We appreciate the opportunity to comment on ICER's draft scope entitled "Digital Therapeutics with Medication Assisted Treatment for Opioid Use Disorder: Effectiveness and Value." My colleague Dr. Aimee Campbell, and myself, are treatment researchers based at New York State Psychiatric Institute and Columbia University Medical Center. Dr. Campbell is a social worker whose career focuses on research on treatment and implementation of treatments for substance use and co-occurring mental and medical health disorders. I am a psychiatrist, Board certified in both Addiction Psychiatry and Addiction Medicine and have devoted my career to research on treatments for substance use disorders, including a number of studies on both medication and behavioral treatments for opioid use disorders.

Dr. Campbell and I collaborated on leadership of a major multisite clinical trial (Campbell, Nunes et al., American Journal of Psychiatry 2014) conducted in the NIDA funded Clinical Trials Network, that tested to academic forerunner of reSET, the Therapeutic Education System (TES), compared to treatment as usual, in a mixed sample of patients with substance use disorders. We found that TES, when added to treatment as usual TAU) at outpatient addiction treatment programs increased the likelihood of abstinence from substances, particularly in patients who had positive urine toxicology for substances at the outset of the trial, and increased retention in treatment compared to TAU. Our trial was presented to the FDA as the pivotal trial supporting the efficacy of reSET. We have subsequently consulted without compensation to Pear Therapeutics to advise them on adapting reSET for marketing as a digital therapeutic, and we are also studying reSET and reSET-O in subsequent NIDA-funded studies that are currently ongoing or preparing to launch. We are broadly familiar with the field of evidence from clinical trials supporting technology-based and digital therapeutics for substance use disorders.

We would like to make several points for you to consider regarding your project to evaluate the effectiveness and economic value of digital therapeutics. First, we would caution that there is a potential 'apples and oranges' type problem in the interventions that you may plan to review. Examining the list of examples of interventions that you plan to review several of them (e.g. PursueCare and Manage Addiction Lifeline) appear to be tele-medicine providers, basically providing in person medication assisted treatment for opioid use disorder and counseling over tele- or video-conference. We do not view such providers as being in the same category as a digital therapeutic, which is an app that automatically provides behavioral therapeutic content without the need for clinician intervention, thus serving in effects as a clinician-extender. This clinician extender function may be uniquely able to

deliver behavioral treatment to support medication adherence and recovery. Such behavioral therapy delivered by expert clinicians is not commonly available across the treatments system.

Second, while a variety of digital therapeutic apps may make claims to effectiveness, relatively few of these claims are supported by any kind of rigorous treatment research, clinical trials or otherwise. We would refer you to an authoritative literature review, conducted by Brian Kiluk and Kathleen Carroll and her group (American Journal of Psychiatry 2011), which highlighted the very limited empirical evidence supporting most apps. Carroll and Roger Weiss (American Journal of Psychiatry 2017) more recently reviewed behavioral treatments of any kind, apps or otherwise, for supporting buprenorphine treatment for opioid use disorder, and similarly found limited empirical evidence, the one exception being behavioral treatments that provide contingency management in combination of cognitive behavioral counseling. Several of the trials supporting this conclusion tested Therapeutic Education System (TES), which delivers contingency management plus community-reinforcement type counseling entirely through the app.

A third point is to focus on how a digital therapeutic manages to pay for contingency management. Contingency management is an effective intervention for substance use disorders with extensive supportive evidence from clinical trials, but a major barrier to its implementation in community-based treatment has always been who will pay for the incentives. In virtually all those impressive clinical trials, the contingent incentives were paid for by research grants. Community based treatment programs don't have the funds to finance such incentives. reSET for example has solved this problem by folding the costs of the incentives into the insurance payment, so that the incentives are available as long as the third party covers provision of reSET. To extent to which other digitial therapeutics have addressed this problem should be an important consideration, which has to do with feasibility and sustainability.

A final point is that retention on medication treatment for opioid use disorder, along with abstinence from opioids and other drugs, are really the key clinical outcomes to look for in clinical trials in this field. Medication treatments for OUD are highly effective, and outcome is poor without them, so a key contribution of digital therapeutics is their potential to support adherence and prevent dropout from treatment.

We hope this input is helpful to you in developing your effectiveness analysis.

Sincerely,

Edward V Nunes MD
Professor of Psychiatry
Columbia University Irving Medical Center

Aimee N Campbell MSW, PhD
Associate Professor of Social Work in Psychiatry
Columbia University Irving Medical Center

June 1, 2020

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

Submitted Electronically via: publiccomments@icer-review.org

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

Dear Dr. Pearson,

Pear Therapeutics, Inc. ("Pear" or "we") appreciates the opportunity to provide comments on ICER's draft scope entitled "Digital Therapeutics with Medication Assisted Treatment for Opioid Use Disorder: Effectiveness and Value." Below, we offer key recommendations and rationale to enhance this review's meaningfulness to the intended audiences and stakeholders.

PICOTS Framework

1. **Recommendation: Evaluate reSET-O® only in populations and settings in which patients have access to a smartphone/tablet**

reSET-O is an FDA-cleared 84-day Prescription Digital Therapeutic (PDT) for OUD intended to increase retention of patients in outpatient treatment by providing neurobehavioral therapy based on the community reinforcement approach (CRA), an intensive form of cognitive behavioral therapy (CBT) validated for substance use disorder (SUD)/OUD, along with contingency management (CM) and fluency training (FT - to enhance learning). The reSET-O therapeutic is used as an adjunct to outpatient treatment that includes transmucosal buprenorphine. The reSET-O software uses the patient's smartphone or tablet to deliver therapeutic content on demand. Given that some settings, such as prisons and detoxification programs do not allow patients to use their smartphones or tablets, patients in these settings will likely not have access to reSET-O. Additionally, including only those OUD patients treated with buprenorphine with access to a smartphone/tablet will aid in more accurately estimating budget impact of reSET-O.

2. **Recommendation: Evaluate only interventions that meet the definition of an FDA-cleared prescription digital therapeutic and satisfy guidelines for reporting OUD-specific outcome measures.**

FDA-Cleared Prescription Digital Therapeutics

Digital Health encompasses a broad category of health and wellness-related products, each with a range of functions that typically do not require any clinical evidence or regulatory oversight. Digital Therapeutics constitute a sub-category of digital health and "deliver evidence-based therapeutic interventions to patients 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". The digital therapeutics category does not

include digital health products that seek solely to provide information (e.g., consumer health information), to collect or transmit data (e.g., fitness tracking), or to provide a platform for patients to connect with clinicians or other patients (e.g., telemedicine, social networks). Digital therapeutics must adhere to industry-adopted core principles and best practices. They must be subject to adequately powered, well-controlled clinical trial(s) establishing efficacy and safety in an appropriate target population using disease-specific clinically validated and standardized endpoints. They should also be compliant to regulatory oversight product claims, labeling, advertising regulations and good manufacturing practices (GMP). Depending on the specific goals and functions of a product, different levels of evidence and regulatory oversight are required. Currently numerous digital health products are in non-compliance with legal and FDA regulatory requirements such as advertising and promotional content, including many which contain clinical elements such as recovery coaches, drug testing support, and biometric data processing, leading to potentially unsubstantiated claims or unproven safety. This is of particular concern in OUD, where false or misleading information could lead to unintended negative consequences, particularly in a patient population with high prevalence of psychiatric comorbidities and high rates of relapse and potential lethal overdose.

Prescription digital therapeutics, on the other hand, are FDA-cleared, require the highest level of evidence (both safety and efficacy), quality management compliance, assure verification and validation that the software works as designed, and can be accessed only via a prescription. Once a PDT is approved by the FDA, PDT manufacturers must ensure that advertising and promotional materials, including content or claims on a PDT website, are accurate and supported with evidence in accordance with FDA regulations and guidance.

As defined in the FDA Code of Federal Regulations (CFR) Title 21 (21CFR882.5801), "a computerized behavioral therapy device for psychiatric disorders is a Class II, prescription only, device (product code PWE) intended to provide a computerized version of condition-specific behavioral therapy as an adjunct to clinician supervised outpatient treatment to patients with psychiatric conditions". The reSET-O therapeutic, which fits this CFR criteria while ensuring good clinical practices (GCP) and good manufacturing practices (GMP), effectively and safely delivers two evidence-based behavioral therapies, CRA and CM. In summary, this is why the review should focus only on reSET-O patients treated with buprenorphine, according to the FDA's label for reSET-O.

OUD Outcomes

The endpoints measured for reSET-O in its clinical trial program are compliant with guidelines for measuring effectiveness of Medication-Assisted Treatments (MAT) published by the FDA and bodies such as the Substance Abuse and Mental Health Services Administration (SAMHSA). The FDA requires the measurement of drug use patterns resulting in abstinence as measured by urine drug screening (UDS) or self-reporting. Additionally, the FDA recommends measuring treatment retention, though not as a stand-alone endpoint, but in addition to abstinence. SAMHSA and the American Society of Addiction Medicine (ASAM) recommend measuring abstinence and retention in OUD. When measuring abstinence using UDS, it is recommended that this be done at frequent intervals, at least once a week, during the initial treatment period.

Primary outcome measures in reSET-O's clinical trial program include the measurement of illicit opioid use during weeks 9-12, a standard that has been used previously and one that the National Institute on Drug Abuse (NIDA) recommends and FDA previously accepted. Illicit opioid use, including abstinence, was measured by thrice-weekly UDS samples and was patient-reported for both the reSET-O + Treatment as Usual (TAU) and the TAU only arm. Abstinence was measured after accounting for treatment retention, which was defined by whether a patient continued background TAU. Retention was measured throughout the trial period in both treatment arms.

Including products that do not satisfy the criteria for being categorized as a digital therapeutic and ones that do not measure standardized OUD-specific clinical endpoints such as illicit opioid use (including abstinence) and retention may hinder the evaluation and interpretation of scientific evidence, and create clinician and payer confusion on this important topic.

3. **Recommendation: The economic costs of the implementation of CM should be captured in the economic evaluation.**

The implementation of best supportive care with MAT requires additional time and resources. Implementing and administering CM alone in a practice costs approximately $315 (inflated to 2020 US dollars) per patient per 12 weeks. These costs are directly offset with a prescription of reSET-O, as the financial incentives provided to patients as part of CM using reSET-O are incorporated into the price of reSET-O.

Other Benefits and Contextual Considerations

With reSET-O, practitioners and providers have access to patient-reported health status data, particularly on substance craving, and self-reported buprenorphine use which aids in informing the appropriate clinical management of these patients. Another key benefit of reSET-O includes enabling patients to receive continued treatment support through CBT and CM beyond physician's office outpatient hours, thus enabling the physician to focus the patient visit on other important aspects of care. By adopting a neurobehavioral therapy delivery model that incorporates reSET-O, care teams (including those using telehealth solutions) may be able to more efficiently allocate personnel, time, and resources towards behavioral treatment (such as counseling), reinforcing positive behaviors, improving the quality of care, and possibly even to providing care for a greater number of patients. This is especially pertinent in the current environment of the Coronavirus Disease 2019 (COVID-19) pandemic, where according to a recent FDA guidance, availability of PDTs such as reSET-O can increase access to patient care during social distancing, while also reducing the burden on health care facilities.

Pear appreciates ICER's consideration of the input provided, and we look forward to collaborating with ICER on this review.

Sincerely,

Michael Pace
VP, Market Access, Value & Evidence | **Pear Therapeutics**
C: 781.277.1660 | O: 617.934.1610
michael.pace@peartherapeutics.com | www.peartherapeutics.com