Digital Therapeutics as an Adjunct to Medication Assisted Therapy for Opioid Use Disorder

Draft Evidence Report

September 17, 2020

Prepared for

AUTHORS:

ICER Staff and Consultants
Jeffrey A. Tice, MD Professor of Medicine University of California, San Francisco
Melanie Whittington, PhD* Associate Director of Health Economics
Noemi Fluetsch, MPH Research Assistant, HEOR
Lorenzo Villa Zapata, PhD, PharmD, Post-doctoral fellow University of Colorado Anschutz Medical Center
Nicholas Mendola, MPH, PhD student University of Colorado Anschutz Medical Center
Rick Chapman, PhD, MS Director of Health Economics
Jonathan Campbell, PhD* Senior Vice President for Health Economics
Steven D. Pearson, MD, MSc President
Pamela Bradt, MD, MPH Chief Scientific Officer

* Dr. Whittington served as the lead health economist. Drs. Whittington and Campbell transitioned during the time of this review from prior roles as academic faculty to full-time ICER employees.

DATE OF PUBLICATION: September 17, 2020

How to Cite this document: 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. https://icer-review.org/material/digital-apps-for-oud-draft-evidence-report/

Acknowledgements:

Jeff Tice served as the lead author for the report. Jeff Tice led the systematic review and authorship of the comparative clinical effectiveness section in collaboration with Noemi Fluetsch. We would also like to thank Kanya Shah for her contributions to the comparative clinical effectiveness section. Zunelly Odhiambo authored the section on coverage policies and clinical guidelines. Pamela Bradt and Steve Pearson provided methodologic guidance on the clinical and economic evaluations. Melanie Whittington and Jonathan Campbell led the development of the cost-effectiveness model and authorship of the cost-effectiveness section. Rick Chapman provided methods guidance on the cost-effectiveness modeling effort and developed the budget impact model. The ICER modeling team would like to thank Lorenzo Villa Zapata and Nicolas Mendola for their contributions. None of the authors above disclosed any conflicts of interest.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Laura and John Arnold Foundation. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 19% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. There were no life science companies relevant to this review who participate in this program. For a complete list of funders and for more information on ICER's support, please visit http://www.icer-review.org/about/support/.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

About Midwest CEPAC

The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The Midwest CEPAC is an independent committee of medical evidence experts from across the Midwest, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about Midwest CEPAC is available at https://icer-review.org/programs/midwest-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials and provider prescribing patterns may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/digital-apps-for-oud-stakeholder-list/

Expert Reviewers

Danielle Tarino
President and CEO
Young People in Recovery
This year, Young People in Recovery (YPR) received the following grants/awards from health-related organizations and entities: a $50,000 conference sponsorship and a $50,000 COVID relief grant from Alkermes, a drug manufacturer; $75,000 from the AmerisourceBergen Foundation for a YPR program in multiple sites in Ohio; $50,000 for COVID relief from the Foundation for Opioid Response Efforts, which is funded by McKesson; and $10,000 for a conference sponsorship from the National Association of Chain Drug Stores Foundation.

Jake Nichols
Principal, Clinical Strategy
axialHealthcare
AxialHealthcare provides services directly to multiple health plans.

Scott Steiger, MD, FACP, FASAM
Deputy Medical Director, Opiate Treatment Outpatient Program; HS Associate Clinical Professor of Medicine and Psychiatry at UCSF
Zuckerberg San Francisco General Hospital and Trauma Center
No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Sean M. Murphy, PhD
Director, Consultation Service, Methodology Core
Cherish Research (Center for Health Econ of Treatment Interventions for Substance Use Disorder, HCV, and HIV)
Weill Cornell Medicine
No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table of Contents

List of Acronyms Used in this Report

A CHESS	Addiction Comprehensive Health Enhancement Support System
AHRQ	Agency for Healthcare Research and Quality
AIC	Akaike Information Criterion
ART	Anti-retroviral Therapy
AWP	Average Wholesale Price
CBT	Cognitive Behavioral Therapy
CBT4CBT	Computer-Based Training for Cognitive Behavioral Therapy
CM	Contingency management
CMS	Center for Medicare and Medicaid Services
CPT	Current Procedural Terminology
CRA	Community Reinforcement Approach
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
ED	Emergency Department
eVLYG	Equal-Value Life Years Gained
FDA	Food and Drug Administration
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
LCD	Local Coverage Determination
LY	Life Year
MAT	Medication assisted treatment
MCO	Managed Care Organization
NCD	National Coverage Determination
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
OR	Odds Ratio
OUD	Opioid use disorder
PBI	Potential Budget Impact
PBM	Pharmacy Benefit Manager
PCP	Primary Care Provider
PDT	Prescription Digital Therapeutic
PICOTS	Population, Intervention, Comparators, Outcomes, Timing, and Settings
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PWID	People Who Inject Drugs
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SoC	Standard of Care
SUD	Substance Use Disorder
TES	Therapeutic Education System
USPSTF	US Preventive Services Task Force
WAC	Wholesale Acquisition Price
WTP	Willingness to Pay

1. Introduction

1.1 Background

Opioid use disorder (OUD) has become a public health crisis in the United States. OUD is defined by the following Diagnostic and Statistical Manual of Mental Disorders (DSM-5) characteristics: impaired control, social impairment, risky use, increased tolerance, and symptoms of withdrawal.[1,2] Most experts believe that it is a chronic disease that requires long-term maintenance treatment.[3]

In addition to its health and social impacts, OUD can lead to death from drug overdose. The number of drug overdose deaths in the US increased continuously from 1999 to mid-2017[4] when it reached a plateau of approximately 70,000 deaths over the previous 12 months of which approximately 50,000 were from opioids.[5,6] Approximately 2 million persons in the US suffer from OUD; about three quarters of this prevalence relate to prescription opioid painkillers and one-quarter to the use of heroin.[7] However, there is evidence that this significantly underestimates the true prevalence of OUD.[8,9] The White House Council of Economic Advisors estimates that the opioid epidemic cost the US $686 billion in 2018 and more than $2.4 trillion from 2015 to 2018.[10]

Several treatment approaches are available to treat OUD, with medication assisted treatment (MAT) being the most effective approach. MAT using medications approved by the Food and Drug Administration (FDA) is the recommended first-line treatment for OUD, and is often provided in combination with counseling and behavioral therapies.[11,12] Treatment of OUD with MAT has been shown to be effective,[3,13] and three types of medications are approved by the FDA: the full opioid agonist methadone, the partial agonist buprenorphine, and the opioid antagonist naltrexone.[14,15]

There are several behavioral therapies that have been shown in some, but not all, trials to increase retention and increase the proportion of negative urine drug screens in patients with substance use disorder, including OUD when added to MAT.[16,17] These include cognitive behavioral therapy (CBT), contingency management (CM), and the community reinforcement approach (CRA). In contingency management, patients are given cash rewards or vouchers for desired behaviors such as demonstrating negative urine drug screens. In the community reinforcement approach, a form of CBT originally developed in the 1970s, patients and clinicians work together try to understand the function that drugs play in their lives and develop individual goals to promote drug free living.

In 2018, ICER updated its 2014 assessment on MAT for the management of patients with OUD.[18] The report found that "long-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" and concluded that coordinated efforts are needed to improve access to OUD treatment.

Digital Therapeutics

There is a tremendous amount of interest and innovation in digital therapeutics, which is reflected in a growing number of National Institutes of Health (NIH) supported grants in this arena.[19] Digital technologies represent a novel approach to enhance care for patients outside of the one-on-one office setting. They hold the potential to enhance access to evidence-based care for patients whose schedules or locations present challenges to therapies delivered via in office appointments. Because they are delivered outside of the clinical setting, they offer the potential to reduce the stigma associated with going to clinics known to treat stigmatized disorders, such as substance use disorder (SUD). Stakeholders directed us to three digitally implemented therapeutics for OUD, described below, because of the research supporting these therapies.

reSET-O

reSET-O is a 12-week prescription digital therapeutic aimed at increasing retention of patients receiving outpatient OUD treatment. The FDA cleared reSET-O, because it was found to be substantially similar to its predicate device reSET.[20] reSET-O is to be used in conjunction with buprenorphine and CM. The app combines CM with OUD-specific CBT known as the CRA. CM gives small rewards (cash, gift cards) for desired behaviors (negative urine drug screen tests, completing CBT modules) and the size of the reward increases, on average, with consecutive desired behaviors.[17] In reSET-O, patients earn on average $110 in Amazon or Starbucks gift cards throughout the 12 week treatment program. reSET-O uses a form of CM called prize-based or fishbowl CM, which lowers the overall cost of CM by introducing an element of chance into the reward, sometimes resulting in a message of positive reinforcement (good job, thumbs up) and sometimes larger value gift certificates. Consecutive positive behaviors give patients a greater chance for receiving a gift certificate.

Connections

The Connections app brings together two different digital programs: A CHESS[21-23] with CBT4CBT.[24-29] A CHESS has been shown to improve retention in programs treating patients with substance use disorders through communication with addiction experts and peer support groups, monitoring with timely feedback, addiction related educational materials, customizable location based services, and one-touch communication with the patient's counselor or case manager. CBT4CBT is a 7-session program that teaches cognitive and behavioral skills such as problem solving, decision making, and affect tolerance that has been shown to improve abstinence in patients with substance use disorders. However, it has not shown to improve abstinence outcomes in people with OUD.

DynamiCare

The DynamiCare app includes 36 CBT modules, video monitoring for alcohol abstinence, a log of substance use screening results, Bluetooth-enabled breathalyzer for alcohol testing, drug saliva testing, appointment monitoring and reminders, and contingency management with up to $100 per month in financial rewards for negative drug tests and appointment attendance.[30] Rewards are provided in the form of funds transferred onto smart debit cards which are specifically coded to prevent the purchase of alcohol, use of paraphernalia, or other potentially harmful items.

1.2 Scope of the Assessment

The scope for this assessment is described using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was abstracted from randomized controlled trials as there were no comparative cohort studies or meta-analyses. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis was provided in a research protocol published on the Open Science Framework website (https://osf.io/6twy4/).

Populations

The key population of interest for the review is patients aged 18 years and above with OUD in various treatment settings.

Interventions

The interventions include MAT plus:

- reSET-O
- Connections
- DynamiCare

Comparators

We compared the interventions to standard of care including MAT. CM was not required for comparator interventions but was included in some trials.

Outcomes

The outcomes of interest are described below. Most outcomes were not reported in the identified trials.

Key outcomes that matter to patients

- Mortality (overdose deaths, suicide)
- Health-related quality-of-life
- Employment-related outcomes
- Housing-related outcomes
- Relationship-related outcomes (family, partners)
- Health system utilization (number of emergency department (ED) visits, number of primary care physician (PCP) visits, days of inpatient hospitalizations

Intermediate / Short-term outcomes

- Abstinence at the conclusion of the treatment period
- Short-term and long-term abstinence from illicit use of opioids
- Retention in treatment
- Engagement with the app
- Diminishing illicit use of opioids
- Opioid withdrawal syndrome severity
- Infectious (HIV, hepatitis), injection site reactions, and other complications from continued use of injectable opioids
- Functional outcomes (cognitive, occupational, social/behavioral)[31]
- Cravings/desire for opioids
- Behavioral health outcomes (depression, anxiety, PTSD)
- Coping strategies
- Other patient-reported outcomes
- Adherence/treatment discontinuation (number of times treated in detox/rehab, duration of abstinence)
- Other adverse events

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any follow-up duration, though outcomes of at least one-year follow-up are preferred as OUD is a chronic disorder.

Settings

The settings of interest will include outpatient (including office-based) and inpatient settings in the US with the emphasis on outpatient use.

1.3 Definitions

Abstinence

Abstinence in OUD trials is defined as urine drug screens that are negative for opioids (other than MAT) and in some trials, this includes other illicit drugs. Missed tests are usually considered to be positive. Studies typically report this as the longest continuous period of abstinence as well as the proportion of patients who are abstinent for some period of time (e.g. 4 weeks) usually at the end of the study.[32]

CM

Contingency management (CM) is an approach to behavior change that provides rewards (cash, gift cards) for desired behaviors (negative urine drug screens, completion of CBT modules). The size of the reward may increase, on average, with consecutive desired behaviors.[17]

MAT

Medication-assisted treatment (MAT) is the first line therapy to help patients with OUD achieve remission using medications approved by the FDA. MAT can be used in combination with individualized psychosocial support.

OUD

Opioid use disorder (OUD) is defined as on a scale (mild, moderate, or severe) by the DSM-5, based on the depending on the number of the following signs and symptoms that are evident: impaired control of opioid use, social impairment, risky use, increased tolerance, and withdrawal. OUD replaces what DSM-5 termed "opioid abuse" and "opioid dependence."[33]

Recovery

Recovery is a process of change through which individuals improve their health and wellness, live self-directed lives, and strive to reach their full potential. Four major dimensions support a life in recovery: health, home, purpose, and community. Though some individuals enter and sustain recovery on their own, recovery is mostly achieved via access to evidence-based clinical treatment and recovery support services.[34] 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 is considered in recovery while on MAT.

Relapse

A process in which a person with OUD who is being treated and is in remission/recovery experiences a loss of control of their opioid use. A relapse is different from a return to opioid use that is limited in scope and time and that does not involve the return of the signs or symptoms of OUD. This is typically referred to as a lapse or slip. The operational definitions of relapse in clinical trials of medications for OUD are based on different levels of return to opioid use as measured by toxicology tests and questionnaires.[3]

Remission

Remission refers to the disappearance of signs and symptoms of the disorder. DSM-5 defines remission as present in people who were diagnosed with OUD but no longer meet OUD criteria, except for craving. Early remission is achieved at 90 days and sustained remission is considered a period of at least 12 months. Remission is an essential element of recovery and a person is considered in remission while on MAT.[3]

Retention

Retention refers to continued attendance and adherence to MAT. Studies report the average number of days of retention and the proportion of patients retained at the end of the study. Retention is associated with improvements in important outcomes such as employment, reduced financial stress, decrease in hospitalizations and emergency room visits, and improved relationships...[35-38]

1.4 Potential Cost-Saving Measures in Opioid Use Disorder

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by therapies for OUD, as these services will be captured in the economic model. Rather, we are seeking services used in the current management of OUD beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with OUD that could be reduced, eliminated, or made more efficient. No suggestions have been received.

2. Patient Perspectives

2.1 Methods

As part of our review, we spoke with organizations working with individuals and families affected by OUD including Young People in Recovery. There was a consensus that MAT is often difficult to access, in part because of the stigma attached to OUD. This stigma is rooted in a widespread belief that SUD is a moral failing rather than a medical condition that is best addressed through treatment. Treatment through primary care, which is available with buprenorphine or naltrexone is a step in the right direction. Supportive therapy as an adjunct to MAT that is delivered through apps on smart phones can also expand access without stigma.

2.2 Impact on Patients

OUD is a chronic disorder that can affect widely varying populations in terms of age, background, and many other factors. The expression, "treatment is not one-size-fits-all," was used by several organizations to stress the importance of patients having access to different treatment options on their road to recovery; some patients enter recovery without the assistance of MAT, while most require MAT for extended periods of time or their entire lives.[12]

It was also mentioned that peer support is particularly important for young people entering the recovery process, as they usually lack a strong existing social network compared to older adults. Culturally competent peer support is challenging to find in many parts of the country.

Several organizations stressed that better daily functioning and well-being, and eventually recovery, are the most important outcomes of treatment. For some this may involve complete abstinence from non-medical opioid use, for others a reduced and/or controlled level of use. It was mentioned that this corresponds specifically to the discussions at the public meeting on Patient-Focused Drug Development for Opioid Use Disorder convened in April 2018 by the FDA.[39] Outcomes such as retention are surrogates for what patients really care about – getting their lives back. For most, this means getting a job, having a place to live, and re-establishing relationships with friends and family.

2.3 Impact on Caregivers and Families

The impact of OUD on families is enormous. The experience often ruptures the bonds between parent and child, whether it is the parent or child who suffers from OUD or two people in a partnership. Trust is at the root of any relationship and OUD often engenders the loss of trust. One of the immeasurable benefits of successful OUD treatment is the re-establishment of these relationships and the restoration of trust.

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

To understand the insurance landscape for digital therapeutics for OUD relevant to this review, we reviewed National and Local Coverage Determinations (NCDs and LCDs) from the Centers for Medicare and Medicaid Services (CMS), publicly available coverage policies from representative national plans including Anthem and Cigna, national and regional private payers including HealthPartners, Blue Cross Blue Shield of MO, Blue Shield of California, and state Medicaid plans (MO Healthnet and IL Health and Family Services). No coverage policies, nor any NCDs or LCDs, were available for digital therapeutics for OUD at the time of the publishing of this report. However, there have been a few partnerships and pilot programs for reSET-O and Connections with states and payers that have been rolled out or recently announced. A summary of these pilot programs is detailed below.

Given the relative novelty of this field for treating substance use disorders, there is still much uncertainty surrounding how payers will cover these digital therapies. In the absence of specific payer coverage policies, this section will explore the payer landscape for other digital health products and outline key payer considerations that may serve as a model for how digital therapeutics for OUD may be covered.

Summary of Pilot Programs and Payer Partnerships

reSET-O (Pear Therapeutics)

Pear Therapeutics announced in June 2020 that RemedyOne, a Pharmacy Benefit Manager (PBM), will reimburse reSET and reSET-O as a covered benefit within existing pharmacy benefit and formulary design.[40] RemedyOne will be providing this benefit to its 2.5 million customers. This marks the first PBM to cover prescription digital therapeutics for the treatment of SUD and/or OUD.

Connections (CHESS Health)

West Virginia

The West Virginia Office of Drug Control Policy started an initiative that entails the roll-out of Connections to support the treatment and recovery of people with SUD to treatment providers. Providers who choose to participate can enroll their patients directly, but no prescription is

necessary. The Connections app is available to individuals and providers across the state at no cost.[41]

Oklahoma

The Oklahoma Department of Mental Health and Substance Abuse Services offers the Connections app for free to support people with SUD in recovery.

Payer Landscape of Coverage for Digital Therapeutics

Public Payers

Currently, CMS does not cover prescription digital therapeutics (PDTs) for treatment of substance use disorders. However, on March 18, 2020, a Senate bill was introduced to amend titles XVIII and XIX of the Social Security Act to allow coverage of PDTs for mental health and substance use disorder treatment under Medicare and Medicaid.[42] 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] The bill is still under review and was referred to the Committee on Finance.

Medicare currently covers other digital health programs such as the National Diabetes Prevention Programs as part of the Medicare Part B benefit for patients who have prediabetes. The program is available once in a lifetime to beneficiaries who meet specific criteria at no cost to them.

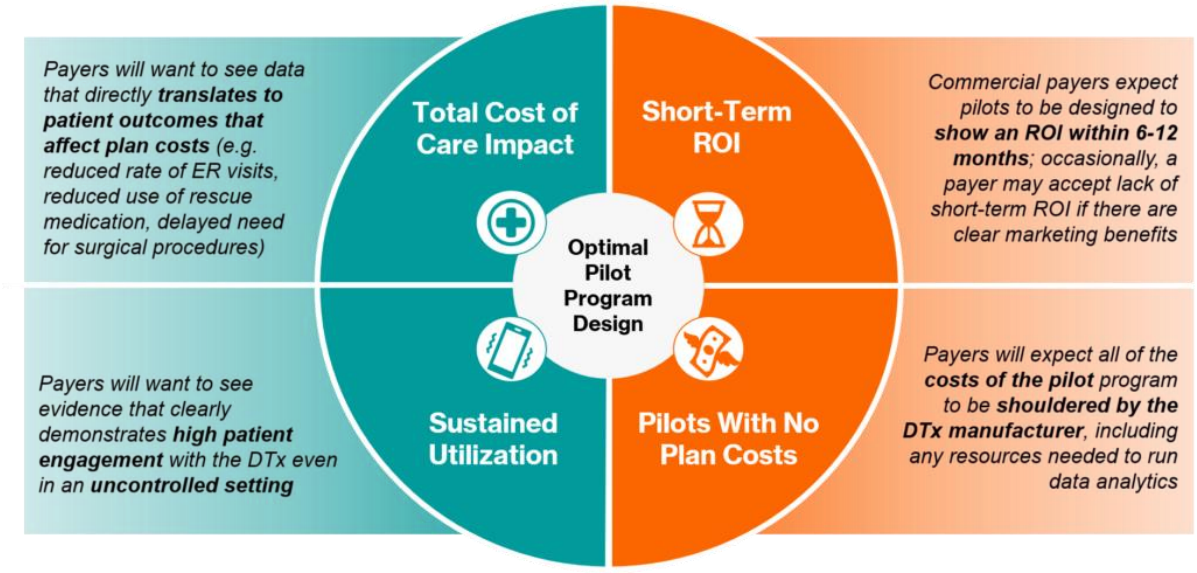
Private Payers and Pharmacy Benefit Managers

The general approach to evaluating coverage for digital therapeutics varies across payer types. Managed Care Organizations (MCOs) are more likely to focus on business needs first before considering adding on a digital health product to their formulary, PBMs have demonstrated more proactive engagement with manufacturers of digital therapeutics, but tend to focus on products in disease areas that are most relevant or have higher potential for cost savings.[43]

Additionally, a key area of uncertainty is whether digital therapeutics will be covered under the pharmacy benefit, the medical benefit, or under a separate digital health formulary. In general, MCOs are more likely to cover digital therapeutics under a pharmacy or medical benefit or a disease-related benefit with none or minimal cost sharing for the patient. On the other hand, PBMs are more open to the idea of creating digital health formularies within specific disease areas.[43] For example, Express-Scripts launched in May 2020 their first ever digital formulary ranging from remote monitoring services and digital therapeutics with a specific focus on these common chronic conditions: diabetes, prediabetes, hypertension, asthma, pulmonary disease, depression, anxiety and insomnia.

Another key area of consideration is the quality of evidence needed before payers consider covering a digital therapeutic. Although there is not a standardized set of criteria, the general consensus has been while robust randomized control trials (RCTs) are extremely important for evaluating clinical effectiveness, real-world evidence will be key to determining coverage. Payers may be hesitant to engage in pilot implementation programs without first considering the long-term adherence to digital therapeutics, direct impact on patient outcomes that translates to health care cost savings, short term return on investment, and the expectation that manufacturers will shoulder the costs of a pilot program. The figure below outlines these considerations:

Figure 3.1. Components of Optimal Digital Therapeutics Uptake[43]



All in all, there is great diversity in the approaches across payer groups regarding digital therapeutics coverage, and how the interventions under this review will be potentially considered by both public and private payers will largely depend on: 1) FDA approval status, 2) evidence requirements to demonstrate long-term efficacy, and 3) financial incentives.

3.2 Clinical Guidelines

At the time of the publishing of this report, there were no clinical guidelines available on the use of digital therapies as treatment for OUD.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our review of the comparative clinical effectiveness of reSET-O, Connections, and DynamiCare as an adjunct to MAT for OUD, we systematically identified and synthesized the existing evidence from available clinical studies. A description of the full PICOTS criteria can be found in Section 1.2. In brief, we compared the efficacy, safety, and effectiveness of reSET-O, Connections, and DynamiCare as an adjunct to MAT for OUD to standard of care alone, which includes MAT. Our review was mainly focused on clinical benefits, as there are no known safety concerns regarding the use of digital therapeutics for OUD. We extracted any relevant data, whether in published or unpublished form (e.g. conference abstracts or presentations, FDA review documents), as well as grey-literature (e.g. whitepapers). Due to important differences in study characteristics, we did not compare the interventions of interest through direct or indirect quantitative assessments. We sought evidence on all outcomes specified in Section 1.2. Methods and findings of our review of the clinical evidence are described in the sections that follow.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on digital therapies for OUD followed established best research methods.[44,45] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[46] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

We searched MEDLINE, EMBASE, and APA PsycInfo for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and

other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/).

Study Selection

Subsequent to the literature search and removal of duplicate citations, study selection was accomplished through two levels of screening, at the abstract and full-text level. Two reviewers independently screened the titles and abstracts of all publications using DistillerSR (Evidence Partners, Ottawa, Canada) and resolved any incongruencies through consensus. No study was excluded at abstract level screening due to insufficient information. For example, an abstract that did not report an outcome of interest in the abstract would be accepted for further review in full text. Citations accepted during abstract-level screening were retrieved in full text for review. Reasons for exclusion were categorized according to the PICOTS elements during full-text review.

Data Extraction and Quality Assessment

Two reviewers extracted data from the full set of included studies into an excel spreadsheet. Extracted data were independently verified by another researcher. Data elements included a description of patient populations, sample size, duration of follow-up, study design features (e.g., RCT or cohort), interventions, outcome assessments (e.g., timing and definitions), results, and quality assessment for each study. We used criteria employed by the US Preventive Services Task Force (USPSTF) that included presence of comparable groups, non-differential loss to follow-up, use of blinding, clear definition of interventions and outcomes, and appropriate handling of missing data to assess the quality of clinical trials and classify into categories "good," "fair," or "poor."[47] For more information on data extraction and quality assessment, refer to Appendix D.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D)[48].

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for "reSET-O", "therapeutic education system (TES)", "TES", "A CHESS", "connections" and "DynamiCare" using the ClinicalTrials.gov database of trials. Given the emerging nature of the evidence of digital therapeutics for opioid use disorder, we scanned the site to identify studies completed more than two years ago that would have met our

inclusion criteria and for which no findings have been published. Any such studies may indicate whether there is bias in the published literature. For this review, we did not find evidence of any study completed more than two years ago that has not subsequently been published.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were abstracted in evidence tables (see Appendix Tables D.1-D.11) and synthesized qualitatively in the body of the report. Due to differences between the studies in terms of the study design, patient characteristics, and outcomes (including definitions and methods of assessments), we were unable to compare the interventions of interest directly or indirectly by quantitative assessments. Hence, we focused on narratively describing the comparisons made within the clinical trials of each intervention.

4.3 Results

Study Selection

The database searches identified 1119 references and one additional reference was identified through a company's website (Appendix Figure A1). The primary reasons for excluding references included duplicate references, no digital intervention, and populations that were not patients with OUD treated with MAT. The final reference list included 11 publications describing 6 randomized trials.

Key Studies

reSET-O

The key randomized trial that formed the basis of the FDA approval of reSET-O was published in 2014.[32] It built on several prior randomized trials of computerized versions of the TES added to MAT for OUD.[49-51] The study compares TES (which includes CM) to MAT plus CM.

Connections

There are no key studies. The application builds on prior National Institute of Mental Health (NIMH)-funded studies of computerized behavioral support and CBT added to MAT. These applications (A CHESS, CBT4CBT) are the foundation for the digital app. There is a small, pilot study with published results for CBT4CBT [29], but the larger randomized trial of the combination of CBT4CBT with A CHESS has only recently been funded.[52]

DynamiCare

There are no published studies, but there is a white paper on the company's website describing the results of a study utilizing DynamiCare for a general substance use population that is not limited to patients with OUD on MAT. [30] Unfortunately, there are no subgroup results presented for the OUD population on MAT and the company did not respond to our request for data on this subgroup, even though they represented the majority of patients in the study.

Quality of Individual Studies

Unfortunately, the quality of the available studies was not high.

reSET-O

The key study (Christensen 2014) of reSET-O was of fair quality.[32] It was neither double-blinded nor were the groups comparable at baseline. The other studies were either of fair[50,51] or poor quality.[49]

Connections

The study of the CBT4CBT portion for the Connections app[29] was rated as fair quality because it was neither double-blinded nor were the groups comparable at baseline. In addition, as a pilot study, it randomized too few patients to produce results with sufficient precision.

DynamiCare

Ryan 2020[30] was an observational study, and thus will not receive a quality rating.

Clinical Benefits

The most important clinical benefit reported in the trials is retention. Long-term retention (six months to two years or longer) is associated with abstinence and with the outcomes that really matter to patients: employment, reduced financial stress, decreased hospitalizations and emergency room visits, and improved relationships.[35-37]

reSET-O App

There were no clinical trials of reSET-O. The trial which supported its FDA application was a fair quality trial that did not meet its primary endpoint and was only 12 weeks in duration. The trial intervention differed in several important ways from the reSET-O app, so the results may not apply.

We found no randomized trials, cohort studies or case series that evaluated the reSET-O app. The FDA clearance of reSET-O was based on its similarity to the reSET app, which is used in other substance use populations and on the results of a 12 week study of a web-based precursor to reSET-O described below.[32,53]

The key study (Christensen 2014) included participants who met the DSM-5 criteria for opioid dependence and the FDA qualification criteria for buprenorphine treatment (Appendix Table D1).[32,53] They could not be pregnant, incarcerated, or have active psychiatric disorder or significant medical illness. Between 2007 and 2010, the study randomized 170 patients at one site in Little Rock, Arkansas to 12 weeks of buprenorphine, CM, and computerized CBT or to buprenorphine plus CM alone. All patients came to the clinic three days a week to pick up their medication and submit urine to test for opioids, benzodiazepines, and cocaine. In addition, they met with a counselor for 30 minutes every two weeks. The study was not blinded.

CM consists of increasing rewards for consecutive urine samples testing negative for drugs. The total potential value of the awards through 12 weeks was $997.50. CBT consisted of a set of 69 topics (Self-Management Planning, Drug Refusal Training, etc.) delivered via a web-based interface on computers at the clinic site for approximately 30 minutes each session. The supervising therapists determined the sequence of the topics individually for each participant based on a functional analysis of their dependence.

There was no significant difference in the primary outcome: number of days of continuous abstinence (difference 5.5 days, 95% CI -3.2 to 14.2 days). However, the participants randomized to the CBT group had an average of 9.7 more days of total abstinence (difference 9.7 days, 95% CI 2.3 to 17.2) and a reduced likelihood of dropping out of treatment (20% versus 36%, HR 0.47, 95% CI 0.26 to 0.85) as compared to those who only received CM in addition to MAT. A pre-specified subgroup analysis by prior treatment for opioid dependence (yes/no) showed that participants with prior treatment experience benefited more from CBT than those with no prior experience (Appendix Tables D.6-D.8). For example, 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.

We judged this study to be of fair quality for a number of reasons. First, it is an open-label trial without a sham intervention for the control group, which raises concerns that participants randomized to the control group would be disappointed because they did not get access to the new therapy. This could lead to less active participation in the trial, higher drop-out rates, and poor adherence to the standard therapy for patients in the control group. Many patients were excluded after signing informed consent (36/206, 17.5%) in some cases for reasons not specified as exclusion

criteria (high urinary concentration of drugs, physician recommendation), which raises concerns about selection bias. In addition, no allocation concealment was described. Despite stating that 1:1 randomization was performed, 92 patients were randomized to the experimental group and 78 to the control group. In addition, there were large baseline differences in several important patient characteristics including monthly income ($1000 versus $1808), sex (48% male versus 62% male), prior treatment (40% versus 53%), and years of regular opioid use (5 versus 6.5).

Furthermore, the authors present the results as positive, but the power calculations suggest that the primary outcome was the difference in mean weeks of continuous abstinence, which was not significant (difference 5.5 days, 95% CI -3.2 to 14.2 days). The authors highlight the greater retention rate for participants randomized to the active treatment group, but note in the introduction that they hypothesized no difference in retention rates. Finally, there are several important concerns about the ability to generalize the results of this trial to the use of reSET-O in other settings. First, it was a single center study with a high intensity, contingency management intervention (three visits per week, three urine toxicology screens a week, incentives of up to $997.50 over the 12 week study, and 30 minutes in person with a therapist every two weeks), which may not be generalizable to other settings. Second, the CM approach is different. In this study, payments are given for negative urine tests only and the participants received payment for every negative urine. When using the reSET-O app, patients are rewarded for completing CBT modules and for negative urines, but they do not always receive gift cards, so that the total incentives average much less (<$300 over 12 weeks). Third, the computer intervention was delivered on site for approximately 30 minutes each visit to the clinic as opposed to the smart-phone based reSET-O application, which is used off site and is not monitored. Thus, it may not produce similar benefits. Finally, the study only lasted 12 weeks, so it is unclear if the small difference in retention rates will translate into long-term changes in the outcomes that matter to patients such as fatal overdoses, return to work, and quality of life. Ideally the study would have assessed retention and abstinence at 6 months and one year, which more closely tracks with long term benefits from MAT.

There are two earlier trials of the same computerized CBT platform compared to therapist delivered CBT or to buprenorphine alone.[49,50] All study arms in those trials received CM. In addition, there is a third trial that compared computerized CBT plus methadone to methadone treatment alone. Table 4.1 summarizes the interventions arms of the trials and the retention rates.

Table 4.1: Outcomes of the computerized CBT Trials

Study	Arms	N	Length of FU	Retention (%)
Christensen 2014[32]	– Computer CBT + CM + BUP – CM + BUP	92 78	12 weeks	80.4 64.1
Bickel 2008[50]	– Computer CBT + CM + BUP – Therapist CBT + CM + BUP – BUP	45 45 45	23 weeks	62.2 53.3 57.7
Chopra 2009[49]	– Computer CBT + CM + BUP – Computer CBT + CM* + BUP – BUP	41 42 37	12 weeks	85.4 59.5 75.7
Marsch 2014[51]	– Computer CBT + Methadone – Methadone	80 80	52 weeks	38.8 38.8

BUP: Buprenorphine; CBT: Cognitive behavioral therapy; CM: Contingency management
*CM in this arm involved changes in the dose and schedule of buprenorphine and not vouchers

As has typically been seen in trials of MAT, retention declines with time, with retention at six months or longer usually less than 50%. In head to head trials, MAT with methadone usually has significantly greater retention than MAT with buprenorphine.[54] It is possible that the treatment retention of 38.8% in Marsch 2014 likely would have been lower if the MAT had been buprenorphine as opposed to methadone.

In the other trials, the differences in retention rates with computerized CBT + CM + buprenorphine and buprenorphine alone were smaller than those observed in Christensen 2014 even though the control group did not receive CM. Indeed, in Bickel 2008 there was no difference between the interventions at 12 weeks (75.5% in both the computerized CBT + CM + buprenorphine arm and the buprenorphine alone arm).

Connections App

There were no clinical trials of the Connections app. The trial of the CBT4CBT portion of the app was a fair quality pilot trial that was promising, but not definitive. The trial intervention differed from the Connections app as it did not include the A CHESS intervention, so the results may not apply.

Shi et al randomized 20 patient ages 18 years and older with OUD to 12 weeks of a web based CBT program known as CBT4CBT plus buprenorphine or buprenorphine alone.[29] Allocation concealment was not reported. This study added a buprenorphine module to the seven module CBT4CBT drug program that has been studied in other settings.[29] The modules include narration, videos, quizzes and exercises intended to improve their outcomes with MAT. They could complete the modules in the clinic during their weekly meetings or at home based on their preference. Urine samples for drug screening were collected weekly. No primary outcome was specified.

There were no significant differences between the two groups at baseline (Appendix Table D.2), though 60% of the CBT4CBT arm were female compared with 20% of the control group (p=0.07). Patients in the CBT4CBT group were more likely to stay in treatment (82.6 days versus 68.6 days, p=0.19) and provided more urine samples (9.3 versus 8.4, p=0.48). They had significantly more urine tests that were free of all illicit drugs (7.3 versus 2.3, p=0.01) and a higher percentage free of illicit drugs (81.6% versus 29.9%, p=0.004).

The results of this study were promising, though the number studied was small and the follow-up short. The baseline differences in sex raise concerns about selection bias but could be due to chance given the small sample size.

DynamiCare App

There was one clinical trial of the DynamiCare app, but it was not solely in the population of interest for this review and no subgroup results were available in the non-peer reviewed report of the trial. Thus, we were unable to assess the potential impact of the app in patients with OUD on MAT.

The study of the DynamiCare app recruited 108 participants with SUD from a single site in Cincinnati, Ohio.[30] They were matched with 95 control patients at another clinic in Cincinnati based on date of enrollment, urine drug testing results, and the type of treatment program. OUD was the most common diagnosis in the DynamiCare intervention group (90%) and the majority were prescribed buprenorphine (94%). Patients were recruited from intensive outpatient programs (27%), outpatient programs (68%), and continuing care programs (4%). The equivalent statistics were not reported for the control group nor were the results reported for patients with OUD on buprenorphine.

Urine drug screen results were compared 30, 60, and 90 days after enrollment. Patients in the DynamiCare group were more likely to have negative urine tests at 30 days (40% versus 21%), 60 days (28% versus 14%), and 90 days (25% versus 8%, p<0.05 for all three comparisons). Patients in the DynamiCare group also attended a higher proportion of their appointments during each 30-day period. For example, 63% versus 53% in the first 30 days and 49% versus 36% in days 61 to 90.

The primary concerns about this study were the lack of randomization, the lack of peer review, and the lack of data specific to the OUD population. In addition, the length of follow-up (90 days) was too short to adequately assess the long-term impact of DynamiCare on the lives of patients with OUD.

Harms

The studies of these apps did not report on adverse events, serious adverse events, or adverse events related to use of the apps.

Heterogeneity and Subgroup Analyses

There are a number of potential important sources of heterogeneity including the proportion of patients using IV opioids, the length of the OUD, the presence of other substance use disorders, the age, sex, education level, employment status, and socioeconomic background of the patient. These varied somewhat across the trials (Appendix Tables D.2-D.5), but subgroup analyses were rarely reported.

Uncertainties and Controversies

The primary source of uncertainty in the clinical evidence for these digital apps is the complete lack of peer reviewed data on the impact of their use for patients with OUD treated with MAT. In addition, the trial designs that demonstrated some efficacy for the components implemented in the digital apps did not measure outcomes with long enough follow-up. The minimum follow-up to demonstrate a meaningful impact on adherence would be 6 months and 12 to 24 months would be more convincing. Finally, no data were reported on key health outcomes that matter to patients like ER visits, hospitalizations, return to work, and improved relationships with family and friends.

4.4 Summary and Comment

The evidence ratings for the digital apps for patients with OUD receiving MAT are summarized in Table 4.2 below. Refer to Figure D1 in the Appendices for ICER's Evidence Rating Matrix.

Table 4.2. Evidence Ratings for Digital Apps for Patients with Opioid Use Disorder Treated with MAT

Digital App	ICER Evidence Rating
reSET-O	C+
Connections	C+
DynamiCare	C+

The evidence rating is the same for all three apps: comparable or incremental. There is no direct, peer reviewed evidence on the efficacy of any of the apps in the population of interest. All three apps are based on implementing behavioral interventions with some randomized trial evidence supporting their efficacy, although the impact of these interventions is modest at best and remains

controversial.[16] The use of the apps is unlikely to be harmful to patients. Thus, there is moderate certainty that the digital apps are comparable to MAT alone (due to no identified harms) and there may be incremental benefits.

5. Long-Term Cost Effectiveness

5.1 Overview

The primary aim of this analysis is to estimate the cost effectiveness of digital therapeutics as an adjunct to MAT for OUD using a decision analytic model. Where data allowed, the model compared a digital therapeutic as an adjunct to outpatient MAT to outpatient MAT alone. The base-case analysis took a health care system perspective (i.e., focused on direct medical care costs only) and a five-year time horizon. We 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.

As data permitted, productivity impacts and other indirect costs were included in a modified societal perspective scenario analysis. The societal perspective is not presented as a co-base case because the societal costs of care were not large relative to the direct health care costs and the impact of the digital therapeutic on these costs was not substantial (See Section 5.2). The target population consisted of adults 18 years and older with OUD receiving outpatient MAT. Two-sub-populations were modeled as a scenario analysis, consisting of individuals who had previously received a treatment for opioid use disorder and separately individuals who were treatment naïve prior to initiating the digital therapeutic.

We developed a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models,[55-59] including ICER's previous review of MAT completed in 2018.[18] Our model included two phases, with Phase 1 modeling the time using the digital therapeutic and its associated clinical and economic outcomes, and Phase 2 capturing continued MAT use beyond the completion of the digital therapeutic and its associated clinical and economic outcomes.

Model outcomes included total life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal-value life years gained (evLYG), percent of patients on MAT, and total costs over a five-year time horizon. A description of the evLYG calculation can be found in the appendix. Costs and outcomes were discounted at 3% per year. Incremental costs per LY gained, incremental costs per QALY gained, incremental costs per evLYG, and incremental costs per additional person on MAT (at 12 weeks) were calculated for all relevant pairwise comparisons.

5.2 Methods

The model used intention-to-treat analyses from trials and other sources, with a hypothetical cohort of patients entering the model with OUD being treated with either a digital therapeutic as an

adjunct to MAT or MAT alone. The model was developed in Microsoft Excel Version 16, with some components of the model (e.g. MAT retention over time) developed in RStudio (version 1.1.442).

Model Structure

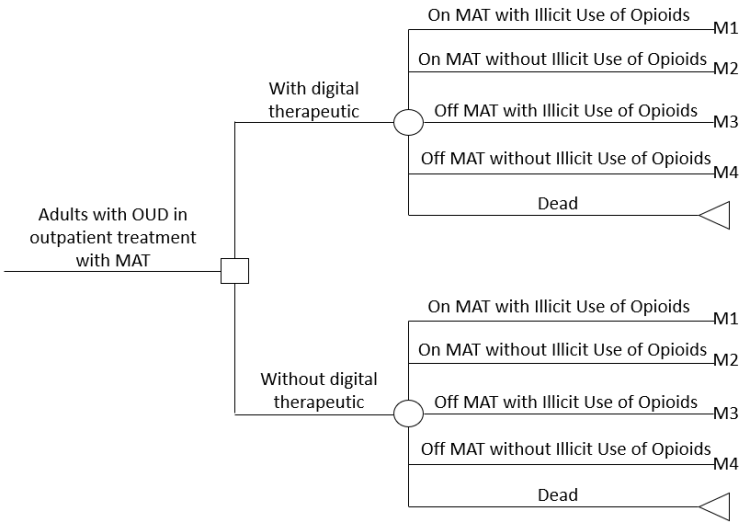
The model schematic for this assessment is depicted in Figures 5.1 and 5.2. Phase 1 of the model (Figure 5.1) followed a decision tree and mirrored the duration of the time on digital therapeutic. While using the digital therapeutic, there were five potential health states an individual could occupy, including: 1) On MAT with Illicit Use of Opioids, defined as those who had not discontinued MAT, had not died, and were illicitly using opioids; 2) On MAT without Illicit Use of Opioids, defined as those who had not discontinued MAT, had not died, and were not illicitly using opioids; 3) Off MAT with Illicit Use of Opioids, defined as those who had discontinued MAT and were illicitly using opioids; 4) Off MAT without Illicit Use of Opioids, defined as those who had discontinued MAT due to persistent abstinence that lasted longer than 12 months; and 5) Dead, defined as those who died over the duration of digital therapeutic use. Discontinuation was defined as leaving the trial at will or failing to attend three clinic visits in a row.[32] Illicit use of opioids was defined as testing positive for opioids during a urine drug screening test or missing a urine drug screening test.[32]

Digital therapeutic trial evidence informed the occupancy of each health state at the end of Phase 1. Individuals retained in treatment and who had opioid negative urine drug screening tests for all assessment points over the last four weeks of digital therapeutic use occupied the On MAT without Illicit Use of Opioids health state. The last four weeks of digital therapeutic use was selected as the assessment duration for the On MAT without Illicit Use of Opioids health state to align with the digital therapeutic evidence and the FDA's recommendation to allow a grace period prior to assessing an intervention's effect. The remaining individuals retained in treatment (i.e. who did not reach the definition of discontinuation), but who continued to illicitly use opioids, occupied the On MAT with Illicit Use of Opioids health state. Individuals that discontinued treatment occupied the Off MAT with Illicit Use of Opioids Health State. Individuals in the On MAT without Illicit Use of Opioids health state for 12 months were eligible to transition to the Off MAT without Illicit Use of Opioids health state. However, because the duration of Phase 1 (i.e. duration of digital therapeutic) for the interventions included in this evaluation was less than 12 months, no one could occupy the Off MAT without Illicit Use of Opioids health state in Phase 1 of the model. More information on the transition to the Off MAT without illicit Use of Opioids health state is provided in the description of Phase 2 of the model. Patients that died during Phase 1 due to all-cause mortality or illicit use of opioids occupied the Dead health state.

Total abstinence days were assessed as total number of days abstinent over the duration of Phase 1, rather than by health state occupancy, to account for the person-level variation in abstinence over Phase 1. Patients in health states that corresponded to "On MAT" were on MAT for the duration of Phase 1. We assumed those that discontinued MAT by the end of Phase 1 discontinued

halfway through Phase 1; therefore, patients in health states that corresponded to "Off MAT" were only on MAT for the first half of Phase 1.

Figure 5.1. Phase 1 Decision Tree Schematic



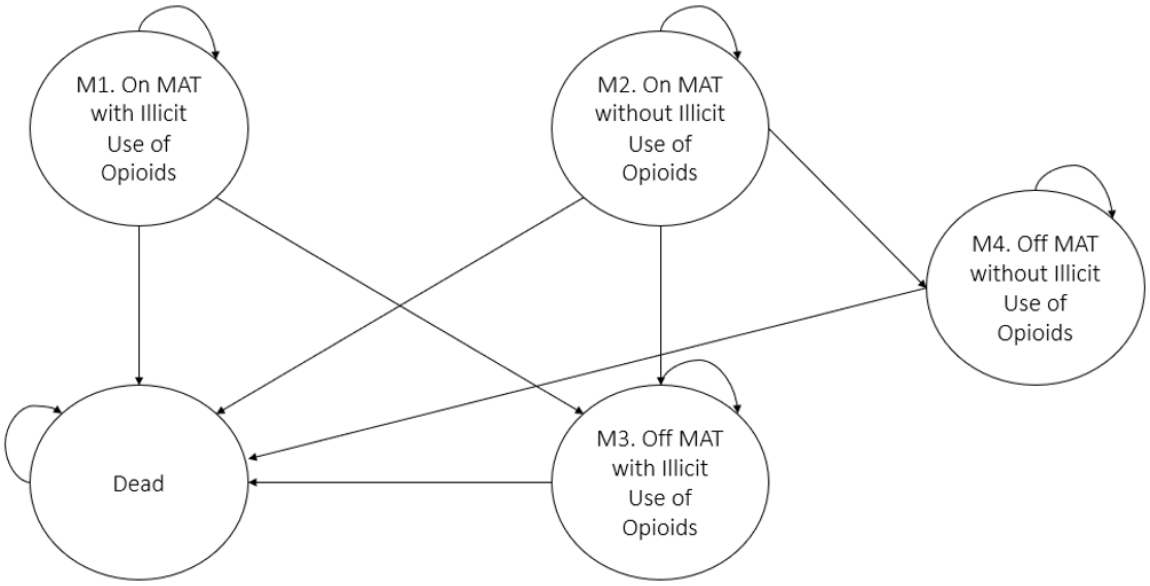
Phase 2 of the model (Figure 5.2) was a Markov model that consisted of the same five health states: 1) On MAT with Illicit Use of Opioids, 2) On MAT without Illicit Use of Opioids, 3) Off MAT with Illicit Use of Opioids, 4) Off MAT without Illicit Use of Opioids, and 5) Dead. Patients entered the Markov model based on their health state occupancy from the end of the Phase 1 decision tree.

Markov model (Phase 2) cycle length was four weeks, based on outcomes reported in clinical data and previously published economic models. During Phase 2 of the model, patients could transition from On MAT with Illicit use of Opioids to Off MAT with Illicit Use of Opioids due to MAT discontinuation. Patients could also discontinue from On MAT without Illicit use of Opioids to Off MAT with Illicit Use of Opioids. Patients in the On MAT without Illicit Use of Opioids health state could transition to Off MAT without Illicit Use of Opioids, which occurred in 10% of the patients who were in the On MAT without Illicit Use of Opioids health state at 12 months.[18]

Once in the Off MAT with Illicit Use of Opioids or in the Off MAT without Illicit Use of Opioids health states, patients could not re-enter either the On MAT with Illicit Use of Opioids or On MAT without Illicit Use of Opioids health states. Like the 2018 ICER MAT review, patient flow through the model was unidirectional, in that once in a progressed health state, patients could not move to an upstream health state. Also, in the Markov model (Phase 2), patients could not transition from On MAT with Illicit Use of Opioids to On MAT without Illicit Use of Opioids. The transition from On MAT with Illicit Use of Opioids to On MAT without Illicit Use of Opioids only occurred while using the digital therapeutic (during the Phase 1 decision tree). Any transitions from illicit use to without illicit use that would occur outside of digital therapeutic use were considered to be the same across treatment arms. Patients remained in the model until death or until the end of the model time

horizon. All patients could transition to death from all causes from any of the alive health states. In addition, patients could die from opioid use in health states that corresponded to the illicit use of opioids. After discontinuing MAT, subsequent lines of MAT were not included in this model given the five-year time horizon and given no evidence to suggest differences in rates of subsequent MAT for the evaluated interventions.

Figure 5.2. Phase 2 Markov Model Schematic



Target Population

The modeled population consisted of adults 18 years and older with OUD in outpatient MAT. Table 5.1 provides the baseline population characteristics for the model that mirror the population characteristics from the pivotal trial used to inform the clinical evidence. Age and sex factor into mortality, and age also influences utility estimates. Injection as the preferred route of illicit use administration influenced the comorbidities associated with OUD. The percent who had a prior OUD treatment was used in a scenario analysis that evaluated different subpopulations based on prior treatment status, and the percent employed full time influenced the scenario analysis from the modified societal perspective.

Table 5.1. Baseline Population Characteristics

Population Characteristics	Value	Notes/Source
Mean age (years)	34	Weighted average from Christensen et al., 2014[32]
Female (%)	46%	Weighted average from Christensen et al., 2014[32]
Injection as preferred route of illicit use administration (%)	14%	Weighted average from Christensen et al., 2014[32]
Prior OUD treatment (%)	46%	Weighted average from Christensen et al., 2014[32]
Employed full time (%)	37%	Weighted average from Christensen et al., 2014[32]

Treatment Strategies

The list of interventions considered for potential inclusion in the cost-effectiveness model was consistent with the clinical review. Data availability dictated the feasibility of each intervention being included in the model. At the posting of this brief report, reSET-O was determined as the only intervention with sufficient peer-reviewed evidence in the OUD population to be included in the cost-effectiveness model. Other interventions may be added to the cost-effectiveness model if appropriate data become available throughout this review.

The comparator was outpatient MAT (i.e. counseling and pharmacological therapy) without the use of a digital therapeutic. The pivotal evidence for reSET-O included contingency management (in addition to counseling and pharmacological therapy) in the comparator of the randomized trial despite contingency management not representing a commonly prescribed component of standard of care. Contingency management is a type of behavioral therapy that provides rewards to patients following positive behaviors, such as negative urine drug screenings and completion of modules. Evidence from the literature was used to adjust the cost and clinical outcomes observed in the contingency management comparator arm of the pivotal trial to generate a standard of care comparator that would consist of outpatient MAT alone (i.e. including counseling and pharmacological therapy, but not including contingency management). The standard of care comparator was the base-case comparator and was used in all subsequent scenario and sensitivity analyses. However, to mirror the pivotal trial design and comparator definition, we included MAT with contingency management as a comparator (i.e. counseling, pharmacological therapy, and contingency management) by way of a scenario analysis.

Key Model Characteristics and Assumptions

Our model was informed by the key choices and assumptions listed in Table 5.2.

Table 5.2. Key Model Choices and Assumptions

Model Choice or Assumption	Rationale
Individuals that have opioid negative urine drug screening tests for all assessment points over the last four weeks of digital therapeutic use entered the On MAT without Illicit Use of Opioids health state in the Markov model.	The final four weeks of digital therapeutic use aligned with the digital therapeutic evidence and the FDA's recommendation to allow a grace period prior to assessing an intervention's effect.
Missing urine drug screening tests were assumed to be positive for opioids.	This is an intent to treat analysis and missing data were considered a failure (i.e. non-abstinent).
The transition to On MAT without Illicit Use of Opioids from On MAT with Illicit Use of Opioids occurred while using the digital therapeutic and while on MAT treatment during Model Phase 1 only.	Any transitions from illicit use to without illicit use that occurred after the digital therapeutic were considered to be the same across treatment arms and were not included in Model Phase 2.
Treatment discontinuation to Off MAT with Illicit Use of Opioids could occur from both On MAT without Illicit Use of Opioids and On MAT with Illicit Use of Opioids. We assumed more individuals would discontinue from an illicit use health state (1.2 times the discontinuation probability) than from a non-illicit use health state (0.8 times the discontinuation probability).	Published evidence on MAT discontinuation based on illicit use status was not identified; therefore, we assumed a higher risk of discontinuation from an illicit use health state.
MAT discontinuation risk after the duration of the digital therapeutic was assumed to be the same across all modeled treatments. We extrapolated this risk from the comparator MAT retention curve (discontinuation=1-retention) in the digital therapeutic clinical evidence.	No robust data exist on long-term discontinuation/relapse for the digital therapeutics to suggest a differential risk of discontinuation after intervention completion.
The clinical outcomes (e.g. abstinence, retention) were the same for the contingency management comparator and the standard of care comparator.	Published research suggests no significant difference between voucher-based contingency management in addition to outpatient MAT and outpatient MAT alone.[60]
We assumed that 10% of patients who remained in the On MAT without Illicit Use of Opioids health state for 12 months transitioned to an Off MAT without Illicit Use of Opioids health state.[18]	We found no published evidence indicating the percentage of MAT recipients remaining off opioids when they stop MAT. We assumed a relatively low rate of persistent abstinence following MAT, given the frequency of relapse in this population.

Mortality from opioid use was held constant over time and could only occur while patients were illicitly using opioids.	We found no robust published evidence on time-dependent mortality from opioid use among OUD patients.
Serious adverse event (SAE)-related costs or disutilities were not included in the model.	MAT trials vary in reporting of SAEs, with most reporting only the percentage of SAEs and not specific non-relapse related SAEs. Individual adverse events when reported were not reported by category of severity. We assumed that background health care costs (sourced from a claims analysis) included costs associated with treating SAEs.
Incidence of Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) infections were modeled as comorbidities associated with OUD but were only attributed to the subpopulation of people who inject drugs (PWID).	A significant proportion of HIV and HCV cases among those who illicitly use opioids occur in PWID. We found no published evidence on HIV and HCV incidence among people with OUD who do not inject drugs.
The model assumed a constant disutility associated with HIV infection and treatment with anti-retroviral therapy (ART). No increase in death due to HIV was modeled separate from the increase in death among those who illicitly use opioids.	We found no robust evidence on time- and disease-status-dependent change in clinical outcomes among those infected and diagnosed with HIV and treated with ART. To avoid double counting of mortality among those who illicitly use opioids and due to the five-year time horizon, no increase in death was attributed specifically to HIV.
Among PWID diagnosed with HCV, disutilities associated with HCV were only assigned for those for whom there was no spontaneous clearance of HCV infection and who fail treatment. No increase in death due to HCV was modeled separate from the increase in death among those who illicitly use opioids.	Patients with spontaneous HCV infection clearance or those successfully treated with direct-acting antiviral therapy are assumed to have no HCV-specific disutilities. To avoid double counting of mortality among those who illicitly use opioids and due to the five-year time horizon, no increase in death was attributed specifically to HCV.

Model Inputs

Clinical Inputs

Digital Therapeutic Efficacy

Digital therapeutic efficacy was measured primarily by abstinence and MAT treatment retention and was derived from relevant trial evidence.[32] Efficacy for the standard of care comparator was derived based on the contingency management comparator efficacy[32] and published literature.[60] A study by Gross and colleagues[60] found no significant difference in abstinence or retention between those who received contingency management in addition to MAT versus those who received MAT alone (i.e. standard of care). Thus, the clinical outcomes for abstinence and retention for standard of care equated to the evidence for the contingency management arm of the pivotal trial.

Abstinence

Abstinence data from the digital therapeutic evidence informed the number of days abstinent during Phase 1 and the percent of the population who started Phase 2 (i.e. the Markov model) in the On MAT without Illicit Use of Opioids health state. The number of total abstinent days reported in the reSET-O pivotal trial was used as the number of days abstinent during Phase 1 of the model. Data on file provided from the manufacturer of reSET-O was used to inform the percent of the population in each arm who start Phase 2 of the model in the On MAT without Illicit Use of Opioids health state. The On MAT without Illicit Use of Opioids health state included those who had urine drug screening tests negative for opioids across all assessment points for the last four weeks of digital therapeutic use. Missing urine drug screenings were assumed to be positive for opioids. The percent of the population that occupied the On MAT without Illicit Use of Opioids health state was not significantly different between the intervention and comparator arms, consistent with a non-significant observed difference in longest continuous abstinence reported in the reSET-O pivotal trial.[32] Abstinence data are presented in Table 5.3.

Table 5.3. Abstinence from Illicit Opioid Use at Completion of Digital Therapeutic

Abstinence	reSET-O	SoC/CM Comparator	Source
Total Days Abstinent Over Phase 1	67.1 days	57.4 days	Christensen et al., 2014[32]
Percent of Population That Enters the On MAT Without Illicit Use of Opioids Health State in Phase 2	[redacted]	[redacted]	Data on file

CM: contingency management, SoC: standard of care

Beyond the digital therapeutic duration, no new cases of abstinence associated with the digital therapeutic was modeled. Any transitions to abstinence that occurred outside of the digital therapeutic duration were assumed to not be the result of digital therapeutic use and would thus equally influence both the intervention and comparator.

MAT Treatment Discontinuation

Over the duration of the digital therapeutic (Phase 1), MAT discontinuation data from the digital therapeutic pivotal evidence informed the percent of the population who started Phase 2 in the Off MAT with Illicit Use of Opioids health state. Discontinuation was equivalent to one minus the MAT retention percent from the pivotal evidence. Table 5.4 presents the MAT retention evidence from the pivotal trial for reSET-O. MAT discontinuation was gradual over the time of digital therapeutic use; thus, for the purposes of assigning outcomes (LYs, QALYs, etc.) in Phase 1 of the model, we assumed discontinuation occurred halfway through the digital therapeutic duration.

Table 5.4. reSET-O MAT Retention

On MAT	reSET-O	SoC/CM Comparator	Intervention Effect	Source/Notes
On MAT at End of Phase 1	80.4%	64.1%	OR: 2.30	Discontinuation was equivalent to 1 minus the number retained on MAT from Christensen et al., 2014[32]

CM: contingency management, MAT: medication assisted treatment, OR: odds ratio, SoC: standard of care

MAT discontinuation after the duration of the digital therapeutic was extrapolated from the comparator MAT retention curve (discontinuation=1-retention) from the digital therapeutic pivotal trial.[32] To derive per-cycle transition probabilities to health states of off MAT treatment, we fit parametric survival curves to the contingency management MAT retention curve utilizing the approach described by Hoyle and Henley.[61] First, we extracted data points from digitized copies of the trial curve, then used the extracted values, the number of remaining patients at each time interval, and maximum likelihood functions to estimate curve fits to the underlying individual

patient data. The fitted model curves included the distributional forms of exponential, Weibull, log-normal, log-logistic, and gamma. The base-case parametric function was selected based on best model fit using Akaike information criterion (AIC) values and visual comparison. Beyond trial duration, discontinuation was extrapolated using the best-fitting curve function observed within the trial period. The shape and scale parameters for this curve are provided in Table 5.5. The derived per-cycle transition probabilities were applied to both intervention and comparator arms due to no evidence suggesting different discontinuation risks after digital therapeutic completion.

Table 5.5. MAT Discontinuation after Phase 1

	Distribution	Shape	Scale	Source/Notes
Discontinuation after Phase 1	Exponential	1.00	179.02	AIC=348.50; Time measured in days; Figure 2 from Christensen et al., 2014[32]

AIC: Akaike information criterion CM: contingency management, OR=odds ratio; SoC: standard of care

Based on the exponential distribution detailed in Table 5.5, the probability of discontinuation during each four-week cycle was 14.5%. Individuals could discontinue from both the On MAT with Illicit Use of Opioids and the On MAT without Illicit Use of Opioids health state in Phase 2. We assumed more individuals would discontinue from an illicit use health state than from a non-illicit use health state. To the per-cycle discontinuation probability, we applied a multiplier of 1.2 for those in the On MAT with Illicit Use of Opioids health state and a multiplier of 0.8 for those in the On MAT without Illicit Use of Opioids health state.

Adverse Events

We had no evidence to suggest adverse events were associated with the use of the digital therapeutic. Further, no MAT-related adverse events were modeled. Informed by the 2018 ICER MAT review, evidence on serious adverse events from MAT lack specificity on which adverse events occurred. Rather, percentages of the treated population that experienced a serious adverse event are typically presented. Because there is no evidence to suggest a disutility associated with serious adverse events associated with MAT, adverse events were not separately modeled in our analysis.

Comorbidities Associated with OUD

Key OUD-related comorbidities with significant public health impact include HCV and HIV infections among PWID. A cohort study and a meta-analysis based on four US-specific surveys on PWID reported annual incidence of HIV and HCV among PWID as 0.055% (95% Confidence Interval: 0.042% to 0.080%) and 26.7%, respectively. These rates were converted to per-cycle probabilities in the model.[62,63] Presence of comorbidities was associated with clinical and economic consequences. However, clinical consequences for HCV were only assigned to patients with HCV

without spontaneous HCV infection clearance (24.4% of HCV cases spontaneously clear)[64] and those who were not successfully treated with direct-acting antiviral therapy (98% of treated cases are effectively cured of HCV).[65] Therefore, the proportion of HCV cases who experienced clinical consequences was quite small (<2%% of HCV cases) given the potential for spontaneous clearance and high cure rates associated with current treatments.

Mortality

Transition to the dead state occurred from any of the alive health states and was based on all-cause gender- and age-specific mortality sourced from the Human Mortality Database's US-specific tables.[66] We had no evidence to suggest a mortality benefit specific to the use of the digital therapeutic; however, an increased risk of death was assigned to those illicitly using opioids in addition to all-cause mortality.[67] No increase in mortality was attributed to HCV or HIV due to the short time horizon, effective treatments in the two infection areas, and to avoid potential double counting due to the inclusion of an increase in death for those illicitly using opioids. Table 5.6 reports the mortality inputs used in the model, all of which were converted to per-cycle transition probabilities for inclusion in the model.

Table 5.6. Mortality Inputs

Parameter	Value	Source
Illicit use of Opioids	13.3 per 100,000 people who illicitly use opioids	Kaiser Family Foundation, 2016[67]
All-Cause Mortality	U.S. Life Tables[66]	

Heterogeneity and Subgroups

As a sub-group scenario analysis, we modeled separate estimates for those that were treatment naïve versus those who had previously received OUD treatment prior to initiating the digital therapeutic. Differences in these sub-groups were driven by differences in total abstinence days over Phase 1 and treatment retention; all other model inputs remained consistent with the base-case analysis due to a paucity of evidence. Table 5.7 presents the data elements used to support these sub-group scenario analyses.

Table 5.7. Heterogeneity and Subgroups

OUD Treatment Naïve	reSET-O	SoC/CM Comparator	Intervention Effect	Source
Total Abstinence Days over Phase 1	63.4 days	60.1 days	3.2 days (-7.7, 14.2)	Christensen et al., 2014[32]
On MAT Treatment at Completion of Digital Therapeutic	72.7%	70.3%	OR=1.13 (0.45,2.84)	Christensen et al., 2014[32]
OUD Treatment Experienced	**reSET-O**	**SoC/CM Comparator**	**Intervention Effect**	**Source**
Total Abstinence Days over Phase 1	72.6 days	54.8 days	17.8 days (8.2, 27.4)	Christensen et al., 2014[32]
On MAT Treatment at Completion of Digital Therapeutic	91.9%	58.5%	OR=8.03 (2.12, 30.47)	Christensen et al., 2014[32]

CM=contingency management; OR=Odds ratio; SoC=standard of care

Health State Utilities

There was no evidence to suggest a utility benefit or decrement associated with time on the digital therapeutic. Health state utilities were the same as those used in the 2018 ICER MAT review. These health state utilities were derived from a study that used an online US cross-sectional survey.[68] The study comprised hypothetical descriptive vignettes for OUD and associated MAT-related health states that were developed based on inputs from literature, clinical expert opinion, and people diagnosed with OUD. Quality of life assessments were undertaken using the standard gamble technique. For each health state, two sets of vignettes were developed, one including physical/emotional descriptors, and another "expanded" version adding societal factors to the

physical/emotional descriptors (i.e., employment, criminal justice, and family relationship-specific aspects). The study excluded comorbidity-associated vignettes because its primary focus was assessing quality of life associated with OUD alone. Health state utilities when on MAT with concurrent use of illicit opioids were calculated by applying the ratio of utilities when illicitly using opioids with and without MAT (from a UK study)[56] to the base utility when illicitly using opioids when off MATs (from the cross-sectional survey).[68] Health state utilities in the Off MAT without Illicit Use of Opioids health state were sourced from a nationally representative survey conducted in the US.[69] Table 5.8 presents the health state utilities used in the model.

Table 5.8. Health State Utilities

Parameter	Value	Source
Off MAT without Illicit Use of Opioids	0.852	Wittenberg et al., 2016[68]
On MAT without Illicit Use of Opioids	0.766	Wittenberg et al., 2016[68]
On MAT with Illicit Use of Opioids – Not Injected	0.700	Connock et al., 2007[56]
Off MAT with Illicit Use of Opioids – Not Injected	0.694	Wittenberg et al., 2016[68]
On MAT with Illicit Use of Opioids – Injected	0.618	Connock et al. 2007[56]
Off MAT with Illicit Use of Opioids – Injected	0.574	Wittenberg et al., 2016[68]

For PWID diagnosed with HIV, we applied a 6.9% absolute reduction (disutility) to their baseline health state utilities. This estimate was calculated in the 2018 ICER MAT review and was derived from an economic evaluation that assessed the cost effectiveness of HIV prevention programs among PWID in the US.[70] Multipliers specific to ART and symptomatic HIV were applied to the literature-reported estimates to arrive at a 6.9% reduction from baseline utility among PWID diagnosed with HIV. The applied disutility was held constant over time.

For PWID diagnosed with HCV, we applied a 7% absolute reduction (disutility) to their baseline health state utilities. This disutility was derived from estimates used in a US cost-effectiveness model assessing anti-HCV treatments in patients diagnosed with HCV.[71] The applied disutility was held constant over time and attributed only to HCV patients for whom there was no spontaneous clearance of HCV infection and for those not cured from HCV drug treatment. Therefore, the proportion of individuals meeting these conditions was quite small (<2% of HCV cases) given the high potential for spontaneous clearance and high cure rates associated with current treatments. Further, the annual incidence of HCV among PWID is less than 30%, and only 14% of our cohort report injecting drugs.[32] Therefore, HCV-specific disutilities are not anticipated to be a key driver of the model.

Intervention Utilization

- Table 5.9 details additional specifics of the digital therapeutic utilization. The digital therapeutic was modeled as an adjunct to MAT. The MAT regimen that was modeled consisted of a generic once daily 16mg sublingual buprenorphine/naloxone tablet.

Table 5.9. Intervention Recommended Utilization

Digital Therapeutic	reSET-O
Innovator	Pear Therapeutics
Intervention Duration	12 Weeks
Average Adherence	Not Available

Cost Inputs

All costs used in the model were updated to 2020 US dollars. The model included direct medical costs, including but not limited to digital therapeutic costs, MAT costs, other intervention-related costs, and health care resource utilization costs.

Intervention Costs

In the absence of manufacturer-provided net prices, the wholesale acquisition cost for reSET-O was used to approximate the cost per patient to access/download the digital therapeutic. Table 5.10 presents the cost for reSET-O per download.

Table 5.10. Intervention Cost per Patient

Digital Therapeutic	AWP per Download	WAC per Download	Source
reSET-O	$1,998	$1,665	Redbook[72]

AWP=average wholesale price, WAC=wholesale acquisition cost

Drug Costs

The only drug costs that were included in the model were the wholesale acquisition cost (WAC) of MAT. No rebates off of WAC were known at the time of this report. The MAT regimen consisted of once daily 16mg generic sublingual buprenorphine/naloxone. Table 5.11 details the average daily and annual cost for generic buprenorphine/naloxone. Costs associated with MAT acquisition were only assigned to patients in health states that corresponded to On MAT.

Table 5.11. Drug Costs

Drug	WAC per Dose	Discount from WAC	Net Price per Dose	Net Price per Year	Source
Generic Sublingual Buprenorphine/Naloxone	$9.81	N/A due to generic product	$9.81	$3,579	Redbook[72]

Non-Drug Costs

Administration Costs

Because the digital therapeutic does not require any administration, and the MAT is an orally administered treatment, no administration costs were modeled.

Health Care Utilization Costs

Intervention-related health care utilization over the duration of the digital therapeutic, not including MAT and the cost of the digital therapeutic, was sourced from evidence specific to each digital therapeutic and from published literature. Table 5.12 presents the other intervention-related health care utilization over the duration of the digital therapeutic for reSET-O.

Table 5.12. Intervention-Related Health Care Utilization while On Digital Therapeutic (Phase 1 of Model)

	reSET-O	SoC Comparator	CM Comparator
Therapist Counseling	6 visits	6 visits	6 visits
Provider Interactions with Digital Therapeutic Platform	[redacted]	0 visits	0 visits
Contingency Management	12 weeks*	0 weeks	12 weeks

*Contingency management is included within the reSET-O intervention.

Table 5.13 provides the unit cost for each health care utilization type. The cost of contingency management is only applied to the contingency management comparator used in a scenario analysis because the cost of contingency management for reSET-O is included in the reSET-O price.

Table 5.13. Intervention-Related Health Care Utilization Unit Costs

	Value	Notes/Source
Therapist Counseling	$128	Average commercial reimbursement for CPT code 90834[73]
Provider-Patient Interaction with Digital Therapeutic Platform	$65	Average Commercial Insurance Allowed for CPT Code of 99212 for Level II Office Visit[74]
Contingency Management*	$326 (over 12 weeks)	Sindelar et al., 2007[75]

CPT: Current procedural terminology

*Contingency management cost is included within the reSET-O price, not in addition to the reSET-O price. Contingency management cost is only applied in addition to other standard of care costs in the comparator that includes contingency management.

OUD-related health care costs were sourced from a cross-sectional, retrospective analysis of health care claims data that examined differences in health care utilization and costs by buprenorphine adherence status.[76] The analysis reported health care utilization paid amounts separately for those who were MAT adherent and those who were not MAT adherent. Significantly fewer total costs were observed in the MAT adherent population, although no propensity score matching or pre/post analysis was conducted. Cost estimates were calculated separately for inpatient care, outpatient

care, ED visits, and pharmacy. Pharmacy costs were excluded to avoid double counting with the MAT health care costs included in the model. Table 5.14 presents the per-cycle OUD health care costs, stratified by On MAT (assumed to correspond to MAT adherent) and Off MAT (assumed to correspond to MAT non-adherent). During Phase 1 of the model, outpatient costs were not included in the model to avoid double-counting of costs associated with the intervention-related health care utilization reported in Table 5.13. For the Off MAT without Illicit Use of Opioids health state, we assigned age-adjusted health care costs based on the general population.[77]

Table 5.14. Average Health Care Utilization Costs, per Model Cycle

Per Cycle Costs (4 weeks)	On MAT with Illicit Use of Opioids [76]	Off MAT with or without Illicit Use of Opioids [76]
Hospitalizations	$379	$1,033
Emergency Department Visits	$55	$101
Outpatient Visits	$136	$159

Costs reported are per cycle (four weeks) and are reflective of average health care utilization for patients with OUD who are or are not adherent to buprenorphine. These estimates are not unit costs, but reflect the unit cost multiplied by the average rate of use of each service per four-week cycle.

Comorbidity Costs

For PWID diagnosed with HIV or HCV, we attributed drug and other non-drug costs associated with these comorbidities.[78,79] The per-cycle costs of HIV and HCV are reported in Table 5.15 and are based on model inputs used in the 2018 ICER MAT review.[18] Other HIV treatment costs include the costs associated with participation in HIV-related community care programs. HCV drug costs are reported per cycle in Table 5.15 and are only applied for two cycles to correspond with the eight-week HCV treatment duration. Other HCV treatment costs were only assigned to individuals treated with HCV drug therapy who were not cured and who did not spontaneously clear.

Table 5.15. HIV and HCV Treatment Costs per Cycle (4-week Duration) per Case

	HIV[70]	HCV[65,78]
Drug Costs	$1,899	$19,744*
Other Treatment Costs	$403†	$865‡

HIV: human immunodeficiency virus, HCV: hepatitis C virus
*HCV drug cost is assumed to be that of glecaprevir 100 mg/pibrentasvir 40 mg (Mavyret) for eight weeks. Price is presented per 4 weeks. This is applied for 8 weeks in total (i.e. 2 model cycles only).
†Assuming only 75% of diagnosed individuals attend HIV-specific community care programs.
‡Only applied to those who fail HCV treatment and who do not spontaneously clear.

Productivity Costs and Other Indirect Costs

Digital therapeutic use could be associated with productivity gains by resulting in more total abstinence days in Phase 1 of the model. Similar to the 2018 ICER MAT review,[18] we included costs associated with lost productivity, criminal justice, and incarceration in a scenario analysis that took a modified societal perspective. For lost productivity, based on the modeled population characteristics, it was estimated that 37% of the population was employed[32]. Birnbaum et al. reported productivity costs which included lost wages, excess disability, medically-related absenteeism, lost wages from incarceration, and presenteeism associated with opioid misuse and OUD in the US.[80] These estimates were combined with SAMHSA data[81] to calculate the productivity loss costs per person (Table 5.16). Additional detail is described elsewhere. [18] These productivity costs were applied to approximately 37% of the modeled cohort [32] while in health states that include illicit use of opioids.

The costs of criminal justice and incarceration were sourced from a retrospective cohort study that included data from the California Outcomes Monitoring System, Automated Criminal History System, Offender Based Information System, and National Death Index referred to in the 2018 ICER MAT review.[82] Patients included in the study were those diagnosed with OUD with uniquely identifiable criminal justice records. Criminal justice and incarceration costs comprised costs of policing, court, corrections, and medical expenses, cash losses, property theft, and consequences related to criminal victimization. Based on an estimate used in the 2018 ICER MAT review,[18] we assumed 43% of the population was involved in criminal justice and incarceration-related events over the five-year time horizon, and therefore applied these costs to the same percentage within our cohort after adjusting to a per-cycle probability. This study reported daily costs of criminal justice and incarceration when on opioid agonist therapy and "post-treatment," which in our model referred to costs when On MAT (with and without Illicit Use of Opioids) and Off MAT (only with Illicit Use of Opioids), respectively (Table 5.16). Details of these calculations can be found in the 2018 ICER MAT review appendix.[18]

Table 5.16. Societal Costs per Cycle (4-week duration)

Societal Cost Type	Per Cycle Value
Productivity Losses (only with Illicit Use of Opioids)	$1,358*
Criminal Justice and Incarceration	
When On MAT (with and without Illicit Use of Opioids)	$1,109¥
When Off MAT (only with Illicit Use of Opioids)	$5,546¥

*
Applied to 37% of patients in applicable health states.
¥Applied to 43% of patients in applicable health states.

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We used beta distributions for inputs bounded by 0 to 1 and gamma and normal distributions for continuous inputs. Additionally, we performed a threshold analysis by systematically altering the price of reSET-O to estimate the maximum prices that would correspond to given willingness to pay (WTP) thresholds.

Scenario Analyses

We conducted the following scenario analyses:

1. Modified societal perspective that included components such as productivity losses, criminal justice and incarceration, or others as applicable.
2. A comparator that included contingency management.
3. Model outcomes and incremental comparisons at a trial time horizon.
4. Sub-populations of treatment naïve and treatment experienced.

5.3 Results

Base Case Results

The addition of reSET-O to outpatient MAT resulted in approximately $1,400 more total payer costs over a 5-year time horizon. The addition of reSET-O to outpatient MAT alone resulted in additional costs to download the digital therapeutic and additional MAT costs; however, health care utilization costs were slightly lower due to the higher percent of individuals retained on MAT. Clinical outcomes of life years, QALYs, and evLYGs with reSET-O were slightly higher than standard of care resulting from the larger number of abstinent days over Phase 1 and the higher percent of individuals retained on MAT treatment. Table 5.17 presents the model outputs for the base-case analysis comparing reSET-O to standard of care.

Table 5.17. Results for the Base Case for reSET-O Compared to Standard of Care

Intervention	Digital Therapeutic Download Cost	Total Health System Costs	Life Years*	QALYs*	evLYGs*	On MAT at 12 Weeks
reSET-O	$1,665	$83,999	4.61821	3.137760	3.137763	80.4%
SoC	$0	$82,558	4.61820	3.134761	3.134761	64.1%

evLYG=equal value life year gained; MAT=medication-assisted treatment; QALY=quality-adjusted life year; SoC=standard of Care

*The number of significant digits displayed was determined based on the significant digits necessary to identify a difference between arms and between outcomes.

The higher health system costs in the reSET-O arm, and the marginal increase in QALYs generated an incremental cost-effectiveness ratio of approximately $480,600 per QALY gained. Results were similar when compared to outcomes of evLYG due to the very small mortality benefit with reSET-O due to the fewer days of illicit use while using the digital therapeutic. Table 5.18 presents the incremental findings for the base case.

Table 5.18. Incremental Cost-Effectiveness Ratios for the Base Case

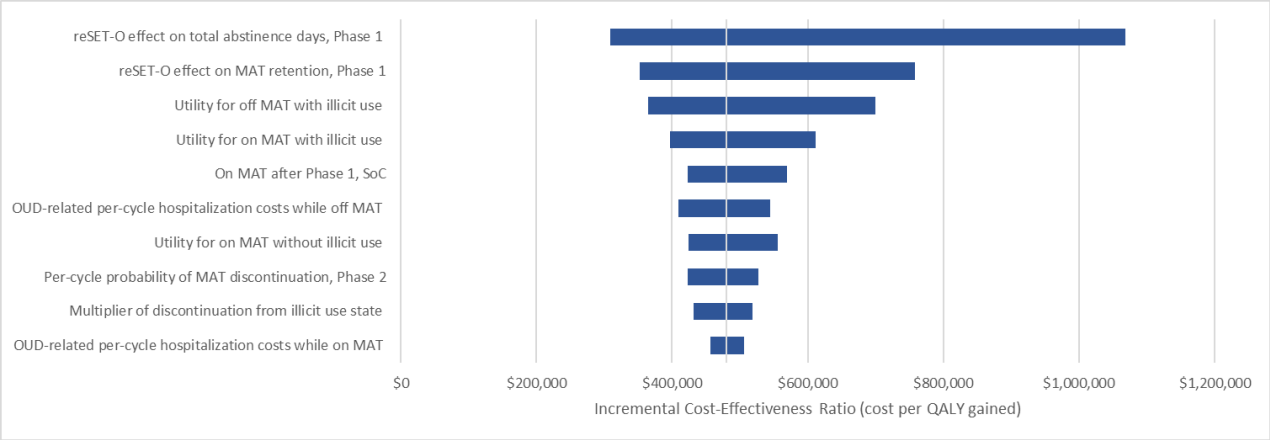
Treatment	Incremental Cost per Life Year Gained	Incremental Cost per QALY Gained	Incremental Cost per evLYG	Incremental Cost per Additional Person on MAT at 12 Weeks
reSET-O vs. SoC	$90,240,000	$480,600	$480,000	$8,800

evLYG=equal value life year gained; MAT=medication-assisted treatment; QALY=quality-adjusted life year; SoC=standard of Care

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. Key drivers of uncertainty included the effect of reSET-O on total abstinence days and the effect of reSET-O on MAT retention. Figure 5.3 presents the tornado diagram resulting from the one-way sensitivity analysis. None of the lower incremental cost-effectiveness ratios resulting from the one-way sensitivity analysis were beneath $150,000 per QALY gained. Additional supporting information for the one-way sensitivity analysis can be found in the appendix.

Figure 5.3. Tornado Diagram for One-Way Sensitivity Analysis of reSET-O versus Standard of Care



A probabilistic sensitivity analysis was conducted to simultaneously vary inputs over multiple iterations. Less than 5% of all iterations would be considered cost-effective at a threshold of $250,000 per QALY gained. Table 5.19 presents the results from the probabilistic sensitivity analysis, with additional supporting information presented in the appendix.

Table 5.19. Probabilistic Sensitivity Analysis Results: reSET-O versus Standard of Care

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY	Cost Effective at $250,000 per QALY
reSET-O vs. SoC	0.0%	0.0%	0.2%	1.4%	4.7%

QALY=quality-adjusted life year; SoC=standard of care

Scenario Analyses Results

Modified Societal Perspective

A modified societal perspective scenario analysis was conducted to incorporate potential benefits of reSET-O on productivity and criminal justice and incarceration costs. reSET-O resulted in fewer lost productivity costs and fewer criminal justice and incarceration costs as compared to standard of care due to fewer total abstinent days and more time on MAT. Table 5.20 presents the total societal cost comparisons between reSET-O and standard of care. The health outcomes (life years, QALYs, and evLYG) for the modified societal perspective are the same as the base case.

Table 5.20. Results for the Modified Societal Perspective for reSET-O Compared to Standard of Care

Intervention	Productivity Loss Costs	Criminal Justice & Incarceration Costs	Total Health System Costs	Total Societal Cost
reSET-O	$27,981	$2,599	$83,999	$114,579
SoC	$28,155	$2,638	$82,558	$113,351

SoC=standard of Care

Due to the incremental costs between reSET-O and standard of care being less in the modified societal perspective than in the base-case health care sector perspective, the incremental cost-effectiveness ratios (Table 5.21) are slightly more favorable.

Table 5.21. Incremental Cost-Effectiveness Ratios for the Modified Societal Perspective

Treatment	Incremental Cost per Life Year Gained	Incremental Cost per QALY Gained	Incremental Cost per evLYG	Incremental Cost per Additional Person on MAT at 12 Weeks
reSET-O vs. SoC	$76,920,000	$410,000	$409,000	$7,500

evLYG=equal value life year gained; QALY=quality-adjusted life year; SoC=standard of Care

Contingency Management Comparator

A scenario analysis was conducted that mirrored the comparator in the reSET-O pivotal trial and included contingency management in addition to outpatient MAT treatment. Although this comparator does not represent standard of care, we conducted a scenario analysis using this comparator to model the pivotal trial study design. The contingency management comparator was equivalent to the standard of care comparator in clinical outcomes but included additional costs to provide contingency management. Table 5.22 presents the model outputs from this comparison.

Table 5.22. Results for reSET-O Compared to Contingency Management

Intervention	Digital Therapeutic Download Cost	Total Health System Cost	Life Years*	QALYs*	evLYGs*	On MAT
reSET-O	$1,665	$83,999	4.61821	3.137760	3.137763	80.4%
CM Comparator	$0	$82,884	4.61820	3.134761	3.134761	64.1%

CM=Contingency Management; evLYG=equal value life year gained; MAT=medication-assisted treatment; QALY=quality-adjusted life year

*The number of significant digits displayed was determined based on the significant digits necessary to identify a difference between arms and between outcomes.

The incremental findings presented in Table 5.23 are slightly more favorable than the base-case incremental findings due to the comparator arm being more costly than the standard of care arm with the addition of contingency management costs.

Table 5.23. Incremental Cost-Effectiveness Ratios for reSET-O compared to Contingency Management

Treatment	Incremental Cost per Life Year Gained	Incremental Cost per QALY Gained	Incremental Cost per evLYG	Incremental Cost per Additional Person on MAT at 12 Weeks
reSET-O vs. CM Comparator	$69,820,000	$371,800	$371,500	$6,800

CM=Contingency Management; evLYG=equal value life year gained; MAT=medication-assisted treatment; QALY=quality-adjusted life year

Trial Time Horizon

A scenario analysis using the trial time horizon of 12 weeks was also conducted. Table 5.24 presents the model outputs and Table 5.25 presents the incremental findings from this scenario analysis. The incremental findings from the shorter time horizon are less favorable than the base-case findings due to no benefit assumed after 12 weeks.

Table 5.24. Results for the Base Case for reSET-O Compared to Contingency Management and to Standard of Care, Trial Time Horizon

Intervention	Digital Therapeutic Download Cost	Total Health System Cost	Life Years*	QALYs*	evLYGs*	On MAT at 12 Weeks (%)
reSET-O	$1,665	$5,207	0.2307043	0.1729890	0.1729891	80.4%
SoC	$0	$3,425	0.2307039	0.1706734	0.1706734	64.1%

evLYG=equal value life year gained; MAT=medication-assisted treatment; QALY=quality-adjusted life year; SoC=standard of Care

*The number of significant digits displayed was determined based on the significant digits necessary to identify a difference between arms and between outcomes.

Table 5.25. Incremental Cost-Effectiveness Ratios for the Base Case, Trial Time Horizon

Treatment	Incremental Cost per Life Year Gained	Incremental Cost per QALY Gained	Incremental Cost per evLYG	Incremental Cost per Additional Person on MAT at 12 Weeks
reSET-O vs. SoC	$4,357,270,000	$770,000	$770,000	$11,000

evLYG=equal value life year gained; MAT=medication-assisted treatment; QALY=quality-adjusted life year; SoC=standard of Care

Sub-Population Scenario Analyses

Two sub-populations were modeled in a scenario analysis. Table 5.26 and 5.27 present the model outputs and incremental findings for the OUD treatment naïve population. Due to the insignificant effect of reSET-O on MAT retention and abstinence in the treatment naïve sub-population, the cost-effectiveness estimates are very high for this sub-population.

Table 5.26. Results for the Base Case for reSET-O Compared to Contingency Management and to Standard of Care, Treatment Naïve Population

Intervention	Digital Therapeutic Download Cost	Total Health System Cost	Life Years*	QALYs*	evLYGs*	On MAT at 12 Weeks (%)
reSET-O	$1,665	$84,207	4.61821	3.136540	3.136541	72.8%
SoC	$0	$82,389	4.61820	3.135692	3.135692	70.3%

evLYG=equal value life year gained; MAT=medication-assisted treatment; QALY=quality-adjusted life year; SoC=standard of Care

*The number of significant digits displayed was determined based on the significant digits necessary to identify a difference between arms and between outcomes.

Table 5.27. Incremental Cost-Effectiveness Ratios for the Base Case, Treatment Naïve Population

Treatment	Incremental Cost per Life Year Gained	Incremental Cost per QALY Gained	Incremental Cost per evLYG	Incremental Cost per Additional Person on MAT at 12 Weeks
reSET-O vs. SoC	$345,160,000	$2,140,000	$2,140,000	$73,000

evLYG=equal value life year gained; MAT=medication-assisted treatment; QALY=quality-adjusted life year; SoC=standard of Care

Table 5.28 and 5.29 present the model outputs and incremental findings for the OUD treatment experienced population. In this population, the effect of reSET-O on MAT retention and abstinence was more favorable than in the base case; thus, the cost-effectiveness estimates are more favorable for this sub-population.

Table 5.28. Results for reSET-O Compared to Standard of Care, Treatment Experienced Population

Intervention	Digital Therapeutic Download Cost	Total Health System Cost	Life Years*	QALYs*	evLYGs*	On MAT at 12 Weeks (%)
reSET-O	$1,665	$83,686	4.61822	3.139503	3.139508	91.9%
SoC	$0	$82,711	4.61819	3.133872	3.133872	58.5%

evLYG=equal value life year gained; MAT=medication-assisted treatment; QALY=quality-adjusted life year; SoC=standard of Care

*The number of significant digits displayed was determined based on the significant digits necessary to identify a difference between arms and between outcomes.

Table 5.29. Incremental Cost-Effectiveness Ratios for reSET-O Compared to Standard of Care, Treatment Experienced Population

Treatment	Incremental Cost per Life Year Gained	Incremental Cost per QALY Gained	Incremental Cost per evLYG	Incremental Cost per Additional Person on MAT at 12 Weeks
reSET-O vs. SoC	$33,280,000	$173,000	$173,000	$2,900

evLYG=equal value life year gained; MAT=medication-assisted treatment; QALY=quality-adjusted life year; SoC=standard of Care

Threshold Analyses Results

Table 5.30 presents the results of the threshold analysis for reSET-O as compared to standard of care. Note that these results are preliminary and for reasons discussed in Section 6 should not be assumed to reflect the health-benefit price benchmarks that will be provided in the next version of this Report. A threshold analysis from the societal perspective is available in the appendix.

Table 5.30. Threshold Analysis Results

	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY
reSET-O	$1,665	N/A	$370	$520	$670

QALY=quality-adjusted life year; WAC=wholesale acquisition cost

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing

findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

We searched the current available literature to identify past economic models that were similar to our analysis in regard to population, settings, perspective, and treatments. A study published in 2016 performed a cost-effectiveness analysis of an internet delivered treatment of substance use disorder from both the payer and provider perspectives.[83] Although only 21% of participants in this study presented with opioid use disorder (and thus there are important differences in both the intervention and comparator from our analysis), it did examine an application of TES. The authors reported estimates from both the provider and payer perspective. The payer perspective is most similar to the health care sector perspective taken in our analysis. From the payer perspective, the prior study calculated 12- and 36-week cost-effectiveness estimates by calculating total direct medical costs per QALY gained and abstinent year, including all provider and medical service costs. This study indicated that the internet delivered treatment, in addition to standard of care, was dominated (e.g. no improvement in QALYs despite more abstinent years, and more costly) compared to standard of care. Similar to our analysis, the cost offsets and clinical gains that may be associated with the digital therapeutic were not enough to reach commonly used cost-effectiveness thresholds for QALYs.

5.4 Summary and Comment

Our base case results suggest 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. At current WAC pricing, and given available evidence, these potential cost offset and clinical gains were not enough to generate incremental cost-effectiveness estimates beneath commonly cited cost-effectiveness thresholds. The results were sensitive to many parameters, especially the effect of the digital therapeutic on retention and abstinence days. However, even given parameter uncertainty, the probability of a cost-effective findings at current pricing was extremely rare. Our model extrapolated potential benefits from increased retention associated with reSET-O over a five-year time horizon, despite no evidence available after time on digital therapeutic. This is a strong model assumption that benefits the digital therapeutic and is an important area for clinical evidence generation. Interestingly, the sub-group scenario analysis for OUD treatment experienced patients was the most favorable cost-effectiveness estimate and was closest to reaching commonly cited

cost-effectiveness benchmarks. However, there are methodological concerns with these sub-groups in the pivotal trial; therefore, this is another area where additional evidence is necessary.

Limitations

This study is primarily limited by the evidence gaps, resulting from a dearth of peer-reviewed evidence and limited applicability of peer-reviewed evidence to the real-world setting. Only one digital therapeutic (reSET-O) had sufficient peer-reviewed evidence to support inclusion in a cost-effectiveness model. However, the applicability of the published evidence for reSET-O is questioned as it used a different delivery setting (internet-delivered at a clinic versus app-delivered at home) and different incentive structure and amount. Further, no evidence from after the completion of the digital therapeutic is available, despite publications of this evidence dating back to 2014. Also, the comparator arm in the pivotal trial for reSET-O was not reflective of standard of care; therefore, we made adjustments to the contingency management comparator to compare reSET-O to standard of care. The impact of contingency management in addition to MAT versus MAT alone differs in the literature, from some sources reporting worse outcomes than MAT alone to some sources reporting better outcomes than MAT alone. Similarly, a driver of the cost effectiveness for an intervention that increases retention is the potential cost offsets associated with MAT use. The published evidence in this space is also contradicting, with some studies reporting cost savings among those on MAT and others presenting no cost savings (to potential cost increases) among those on MAT. Last, the cost-effectiveness model used population characteristics that mirrored the population characteristics of the reSET-O evidence. The cost-effectiveness findings may differ given different population characteristics.

Conclusions

Given available evidence and plausible assumptions, the cost effectiveness of reSET-O greatly exceeds commonly used thresholds of $100,000-$150,000 per QALY gained. This was robust to numerous sensitivity and scenario analyses.

6. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of digital apps plus MAT for OUD to MAT alone. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 6.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework... The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 6.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic
Very similar mechanism of action to that of other active treatments		New mechanism of action compared to that of other active treatments
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials
The intervention offers no special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits
This intervention could reduce or preclude the potential effectiveness of future treatments.		This intervention offers the potential to increase access to future treatment that may be approved over the course of a patient's lifetime.
This intervention will not differentially benefit a historically disadvantaged or underserved community		This intervention will differentially benefit a historically disadvantaged or underserved community
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
Small health loss without this treatment as measured by proportional QALY shortfall		Substantial health loss without this treatment as measured by proportional QALY shortfall
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator
Other		Other

6.1 Potential Other Benefits and Contextual Considerations

There is considerable uncertainty about the efficacy inputs to the model particularly over the long term. The model's assumptions bias the model in favor of the digital apps.

The mechanism of action is fairly similar to available web based and in person versions of the behavioral interventions.

The delivery mechanism (smart phone at home, rather than clinic based) has the potential to increase real world adherence, but it could also decrease adherence. There are no data yet.

The intervention does not impact the timing of risks and benefits.

The intervention should not affect the potential impact of future innovations.

There is the possibility that these apps could exacerbate differences due to limited health literacy, limited English proficiency, and facility with digital tools due to limited current access or prior experience.

The proportional QALY shortfall (0.253) suggests that other health technology assessment groups would interpret this disease space as being of important burden, but of lower importance than diseases that have larger impacts on mortality and/or morbidity. However, the relatively short time horizon of our analysis (5-years) may bias the estimated QALY shortfall towards the low end as we may not capture the full negative impact of OUD.

It is unclear whether the use of a digital app will reduce the impact of OUD on the family and caregivers or on the ability of the patient to return to work or increase their productivity.

7. Health-Benefit Price Benchmarks

ICER does not provide health-benefit price benchmarks as part of the draft report because results are likely to change based on public comment. Health-benefit price benchmarks will be included in the revised Evidence Report that will be released on November 6th, 2020. We strongly caution readers against assuming that the values provided in the Threshold Prices section will approximate the health-benefit price benchmarks that will be presented in the next version of this Report. Based on reviewer and public input as well as manufacturer and internal model review, these results may change substantially.

8. Potential Budget Impact

8.1 Overview

Note that these results are preliminary and for reasons discussed in Section 6 should not be assumed to reflect the health-benefit price benchmarks that will be provided in the next version of this Report.

We used results from the cost-effectiveness model to estimate the potential total budgetary impact of treatment with reSET-O for adults 18 years and older with OUD in outpatient MAT. We used the WAC ($1,665) and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) for reSET-O in our estimates of budget impact. Consistent with ICER's Value Assessment Framework, we do not provide a reference to a potential budget impact threshold for non-drug topics.

8.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis includes the estimated number of individuals in the US who would be eligible for these treatments. To estimate the size of the potential candidate population for treatment, we used the prevalence of adults 18 years and older with OUD in outpatient MAT.

The prevalence of OUD treated with MAT is estimated to be 648,864 patients[84]. We assumed that this annual eligible prevalence (478,278) holds as fixed for each of the five years in the projection. We assumed that patients eligible for reSET-O would need to speak English and to have a cell phone. We applied the probability of speaking English in the US (0.91) [85] and the probability of an adult owning a smartphone in the US (0.81)[86]. Assuming these are independent, we multiplied these proportions by the estimated prevalence (648,864) to arrive at an estimate of 478,278 individuals as the eligible population for these treatments. Among these eligible patients, we assumed a 20% uptake each year over five years, or 95,656 patients per year.

We evaluated whether the new treatments would take market share from one or more existing treatments to calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that patients eligible for reSET-O

would otherwise have been treated with standard of care (SoC, i.e., MAT with no additional OUD-related treatment).

ICER's methods for estimating potential budget impact are described in detail elsewhere[87] and have been recently updated.

8.3 Results

Figure 8.1 illustrates the cumulative per-patient budget impact calculations for reSET-O compared to SoC, based on the WAC of $1,665 for one-time treatment. The average potential budgetary impact for reSET-O was an additional per-patient cost of approximately $1,486 in year one, with slight net savings in years two and three and no net difference by years four and five, leading to a small decline in cumulative costs to approximately $1,435 by year five. (Additional net costs per year are presented along with cumulative net costs in Appendix Table E.7.)

Figure 8.1. Cumulative Net Cost Per Patient Treated with reSET-O at WAC Over a Five-year Time Horizon

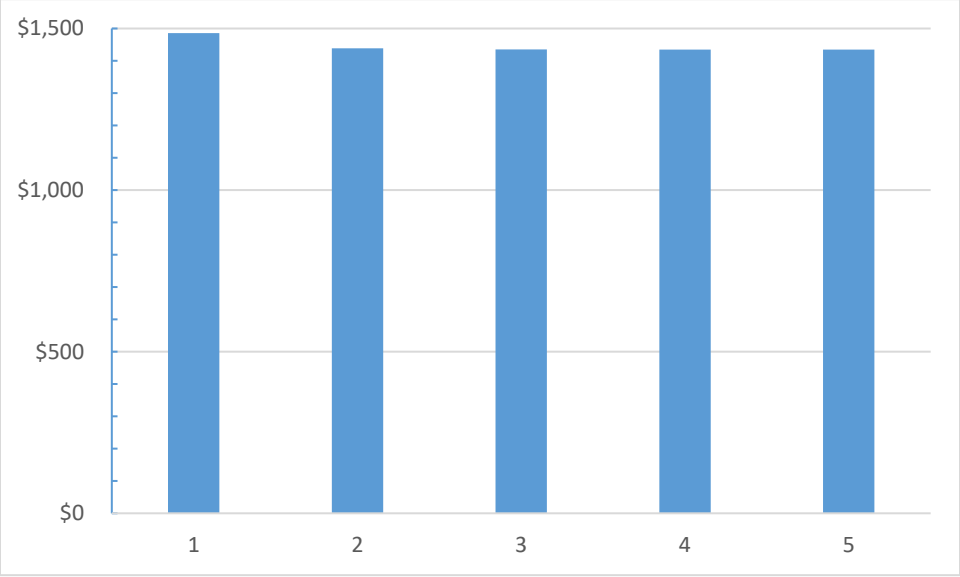


Table 8.1 illustrates the potential budget impact of treatment of the eligible population with reSET-O, based on the WAC ($1,665 per download), and the threshold prices to reach $150,000, $100,000, and $50,000 per QALY compared to SoC. For reSET-O, the annual potential budgetary impact of treating the entire eligible population was $138.3 million, assuming the WAC download price. This was largely due to assumption of one-time download cost with the digital therapeutic and the slight savings with no additional costs in subsequent years.

Table 8.1. Estimated Total Potential Budget Impact of One-Time Download with reSET-O Using WAC and Threshold Prices Over a Five-year Time Horizon (N = 95,656 per Year)

	Annual PBI (millions)	Total 5-Year PBI (millions)
WAC	$138.3	$691.5
$150,000/QALY Threshold Price	$43.5	$217.5
$100,000/QALY Threshold Price	$29.2	$145.8
$50,000/QALY Threshold Price	$14.8	$74.1

PBI: potential budget impact, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. DSM-5.* 2013.
2. SAMHSA. EXHIBIT 2.13. DSM-5 Criteria for OUD in TIP 63: Medications for Opioid Use Disorder. 2018. 2018.
3. SAMHSA. TIP 63: Medications for Opioid Use Disorder. *Treatment Improvement Protocol (TIP) series.* 2018.
4. Kolodny A CD, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annual Review of Public Health.* 2015;36:559-574.
5. Centers for Disease Control and Prevention. Provisional Drug Overdose Death Counts. 2018; https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm.
6. HHS. National Opioid Crisis. October 2019; http://www.hhs.gov/opioids.
7. Substance Abuse and Mental Health Services Administration. *Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health.* Rockville, MD2019.
8. Barocas JA, White LF, Wang J, et al. Estimated Prevalence of Opioid Use Disorder in Massachusetts, 2011–2015: A Capture–Recapture Analysis. *American Journal of Public Health.* 2018;108(12):1675-1681.
9. Bharel M. The True Prevalence of Opioid Use Disorder Nationally Is Likely Underestimated. *American Journal of Public Health.* 2019;109(2):214-215.
10. Council of Economic Advisors. The Full Cost of the Opioid Crisis: $2.5 Trillion Over Four Years. 2019. https://www.whitehouse.gov/articles/full-cost-opioid-crisis-2-5-trillion-four-years/.
11. SAMHSA. Medication-Assisted Treatment (MAT). 2018; https://www.samhsa.gov/medication-assisted-treatment.
12. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. *Journal of addiction medicine.* 2015;9(5):358-367.
13. California Health Benefits Review Program. Analysis of California Assembly Bill 2384 Medication-Assisted Treatment. 2018.
14. Volkow N. Medications for opioid use disorder: bridging the gap in care. *Lancet.* 2018;391(10118):285-287.
15. Volkow NF, TR; Hyde, PS; Cha, SS. Medication-assisted therapies--tackling the opioid-overdose epidemic. *N Engl J Med.* 2014;370(22):2063-2066.
16. Carroll KM, Weiss RD. The Role of Behavioral Interventions in Buprenorphine Maintenance Treatment: A Review. *Am J Psychiatry.* 2017;174(8):738-747.
17. Rash CJ, Stitzer M, Weinstock J. Contingency Management: New Directions and Remaining Challenges for An Evidence-Based Intervention. *J Subst Abuse Treat.* 2017;72:10-18.
18. Institute for Clinical and Economic Review. Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value. 2018.
19. Riley WT, Oh A, Aklin WM, Wolff-Hughes DL. National Institutes of Health Support of Digital Health Behavior Research. *Health Educ Behav.* 2019;46(2_suppl):12-19.

20. US Food and Drug Administration. 510(k) Premarket Notification K173681. 2019; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?id=K173681. Accessed August 28, 2020.
21. Gustafson DH, Sr., Landucci G, McTavish F, et al. The effect of bundling medication-assisted treatment for opioid addiction with mHealth: study protocol for a randomized clinical trial. *Trials.* 2016;17(1):592.
22. Gustafson DH, McTavish FM, Chih MY, et al. A smartphone application to support recovery from alcoholism: a randomized clinical trial. *JAMA Psychiatry.* 2014;71(5):566-572.
23. Gustafson DH, Quanbeck AR, Robinson JM, et al. Which elements of improvement collaboratives are most effective? A cluster-randomized trial. *Addiction.* 2013;108(6):1145-1157.
24. Carroll KM, Ball SA, Martino S, et al. Computer-assisted delivery of cognitive-behavioral therapy for addiction: a randomized trial of CBT4CBT. *Am J Psychiatry.* 2008;165(7):881-888.
25. Carroll KM, Ball SA, Martino S, Nich C, Babuscio TA, Rounsaville BJ. Enduring effects of a computer-assisted training program for cognitive behavioral therapy: a 6-month follow-up of CBT4CBT. *Drug Alcohol Depend.* 2009;100(1-2):178-181.
26. Carroll KM, Kiluk BD, Nich C, et al. Computer-assisted delivery of cognitive-behavioral therapy: efficacy and durability of CBT4CBT among cocaine-dependent individuals maintained on methadone. *Am J Psychiatry.* 2014;171(4):436-444.
27. Kiluk BD, Devore KA, Buck MB, et al. Randomized Trial of Computerized Cognitive Behavioral Therapy for Alcohol Use Disorders: Efficacy as a Virtual Stand-Alone and Treatment Add-On Compared with Standard Outpatient Treatment. *Alcohol Clin Exp Res.* 2016;40(9):1991-2000.
28. Kiluk BD, Nich C, Buck MB, et al. Randomized Clinical Trial of Computerized and Clinician-Delivered CBT in Comparison With Standard Outpatient Treatment for Substance Use Disorders: Primary Within-Treatment and Follow-Up Outcomes. *Am J Psychiatry.* 2018;175(9):853-863.
29. Shi JM, Henry SP, Dwy SL, Orazietti SA, Carroll KM. Randomized pilot trial of Web-based cognitive-behavioral therapy adapted for use in office-based buprenorphine maintenance. *Subst Abus.* 2019;40(2):132-135.
30. Ryan S, Rezania, S. Improving Inner-city Substance Use Outcomes with Technology: Implementing DynamiCare Health's Motivational Incentives & Cognitive Behavioral Therapy App. 2020; https://static1.squarespace.com/static/5bfc6a4db98a78e1c648c1bd/t/5e37a2db12092f158789ef49/1580704479790/2020-01-25+DynamiCare_Brightview+White+Paper.pdf.
31. Maglione MR, L; Chen, C; et al. Effects of medication assisted treatment (MAT) for opioid use disorder on functional outcomes: A systematic review. *Journal of substance abuse treatment.* 2018(89):28-51.
32. Christensen DR, Landes RD, Jackson L, et al. Adding an Internet-delivered treatment to an efficacious treatment package for opioid dependence. *J Consult Clin Psychol.* 2014;82(6):964-972.
33. American Psychiatric Association. Substance-Related and Addictive Disorders. In: *Diagnostic and Statistical Manual of Mental Disorders.* American Psychiatric Association; 2013.
34. SAMHSA. Recovery and Recovery Support. 2018; https://www.samhsa.gov/find-help/recovery.
35. Fiellin DA, Moore BA, Sullivan LE, et al. Long-term treatment with buprenorphine/naloxone in primary care: results at 2-5 years. *Am J Addict.* 2008;17(2):116-120.
36. Hser YI, Evans E, Huang D, et al. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. *Addiction.* 2016;111(4):695-705.

37. Parran TV, Adelman CA, Merkin B, et al. Long-term outcomes of office-based buprenorphine/naloxone maintenance therapy. *Drug Alcohol Depend.* 2010;106(1):56-60.
38. Murphy SM, Polsky D. Economic Evaluations of Opioid Use Disorder Interventions. *PharmacoEconomics.* 2016;34(9):863-887.
39. Food and Drug Administration. Public Meeting on Patient-Focused Drug Development for Opioid Use Disorder. 2018; https://www.fda.gov/industry/prescription-drug-user-fee-amendments/public-meeting-patient-focused-drug-development-opioid-use-disorder.
40. PEAR THERAPEUTICS AND REMEDYONE ANNOUNCE PHARMACY BENEFIT MANAGER COVERAGE FOR PRESCRIPTION DIGITAL THERAPEUTICS RESET® & RESET-O® FOR PEOPLE WITH SUBSTANCE AND OPIOID USE DISORDERS [press release]. Pear Therapeutics2020.
41. Help & Hope WV. 2020; https://helpandhopewv.org/connections-for-recovery.html. Accessed 8/26/2020.
42. Sen Capito SM. Prescription Digital Therapeutics to Support Recovery Act. In. Vol S.35322020.
43. Rutowkski TY, Eric; Bernath, Eric; Coker, Temitope; Ricard, Manon. Access and Reimbursement: Access to Digital Therapeutics in a Post-COVID-19 World. In. Vol 2020: CBPartners; 2020.
44. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
45. Higgins J, Green, S (editors),. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011].* The Cochrane Collaboration. Available from http://handbook.cochrane.org.; 2011.
46. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine.* 2009;6(7):e1000097.
47. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force Procedure Manual. 2008.
48. Ollendorf D, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.
49. Chopra MP, Landes RD, Gatchalian KM, et al. Buprenorphine medication versus voucher contingencies in promoting abstinence from opioids and cocaine. *Experimental and clinical psychopharmacology.* 2009;17(4):226-236.
50. Bickel WK, Marsch LA, Buchhalter AR, Badger GJ. Computerized behavior therapy for opioid-dependent outpatients: a randomized controlled trial. *Experimental and clinical psychopharmacology.* 2008;16(2):132-143.
51. Marsch LA, Guarino H, Acosta M, et al. Web-based behavioral treatment for substance use disorders as a partial replacement of standard methadone maintenance treatment. *J Subst Abuse Treat.* 2014;46(1):43-51.
52. CHESS Health. CHESS Health Selected for Nationwide NIDA Study on Medication for Opioid Use Disorder. 2020; https://www.prweb.com/releases/chess_health_selected_for_nationwide_nida_study_on_medication_for_opioid_use_disorder/prweb17272115.htm.
53. Nunes EV, Bickel, W.K., Maricich, Y.A. Prescription Digital Therapeutics: A New Treatment Modality for Substance and Opioid Use Disorder. ASAM Annual Conference; April 4-7, 2019, 2019; Orlando, FL.
54. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev.* 2014(2):CD002207.

55. Carter JA, Dammerman R, Frost M. Cost-effectiveness of subdermal implantable buprenorphine versus sublingual buprenorphine to treat opioid use disorder. *J Med Econ.* 2017;20(8):893-901.
56. Connock M, Juarez-Garcia A, Jowett S, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technol Assess.* 2007;11(9):1-171, iii-iv.
57. Jackson H, Mandell K, Johnson K, Chatterjee D, Vanness DJ. Cost-Effectiveness of Injectable Extended-Release Naltrexone Compared With Methadone Maintenance and Buprenorphine Maintenance Treatment for Opioid Dependence. *Subst Abus.* 2015;36(2):226-231.
58. Nosyk B, Guh DP, Bansback NJ, et al. Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment. *CMAJ.* 2012;184(6):E317-328.
59. Schackman BR, Leff JA, Polsky D, Moore BA, Fiellin DA. Cost-effectiveness of long-term outpatient buprenorphine-naloxone treatment for opioid dependence in primary care. *J Gen Intern Med.* 2012;27(6):669-676.
60. Gross A, Marsch LA, Badger GJ, Bickel WK. A comparison between low-magnitude voucher and buprenorphine medication contingencies in promoting abstinence from opioids and cocaine. *Experimental and clinical psychopharmacology.* 2006;14(2):148-156.
61. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. *BMC Med Res Methodol.* 2011;11:139.
62. Lansky A, Finlayson T, Johnson C, et al. Estimating the number of persons who inject drugs in the united states by meta-analysis to calculate national rates of HIV and hepatitis C virus infections. *PLoS One.* 2014;9(5):e97596.
63. Page K, Morris MD, Hahn JA, Maher L, Prins M. Injection drug use and hepatitis C virus infection in young adult injectors: using evidence to inform comprehensive prevention. *Clin Infect Dis.* 2013;57 Suppl 2:S32-38.
64. Smith DJ, Jordan AE, Frank M, Hagan H. Spontaneous viral clearance of hepatitis C virus (HCV) infection among people who inject drugs (PWID) and HIV-positive men who have sex with men (HIV+ MSM): a systematic review and meta-analysis. *BMC Infect Dis.* 2016;16:471.
65. Food and Drug Administration. *MAVYRET TM (glecaprevir and pibrentasvir) tablets, for oral use.* 2007.
66. Human Mortality Databases. 2016; https://usa.mortality.org/. Accessed 07/15/2018.
67. Opioid Overdose Death Rates and All Drug Overdose Death Rates per 100,000 Population (Age-Adjusted). 2016.
68. Wittenberg E, Bray JW, Aden B, Gebremariam A, Nosyk B, Schackman BR. Measuring benefits of opioid misuse treatment for economic evaluation: health-related quality of life of opioid-dependent individuals and their spouses as assessed by a sample of the US population. *Addiction.* 2016;111(4):675-684.
69. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making.* 2006;26(4):410-420.
70. Bernard CL, Brandeau ML, Humphreys K, et al. Cost-Effectiveness of HIV Preexposure Prophylaxis for People Who Inject Drugs in the United States. *Ann Intern Med.* 2016;165(1):10-19.
71. Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med.* 2015;162(6):397-406.
72. Redbook. Accessed July 23, 2020, 2020.

73. Reifsneider D. Therapy Session Rates by CPT Code. 2019; https://www.simplepractice.com/blog/median-therapy-session-rates-by-state-and-city-cpt-codes/.
74. UNITED HOSPITAL DISTRICT'S TOP 25 PRIMARY CARE CPT CODES AND 2019 PRICING. 2019.
75. Sindelar JL, Olmstead TA, Peirce JM. Cost-effectiveness of prize-based contingency management in methadone maintenance treatment programs. *Addiction.* 2007;102(9):1463-1471.
76. Ruetsch C, Tkacz J, Nadipelli VR, et al. Heterogeneity of nonadherent buprenorphine patients: subgroup characteristics and outcomes. *Am J Manag Care.* 2017;23(6):e172-e179.
77. Services CfMaM. National Health Expenditure Data. 2019; https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Age-and-Gender.
78. Johnson RL BH, Ferro C. . The burden of hepatitis C virus disease in commercial and managed Medicaid populations. *Milliman.* 2015.
79. Bernard CL, Owens DK, Goldhaber-Fiebert JD, Brandeau ML. Estimation of the cost-effectiveness of HIV prevention portfolios for people who inject drugs in the United States: A model-based analysis. *PLoS Med.* 2017;14(5):e1002312.
80. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Med.* 2011;12(4):657-667.
81. Archive SAMHD. National Survey on Drug Use and Health (NSDUH-2007). 2007.
82. Krebs E, Urada D, Evans E, Huang D, Hser YI, Nosyk B. The costs of crime during and after publicly funded treatment for opioid use disorders: a population-level study for the state of California. *Addiction.* 2017;112(5):838-851.
83. Murphy SM, Campbell AN, Ghitza UE, et al. Cost-effectiveness of an internet-delivered treatment for substance abuse: Data from a multisite randomized controlled trial. *Drug Alcohol Depend.* 2016;161:119-126.
84. McCance-Katz EF, MD, PhD:. The National Survey on Durg Use and Health. In: SAMSHA, ed: SAMSHA; 2018.
85. Batalova J, Zong, J. . Language Diversity and English Proficiency in the United States 2016.
86. Mobile Fact Sheet. 2019.
87. Pearson SD. Overview of the ICER value assessment framework and update for 2017-2019. 2018.
88. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. 2020. 2020; https://icer-review.org/methodology/icers-methods/icer-evidence-rating-matrix/. .
89. Acosta MC, Marsch LA, Xie H, Guarino H, Aponte-Melendez Y. A Web-Based Behavior Therapy Program Influences the Association Between Cognitive Functioning and Retention and Abstinence in Clients Receiving Methadone Maintenance Treatment. *Journal of dual diagnosis.* 2012;8(4):283-293.
90. Kim SJ, Marsch LA, Acosta MC, Guarino H, Aponte-Melendez Y. Can persons with a history of multiple addiction treatment episodes benefit from technology delivered behavior therapy? A moderating role of treatment history at baseline. *Addictive behaviors.* 2016;54:18-23.
91. Neumann PJ SG, Russell LB, Siegel JE, Ganiats TG. Cost-effectiveness in health and medicine. *Oxford University Press.* 2016.
92. Pickard AS LE, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. 2019;22(8):931-941.

APPENDICES

Appendix A. Search Strategic Results

Table A.1. PRISMA 2009 Checklist

Checklist Items		
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table A.2. Search Strategies for Digital Therapeutics for OUD

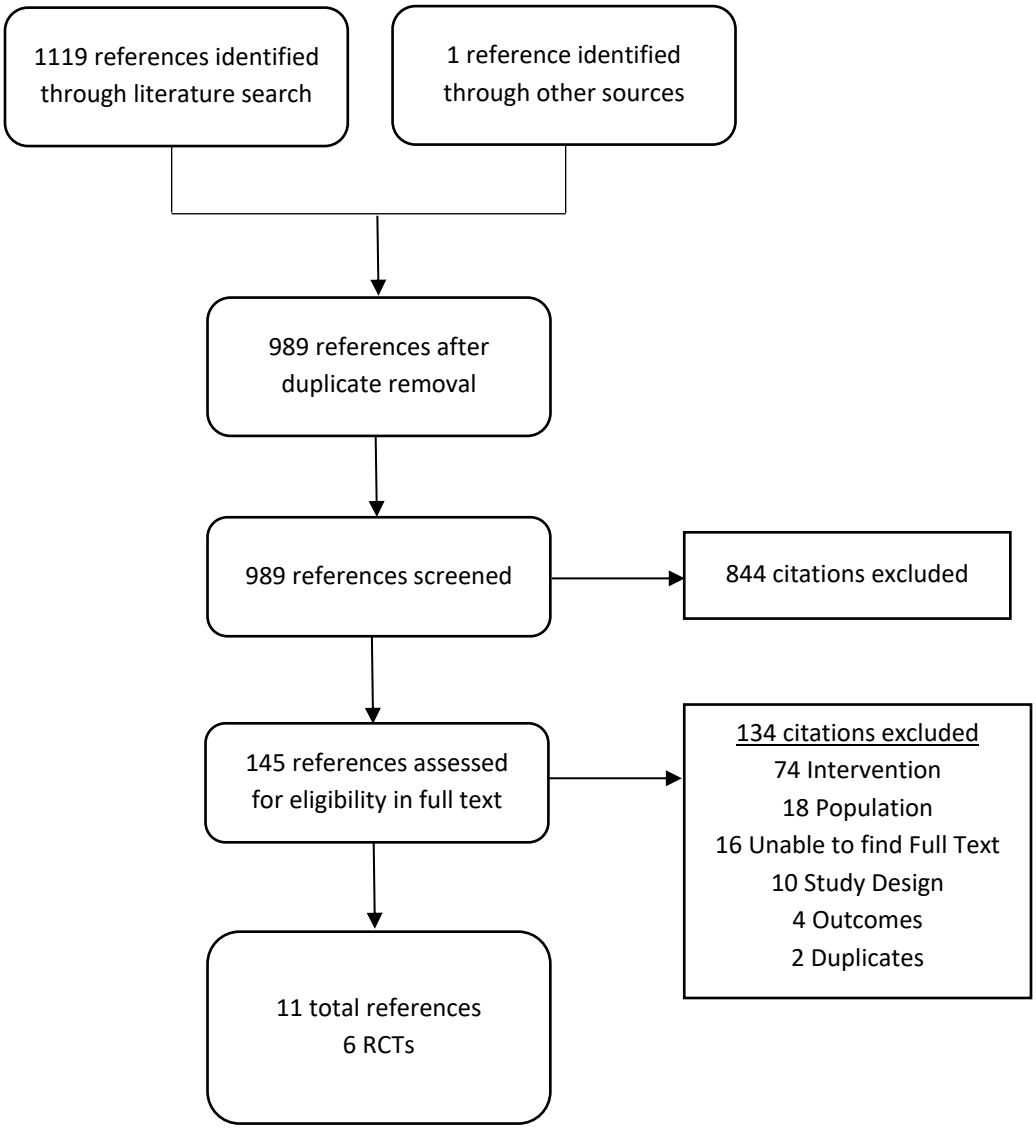
Table A.2.1. Search Strategy of Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present and APA PsycInfo

1	Exp opioid-related disorders/ or analgesics, opioid/ or substance-related disorders/ or narcotic-related disorders/
2	(Opioid OR opioid*related disord* OR opioid addict* OR opioid dependen* OR opioid abus* OR addiction, opioid OR dependence, opioid OR abuse, opioid OR opiate OR opiate addict* OR opiate dependen* OR opiate abus* OR addiction, opiate OR dependence, opiate OR abuse, opiate OR substance abuse).ti,ab.
3	1 OR 2
4	(Exp buprenorphine/ OR buprenorphine, naloxone drug combination/ OR opiate substitution treatment/) AND (exp cognitive behavioral therapy/ OR exp behavior therapy/ OR token economy/ OR exp reinforcement, psychology/)
5	(buprenorphine.ti,ab OR (buprenorphine adj+ naloxone).ti,ab OR opiate substitution treatmen$.ti,ab OR opioid substitution treatmen$.ti,ab OR opioid replacement therapy.ti,ab OR medication*assisted treatment.ti,ab or MAT.ti,ab) AND (cognitive behavioral therapy.ti,ab OR CBT.ti,ab OR behavioral therapy, cognitive.ti,ab OR therapy, cognitive behavioral.ti,ab OR cognitive therapy.ti,ab OR therapy, cognitive.ti,ab OR cognition therapy.ti,ab OR therapy, cognition.ti,ab OR behavioral therapy.ti,ab OR internet*delivered cognitive behavior therapy.ti,ab OR positive reinforcement.ti,ab OR reinforcement, positive.ti,ab OR psychology reinforcement.ti,ab OR community reinforcement approach.ti,ab OR contingency management.ti,ab OR therapeutic education system.ti,ab OR tes.ti,ab OR reset*o.ti,ab OR achess.ti,ab OR a-chess.ti,ab OR a chess.ti,ab OR connections.ti,ab OR dynamicare.ti,ab OR dynamicare health.ti,ab OR digital.ti,ab OR smartphone.ti,ab OR internet.ti,ab OR web.ti,ab OR mobile.ti,ab or app.ti,ab)
6	4 OR 5
7	3 AND 6
8	(addresses OR autobiography OR bibliography OR biography OR case reports OR comment OR congresses OR consensus development conference OR dictionary OR directory OR editorial OR encyclopedia OR festschrift OR guideline OR interactive tutorial).pt
9	7 NOT 8
10	animals not (humans and animals).sh.
11	9 NOT 10
12	Limit 11 to English language
13	Remove duplicates from 12

Table A.2.1. Search Strategy of EMBASE

#1	'opiate addiction'/exp OR 'opiate'/exp OR 'substance abuse'/de OR 'opiate agonist'/exp
#2	'opioid' OR 'opioid addict*':ti,ab OR 'opioid use disorder':ti,ab OR 'opioid dependen*':ti,ab OR 'opioid*related disord*':ti,ab OR 'opioid abus*':ti,ab OR 'opiate' OR 'opiate addict*':ti,ab OR 'opiate dependen*':ti,ab OR 'opiate abus*':ti,ab OR 'substance use disorder':ti,ab OR 'substance abuse':ti,ab OR 'opioid misuse':ti,ab OR 'opiate misuse':ti,ab
#3	#1 OR #2
#4	('buprenorphine'/de OR 'buprenorphine plus naloxone'/de OR 'opiate antagonist'/exp OR 'opiate substitution treatment'/de OR 'drug dependence treatment'/exp) AND ('reinforcement'/de OR 'cognitive behavior therapy'/exp OR 'behavior therapy'/exp)
#5	('buprenorphine':ti,ab OR 'mat':ti,ab OR 'medication*assisted treatment':ti,ab OR 'medication for addiction treatment':ti,ab) AND ('behavior therapy' OR 'community reinforcement approach':ti,ab OR 'internet*delivered cognitive behavior therapy':ti,ab OR 'contingency management':ti,ab OR 'therapeutic education system':ti,ab OR 'tes':ti,ab OR 'reset*o':ti,ab OR 'a-chess':ti,ab OR 'a chess':ti,ab OR 'connections':ti,ab OR 'digital':ti,ab OR 'smartphone':ti,ab OR 'internet':ti OR 'web':ti,ab OR 'mobile':ti,ab OR 'dynamicare':ti,ab OR 'dynamicare health':ti,ab)
#6	#4 OR #5
#7	#3 AND #6
#8	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#9	#7 NOT #8
#10	#9 AND [english]/lim
#11	#10 AND ('chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it OR 'case report')
#12	#10 NOT #11

Figure A.1. PRISMA flow Chart Showing Results of Literature Search for Digital Therapeutics for OUD



Appendix B. Previous Systematic Reviews and Technology Assessments

We did not identify any previous systematic reviews related to reSET-O, Connections, or DynamiCare.

Appendix C. Ongoing Studies

Table C.1. Ongoing Trials for reSET-O, Connections, and DynamiCare

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion Date
reSET-O					
reSET-O RCT **NCT04129580** **Sponsor:** **Milton S. Hershey Medical Center**	Randomized controlled, open label, single group assignment trial Estimated N: 200	**Experimental**: – Treatment-As-Usual (TAU) + reSET-O **Control**: – TAU only	**Inclusion Criteria**: – 18 years of age or older – OUD diagnosis – Recently starting outpatient treatment for OUD within the Penn State Health Hub and Spoke System of Care – Initiating MAT with BUP-NLX, BUP, or methadone **Exclusion Criteria:** – Planning an outpatient detoxification – Judged by the evaluating physician or allied clinician to need a higher level of care	*[Time frame: 6 months]* **Primary Outcome**: – Retention in treatment on MAT **Secondary Outcomes**: – Opioid and other substance abuse – Cravings to use drugs – Mental health outcomes – Health status – Coping strategies – Social connectedness – HIV risk – Satisfaction of using reSET-O as a form of treatment – Effectiveness of the reSET-O app	June 2021

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion Date
Optimizing Retention, Duration and Discontinuation Strategies for Opioid Use Disorder Pharmacotherapy (RDD) **NCT04464980** **Sponsor: NYU Langone Health**	Phase 4, randomized, open label, factorial assignment, two phase study **Phase 1**: Retention **Phase 2**: Discontinuation Estimated N: 1630	**Experimental (Drug):** – Sublingual BUP (standard dose) – Sublingual BUP (high dose) – Extended-release injection BUP – Extended-release injection naltrexone **Experimental (Behavioral):** – Sublingual BUP (standard dose) + reSET-O – Sublingual BUP (high dose) + reSET-O – Extended-release injection BUP + reSET-O – Extended-release injection naltrexone + reSET-O	**Inclusion Criteria:** – ≥18 years of age – Meet DSM-5 criteria for current OUD – Able to speak English sufficiently to understand the study procedures **Exclusion Criteria**: – Serious medical, psychiatric, or co-occurring SUD – Suicidal or homicidal ideation or behavior – Maintenance on methadone at the time of signing consent – Are currently in jail, prison, or have pending legal action – Have used the reSET or reSET-O mHealth app in the 3 months prior to consent	**Primary Outcome**: – Continuous retention in treatment at 26 weeks – Completed d/c without relapse at 24 weeks follow-up **Secondary Outcomes (Retention):** – Continuous opioid abstinence *[Time Frame: weeks 23-26, weeks 47-50, and weeks 71-74]* – Weekly Abstinence *[Time Frame: 98 weeks]* – Craving *[Time Frame: 98 weeks]* – Stable abstinence *[Time Frame: weeks 26, week 50, and week 74]* – Retention *[Time Frame: week 50, week 74]* – Dropout from Treatment *[Time Frame: 74 weeks]* **Secondary Outcomes (D/C):** *[Time Frame: 24 Weeks]* – D/C Completion	July 2025

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion Date
				– Relapse – Withdrawal symptoms	
Connections					
A Method to Increase Buprenorphine Treatment Capacity **NCT03580902** **Sponsor:** **CBT4CBT, LLC**	Phase I/II, randomized, open label, parallel assignment study Estimated N: 100	**Experimental:** – CBT4CBT + BUP **Comparator:** – BUP / NLX	**Inclusion Criteria:** – 18-65 years of age – Meets DSM-5 criteria for OUD – Requesting BUP maintenance treatment at Central Medical Unit of the APT Foundation **Exclusion Criteria:** – Unstable psychotic disorder – Currently suicidal or homicidal – Current cocaine, benzodiazepine, or alcohol use disorder – History of PCP (phencyclidine) use.	**Primary Outcome:** *[Time Frame: 12 weeks]* – Percent of urine toxicology screens negative for opioids	January, 2021
DynamiCare					
Encouraging Opioid Abstinence Behavior:	Randomized, parallel assignment interventional study	**Experimental:**	**Inclusion Criteria:** – ≥18 years of age	**Primary Outcomes:**	July 2021

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion Date

Incentivizing Inputs and Outcomes – Pilot
 	
NCT04235582
 	
Sponsor:
Aurora Health Care
	Estimated N: 30	– Outcomes Group (DynamiCare App + Outcomes CM)
		– Inputs Group (DynamiCare App + Inputs CM)
		– Combination Group (DynamiCare App + Outputs and Inputs CM)
			– Meet DSM-5 criteria for OUD
			– Access to smartphone
			– Enrolled in Aurora Health's Behavioral Health Program
			– Currently, or will be, prescribed within 4 days, oral BUP for OUD
			– Meet one of the following:
			  – Enrolled in OUD program for ≤ 1 week before study enrollment
			  – Currently using non-medical opioids
			  – Regularly missing scheduled AODA appointments
			– Understands English
			
			Exclusion Criteria:
			– Evidence of active non-substance related psychosis
				– Continuous abstinence from opioid use at 4, 8 and 12 weeks
				
				Secondary Outcomes:
				[*Time Frame: 12 weeks]*
				– Negative Urinalysis Frequency
				– Negative Saliva Analysis Frequency
				– Psychotherapy Attendance
				– Psychotherapy Completion
				– Medication Adherence
				– Quality of Life (at 4, 8, 12 weeks)	

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion Date
			– Significant cognitive impairment		

AODA: Alcohol or other drug abuse, BUP: buprenorphine, CM: contingency management, d/c: discontinuation, DSM-5: Diagnostic and Statistical Manual of Mental Disorders 5th edition, HIV: human immunodeficiency virus, MAT: medication assisted treatment, MM: medical management, NLX: naloxone, OUD: opioid use disorder, SUD: substance-use disorder

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. Two investigators independently screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Two investigators independently reviewed full papers and provided justification for exclusion of each excluded study. Issues of conflict were resolved through consensus.

We also included FDA documents related to reSET-O. These included the manufacturer's submission to the agency, as well as documents submitted to the FDA as part of the 510(k) application. All literature that did not undergo a formal peer review process is described separately.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[47] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking*

outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

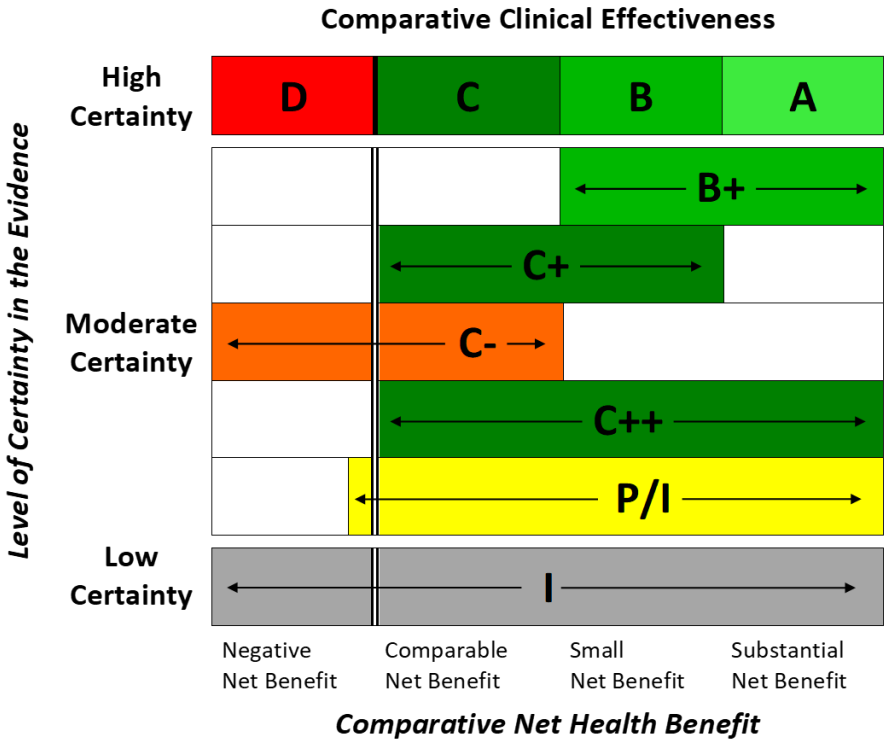
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

5. The magnitude of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects; and
6. The level of certainty in the best point estimate of net health benefit.[48,88]

Figure D.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Table D.1. Study Design

Author	Design, Location, and Duration of Follow-up	N	Inclusion Criteria	Exclusion Criteria	Definitions of Key Outcomes	Interventions Defined
reSET-O						
Christensen 2014[32] **Nunes 2019**[53]	Block-randomized, unblinded, parallel treatment trial Location: University of Arkansas for Medical Sciences (single site) Follow-Up: 12 weeks	170	– ≥18 years of age – Participants meet DSM-4 criteria for OUD – Significant current opioid use – Participants meet FDA qualification criteria for BUP treatment	– Unstable medical or psychiatric condition – Pregnancy – Incarceration	Retention: Number of days from the start of the 12-Week intervention until the participant either left the trial or completed the trial. If participants missed 3 consecutive clinic visits, they were removed from the trial. Abstinence: Proportion of negative urine tests during 12-week study period (for both opioids and cocaine; tested 3x weekly). Missed visits were treated as positive results.	All participants received BUP treatment and bi-weekly therapist counseling. CM: Vouchers earned for cocaine and opioid negative urine tests (three times weekly). Participants received bonus for full week of negative urine samples. Computer-CBT: web-based tool that participants completed at each clinic visit (three times weekly).

Author	Design, Location, and Duration of Follow-up	N	Inclusion Criteria	Exclusion Criteria	Definitions of Key Outcomes	Interventions Defined
Bickel 2008[50]	Randomized, unblinded, controlled trial Location: University of Vermont (single site) Follow-Up: 23 Weeks	135	– ≥18 years of age – Participants meet DSM-4 criteria for OUD – Participants meet FDA methadone treatment qualification criteria	– Medical or psychiatric condition – Pregnancy	Retention: Proportion of participants who completed treatment through the maintenance treatment phase (23 Weeks). If participants missed 3 consecutive medication doses, they were considered discontinued. Abstinence: Number of urine tests negative for opioids and other drugs (tested 3x weekly). Missed urine samples were considered positive.	All participants received BUP treatment. Therapist Derived CBT: three 30-minute individual counseling sessions per week for 12 weeks, then one 30-minute and two 20-minute session for the remaining 11 weeks. Computer-CBT: three 30-minute individual sessions per week. Participants meet with counselor biweekly to discuss progress. CM: vouchers earned for cocaine and opioid negative urine samples (3 times weekly). Participants received bonus for full week of negative urine samples. Standard Treatment: therapist counseling (once weekly for 37 min).

Author	Design, Location, and Duration of Follow-up	N	Inclusion Criteria	Exclusion Criteria	Definitions of Key Outcomes	Interventions Defined
Chopra 2009[49]	Randomized, unblinded controlled trial Location: initiated at the University of Vermont and completed at the University of Arkansas for Medical Sciences Follow-Up: 12 Weeks	120	– 18 - 55 years of age – Participants meet DSM-4 criteria for OUD – Significant current opioid use – Participants meet FDA qualification criteria for BUP treatment	– Unstable medical or psychiatric condition – Pregnancy	Retention: Number of days between study initiation and either the completion of the 12-week study period, or the day the patient discontinued treatment or left the study. Abstinence: Proportion of urine tests negative for opioids and other drugs (tested 3x weekly). Missed urine tests were considered positive.	All participants received BUP treatment. Medication CM: medication dose & schedule depending on urine samples free opioids and cocaine (tested 3x weekly). Voucher CM: vouchers earned for cocaine and opioid negative urine samples (3 times weekly). Participants received bonus for full week of negative urine samples. Computer-CBT: three 30-minute sessions each week. Participants meet with counselor biweekly to discuss progress. Standard Treatment: Once weekly methadone-style counseling.

Marsch 2014[51] **Acosta 2012[89]** **Kim 2016[90]**	Randomized, unblinded controlled trial Location: northeastern US (single site) Follow-Up: 12 months	160	– ≥18 years of age – Participants had to have initiated methadone treatment within the past 30 days – Sufficient English-language ability – Must meet DSM criteria for opioid dependence – Meet federal register criteria for using drugs to treat opioid addiction		Retention: Proportion of participants completing treatment for the 12-month study period. Abstinence: Proportion of urine tests negative for opioids and other drugs (tested once weekly.	All participants received daily methadone treatment. Standard Treatment: 1 hour long counseling sessions once weekly for the first 4 weeks, then twice monthly thereafter. Patients with recurring drug-positive results received counseling more frequently. Computer-CBT* + Reduced Standard Treatment**:** 30 minutes of each 1 hour long counseling session was spent using the web-based CBT tool. The other 30 minutes were spent with their counselor. Compensation: Participants received $50 for completing their baseline and monthly clinical assessments and $10 for each urine sample provided.

Author	Design, Location, and Duration of Follow-up	N	Inclusion Criteria	Exclusion Criteria	Definitions of Key Outcomes	Interventions Defined
Connections						
Shi 2019[29]	Randomized pilot trial Location: NR Follow-Up: 12 weeks	20	– ≥18 years of age – Participants meet DSM-5 criteria for OUD	– Current unstabilized psychotic disorder – Currently suicidal or homicidal – Pregnant or lactating – Any condition that would contraindicate BUP treatment – Current cocaine, benzodiazepine, or alcohol use disorder	Abstinence: Percentage of urine toxicology screens negative for all drugs tested (amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamine, opiates, oxycodone, tetrahydrocannabinol)	All participants received BUP treatment. CBT4CBT: Based on preference, participants were able to complete web-based modules within the clinic at the time of their meetings or at home. Standard: BUP treatment alone CM: Participants received $10 for each weekly assessment completed

Author	Design, Location, and Duration of Follow-up	N	Inclusion Criteria	Exclusion Criteria	Definitions of Key Outcomes	Interventions Defined
DynamiCare						
Ryan 2020[30]	Prospective cohort study Location: Metro Cincinnati (single site) Follow-Up: 4 months	108	– ≥18 years of age – SUD as a primary diagnosis – Sufficient English language capabilities	N/A	Substance Use: Proportion of patients using the app testing consistent only for prescribed substances in random clinical urine tests. Retention: of patients who are still active in the DynamiCare app and attending treatment sessions at 1, 2, 3, and 4 months	DynamiCare: The mobile app included appointment reminders and attendance tracking, CBT modules Compensation: Financial rewards for healthy behaviors of up to $100 per month were transferred in real-time via a smart debit card that blocks risky expenditures

BUP: buprenorphine, CBT: cognitive behavioral therapy, CM: contingency management, DSM-4: Diagnostic and Statistical Manual of Mental Disorders 4th edition, DSM-5: Diagnostic and Statistical Manual of Mental Disorders 5th edition, FDA: US Food and Drug Administration, N/A: not available, N: total number of participants, NR: not reported, OUD: opioid-use disorder, SUD: substance use disorder

Table D.2. Baseline Characteristics I

Trial	Arms	N	Female, n (%)	Age, Mean Years (SD)	Race / Ethnicity, n (%)			Education		Employed, n (%)			Monthly Income, Median USD (IQR)
					Caucasian / White	Black / African American	Hispanic / Latino	Education, Median Years (IQR)	Completed High School, n (%)	Full-Time	Part-Time	Not Employed	
reSET-O													
Christensen 2014[32] Nunes 2019[53]	Computer-CBT + CM + BUP	92	48 (52)	34 (10.2)	87 (95)	NR	NR	12 (12-14)	NR	35 (38)	NR	NR	1000 (0, 2167)*†
	CM + BUP	78	30 (38)	34.8 (9.6)	75 (96)	NR	NR	12 (12-14)	NR	27 (35)	NR	NR	1808 (55, 2500)*‡
Bickel 2008[50]	Computer-CBT + CM + BUP	45	21 (47)	29.7 (8.9)*	42 (93)	NR	NR	NR	31 (69)	22 (49)	NR	NR	675 (300, 1100)
	Therapist-CBT + CM + BUP	45	20 (44)	26.1 (6.9)*	44 (98)	NR	NR	NR	30 (67)	20 (44)	NR	NR	698 (220, 1500)
	BUP	45	19 (42)	30.1 (9.2)*	44 (98)	NR	NR	NR	32 (71)	21 (47)	NR	NR	523 (50, 1236)
Chopra 2009[49]	Computer-CBT + CM (voucher) + BUP	41	16 (39.0)	30.6 (9.1)	40 (97.6)	NR	NR	NR	33 (80.5)	22 (53.7)	NR	NR	1200 (490, 3200)
	Computer-CBT + CM (medication) + BUP	42	22 (52.4)	31.6 (10.1)	41 (97.6)	NR	NR	NR	35 (83.3)	14 (33.3)*	NR	NR	1010 (600, 2100)

Trial	Arms	N	Female, n (%)	Age, Mean Years (SD)	Race / Ethnicity, n (%)			Education		Employed, n (%)			Monthly Income, Median USD (IQR)
					Caucasian / White	Black / African American	Hispanic / Latino	Education, Median Years (IQR)	Completed High School, n (%)	Full-Time	Part-Time	Not Employed	
	BUP	37	13 (35.1)	33.5 (11.1)	36 (97.3)	NR	NR	NR	29 (78.4)	23 (62.2)*	NR	NR	1200 (700, 1933)
Marsch 2014[51] Acosta 2012[89] Kim 2016[90]	Computer-CBT + Methadone	80	17 (21.2)	40.9 (10.7)	37 (47.4)	23 (29.5)	20 (25.3)	Mean (SD): 12.4 (2.0)	NR	25 (31.3)	12 (15.0)	43 (53.8)	NR
	Methadone	80	23 (28.7)	40.4 (8.9)	33 (41.2)	27 (33.8)	23 (29.5)	Mean (SD): 12.4 (1.7)	NR	37 (47.4)	10 (12.8)	31 (39.7)	NR
Connections													
Shi 2019[29]	CBT4CBT + BUP	10	6 (60)	41.3 (12.0)	10 (100)	0 (0)	1 (10)	NR	8 (80)	4 (40)		6 (60)	NR
	BUP	10	2 (20)	39.6 (13.0)	10 (100)	0 (0)	0 (0)	NR	9 (90)	5 (50)		5 (50)	NR
DynamiCare													
Ryan 2020[30]	DynamiCare App	108	50 (46.0)	39 (NR)	92 (85.0)	NR	NR	NR	NR	NR		NR	NR

BUP: buprenorphine, CBT: cognitive behavioral therapy, CBT4CBT: Computer Based Training for Cognitive Behavioral Therapy, CM: contingency management, IQR: interquartile range, N: total number of participants, n: number, NR: not reported, SD: standard deviation, USD: US Dollar

*: significant differences across treatment groups

†: n=81

‡: n=60

Table D.3. Baseline Characteristics II

Trial	Arms	N	Regular Opioid Use, Median Years (IQR)	Age of First Opioid Use, Mean years (SD)	Preferred Route of Administration, n (%)			Prior Opioid Use Treatment, n (%)	Other Drug Dependence, n (%)				Regular Use of Cocaine, Median Years (IQR)
					Injection	Intranasal	Oral		Alcohol	Cocaine	Sedative	Marijuana	
reSET-O													
Christensen 2014[32] Nunes 2019[53]	Computer-CBT + CM + BUP	92	5* (3, 10)	NR	11* (13)	7* (8)	66* (79)	37 (40)	11* (13)	3* (4)	13* (15)	23* (27)	0 (0, 1.5)
	CM + BUP	78	6.5† (3.5, 12.5)	NR	10† (15)	6 (9)	52† (76)	41 (53)	9† (13)	5† (7)	6† (9)	22† (32)	0 (0, 2)
Bickel 2008[50]	Computer-CBT + CM + BUP	45	Mean (SD): 6.4 (6.3)	21.8 (8.2)	31 (68)	14 (32)	0 (0)	32 (70)	7 (16)	12 (27)	4 (9)	6 (14)	NR
	Therapist-CBT + CM + BUP	45	Mean (SD): 5.2 (4.4)	18.9 (5.3)	36 (80)	9 (20)	0 (0)	31 (68)	4 (9)	7 (16)	3 (7)	8 (18)	NR
	BUP	45	Mean (SD): 5.6 (6.2)	22.4 (7.9)	28 (62)	17 (38)	0 (0)	29 (64)	8 (18)	11 (24)	6 (13)	7 (16)	NR

Trial	Arms	N	Regular Opioid Use, Median Years (IQR)	Age of First Opioid Use, Mean years (SD)	Preferred Route of Administration, n (%)			Prior Opioid Use Treatment, n (%)	Other Drug Dependence, n (%)				Regular Use of Cocaine, Median Years (IQR)
					Injection	Intranasal	Oral		Alcohol	Cocaine	Sedative	Marijuana	
Chopra 2009[49]	Computer-CBT + CM (voucher) + BUP	41	Mean (SD): 5.6 (6.1)	21.5 (7.7)	16 (39.0)	16 (39.0)	9 (22.0)	33 (80.5)	6 (14.6)	10 (24.4)	6 (14.6)	16 (39.0)	1 (0, 5)
	Computer-CBT + CM (medication) + BUP	42	Mean (SD): 6.1 (5.7)	22.6 (7.7)	16 (38.1)	15 (35.7)	11 (26.2)	30 (71.4)	1 (2.4)	5 (11.9)	3 (7.1)	14 (33.3)	1 (0, 3)
	BUP	37	Mean (SD): 7.0 (6.9)	22.5 (8.3)	12 (32.4)	13 (35.1)	12 (32.4)	25 (67.6)	4 (10.8)	7 (18.9)	3 (8.1)	16 (43.2)	1 (0, 5)
Marsch 2014[51] Acosta 2012[89] Kim 2016[90]	Computer-CBT + Methadone	80	Mean (SD): 15.2 (12.5)	NR	NR	NR	NR	Mean (SD): 9.9 (10.4)‡	NR	NR	NR	NR	Mean (SD): 8.1 (9.8)#
	Methadone	80	Mean (SD): 14.7 (10.9)	NR	NR	NR	NR	Mean (SD): 10.4 (10.3)‡	NR	NR	NR	NR	Mean (SD): 6.5 (8.2)#
Connections													
Shi 2019[29]	CBT4CBT + BUP	10	NR	24.4 (12.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	BUP	10	NR	30.6 (12.3)	NR	NR	NR	NR	NR	NR	NR	NR	NR

Trial	Arms	N	Regular Opioid Use, Median Years (IQR)	Age of First Opioid Use, Mean years (SD)	Preferred Route of Administration, n (%)			Prior Opioid Use Treatment, n (%)	Other Drug Dependence, n (%)				Regular Use of Cocaine, Median Years (IQR)
					Injection	Intranasal	Oral		Alcohol	Cocaine	Sedative	Marijuana	
DynamiCare													
Ryan 2020[30]	DynamiCare App	108	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

BUP: buprenorphine, CBT: cognitive behavioral therapy, CBT4CBT: Computer Based Training for Cognitive Behavioral Therapy, CM: contingency management, IQR: interquartile range, N: total number of participants, n: number, NR: not reported, SD: standard deviation, USD: US Dollar

*: N=84

†: N=68

‡: Substance Use Disorder treatments

#: cocaine or crack

Table D.4. Baseline Characteristics III

Trial	Arms	N	ASI Composite Scale, Median Score (IQR)									Beck Depression Inventory, Mean Score (SD)
			Medical	Employment	Alcohol	Drug	Psychiatric	Legal	Family / Social	Cocaine	Opioids	
reSET-O												
Christensen 2014[32] Nunes 2019[53]	Computer-CBT + CM + BUP	92	0 (0, 0.67)	0.50 (0.14, 0.50)	0.01 (0, 0.06)	0.12 (0.08, 0.22)	0.10 (0, 0.42)	0 (0, 0.03)	0.10 (0, 0.46)	0 (0, 0)	0.64 (0.57, 0.69)	NR
	CM + BUP	78	0 (0, 0.63)	0.50 (0.12, 0.50)	0.01 (0, 0.09)	0.11 (0.08, 0.23)	0.16 (0, 0.36)	0 (0, 0.10)	0.15 (0, 0.20)	0 (0, 0)	0.64 (0.54, 0.70)	NR
Bickel 2008[50]	Computer-CBT + CM + BUP	45	Mean (SD): 0.17 (0.29)	Mean (SD): 0.62 (0.33)	Mean (SD): 0.06 (0.10)	Mean (SD): 0.39 (0.08)	Mean (SD): 0.31 (0.22)	Mean (SD): 0.25 (0.24)	Mean (SD): 0.23 (0.24)	NR	NR	19.5 (9.8)
	Therapist-CBT + CM + BUP	45	Mean (SD): 0.19 (0.31)	Mean (SD): 0.66 (0.31)	Mean (SD): 0.06 (0.11)	Mean (SD): 0.38 (0.08)	Mean (SD): 0.36 (0.26)	Mean (SD): 0.35 (0.28)	Mean (SD): 0.21 (0.21)	NR	NR	21.6 (9.7)
	BUP	45	Mean (SD): 0.20 (0.32)	Mean (SD): 0.59 (0.30)	Mean (SD): 0.05 (0.11)	Mean (SD): 0.39 (0.09)	Mean (SD): 0.32 (0.22)	Mean (SD): 0.34 (0.25)	Mean (SD): 0.31 (0.24)	NR	NR	20.5 (9.1)
Chopra 2009[49]	Computer-CBT + CM (voucher) + BUP	41	0.00 (0, 0.34)	0.50 (0.18, 0.52)	0.00 (0, 0.08)	0.32 (0.20, 0.37)	0.27 (0.09, 0.38)	0.20 (0, 0.31)	0.11 (0, 0.33)	0 (0, 0.03)	0.70 (0.63, 0.74)	NR

Trial	Arms	N	ASI Composite Scale, Median Score (IQR)									Beck Depression Inventory, Mean Score (SD)
			Medical	Employment	Alcohol	Drug	Psychiatric	Legal	Family / Social	Cocaine	Opioids	
	Computer-CBT + CM (medication) + BUP	42	0.08 (0, 0.51)	0.50 (0.29, 0.69)	0.00 (0, 0.04)	0.30 (0.20, 0.36)	0.29 (0.09, 0.50)	0.13 (0, 0.40)	0.14 (0.02, 0.35)	0.00 (0, 0.01)	0.65 (0.55, 0.72)	NR
	BUP	37	0.08 (0, 0.49)	0.50 (0.31, 0.62)	0.00 (0, 0.06)	0.31 (0.18, 0.41)	0.32 (0.05, 0.50)	0.19 (0, 0.35)	0.19 (0, 0.40)	0.00 (0, 0.01)	0.70 (0.61, 0.73)	NR
Marsch 2014[51] Acosta 2012[89] Kim 2016[90]	Computer-CBT + Methadone	80	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Methadone	80	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Connections												
Shi 2019[29]	CBT4CBT + BUP	10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	BUP	10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
DynamiCare												
Ryan 2020[30]	DynamiCare App	108	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

BUP: buprenorphine, CBT: cognitive behavioral therapy, CBT4CBT: Computer Based Training for Cognitive Behavioral Therapy, CM: contingency management, IQR: interquartile range, N: total number of participants, NR: not reported, SD: standard deviation

Table D.5. Baseline Characteristics IV

Trial	Arms	N	Cognitive Functioning, Mean MicroCog Indices Scores (SD)								
			General Cognitive Functioning	General Cognitive Proficiency	Information Processing Speed	Information Processing Accuracy	Attention/ Mental Control	Memory	Spatial Processing	Reasoning/ Calculation	Reaction Time
reSET-O											
Christensen 2014[32] Nunes 2019[53]	Computer-CBT + CM + BUP	92	NR	NR	NR	NR	NR	NR	NR	NR	NR
	CM + BUP	78	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bickel 2008[50]	Computer-CBT + CM + BUP	45	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Therapist-CBT + CM + BUP	45	NR	NR	NR	NR	NR	NR	NR	NR	NR
	BUP	45	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chopra 2009[49]	Computer-CBT + CM (voucher) + BUP	41	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Computer-CBT + CM (medication) + BUP	42	NR	NR	NR	NR	NR	NR	NR	NR	NR
	BUP	37	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Computer-CBT + Methadone	80	78.5 (16.6)	77.7 (13.9)	85.0 (19.5)	80.8 (16.2)	83.5 (17.8)	82.8 (17.5)	96.6 (14.7)	81.7 (17.5)	95.5 (17.3)

Trial	Arms	N	Cognitive Functioning, Mean MicroCog Indices Scores (SD)								
			General Cognitive Functioning	General Cognitive Proficiency	Information Processing Speed	Information Processing Accuracy	Attention/ Mental Control	Memory	Spatial Processing	Reasoning/ Calculation	Reaction Time
Marsch 2014[51] Acosta 2012[89] Kim 2016[90]	Methadone	80									
Connections											
Shi 2019[29]	CBT4CBT + BUP	10	NR	NR	NR	NR	NR	NR	NR	NR	NR
	BUP	10	NR	NR	NR	NR	NR	NR	NR	NR	NR
DynamiCare											
Ryan 2020[30]	DynamiCare App	108	NR	NR	NR	NR	NR	NR	NR	NR	NR

BUP: buprenorphine, CBT: cognitive behavioral therapy, CBT4CBT: Computer Based Training for Cognitive Behavioral Therapy, CM: contingency management, IQR: interquartile range, N: total number of participants, NR: not reported, SD: standard deviation

Table D.6. Efficacy Outcomes I

Trial	Arms	N	Follow-Up	Drop-Out, HR (95% CI); p-value	Retention		Days in Treatment		Opioid Abstinence	
					n (%)	OR (95% CI); p-value	Mean (SD)	p-value	n (%)	OR (95% CI); p-value
reSET-O										
Christensen 2014[32] Nunes 2019[53]	Computer-CBT + CM + BUP	92	12 Weeks	2.12 (1.17, 3.83); p=0.013	74 (80.4)	2.3 (1.15, 4.60); p=0.018	NR	NR	71 (77.3)	2.08 (1.10, 3.95); p=0.0248
	CM + BUP	78			50 (64.1)		NR		48 (62.1)	
	Computer-CBT + CM + BUP (Treatment Naïve)	55		1.15 (0.53, 2.51); p=0.718	40 (72.7)	1.13 (0.45, 2.84); p=0.798	NR	NR	NR	NR
	CM + BUP (Treatment Naïve)	37			26 (70.3)		NR		NR	
	Computer-CRA + CM + BUP (Treatment Experienced)	37		6.57 (1.92, 22.45); p=0.003	34 (91.9)	8.03 (2.21, 30.47); p=0.002	NR	NR	NR	NR
	CM + BUP (Treatment Experienced)	41			24 (58.5)		NR		NR	
Bickel 2008[50]	Computer-CBT + CM + BUP	45	23 Weeks	NR	28 (62)	n.s.	NR	NR	NR	NR
	Therapist-CBT + CM + BUP	45		NR	24 (53)	n.s.	NR	NR	NR	NR
	BUP	45		---	26 (58)	---	NR	---	NR	---

Trial	Arms	N	Follow-Up	Drop-Out, HR (95% CI); p-value	Retention		Days in Treatment		Opioid Abstinence	
					n (%)	OR (95% CI); p-value	Mean (SD)	p-value	n (%)	OR (95% CI); p-value
Chopra 2009[49]	Computer-CBT + CM (voucher) + BUP	41	12 Weeks	NR	35 (85.4)	NR; p=0.009	NR	NR	NR	NR
	Computer-CBT + CM (medication) + BUP	42		NR	25 (59.5)	---	NR	NR	NR	NR
	BUP	37		---	28 (75.7)	Sign. Diff. (p-value NR)	NR	---	NR	---
Marsch 2014[51] Acosta 2012[89] Kim 2016[90]	Computer-CBT + Methadone	80	12 Months	0.94 (NR); p=0.74	31 (38.8)	1 (0.50, 1.20); p=0.56	218.46 (132.19)	p=0.295	NR	2.04 (1.48, 1.85); p<0.05
	Methadone	80			31 (38.8)		207.02 (136.16)		NR	
Connections										
Shi 2019[29]	CBT4CBT + BUP	10	12 Weeks	NR	9 (90.0)	NR	82.6 (4.4)	p=0.19	NR	NR
	BUP	10			8 (80.0)		68.6 (32.6)		NR	
DynamiCare										
Ryan 2020[30]	DynamiCare App	108	4 Months	NR	56 (49.0)*	p<0.05	NR	NR	27 (25.0)	3.92 (NR); p<0.05†‡

BUP: buprenorphine, CBT: cognitive behavioral therapy, CBT4CBT: Computer Based Training for Cognitive Behavioral Therapy, CM: contingency management, diff.: difference, IQR: interquartile range, N: total number of participants, n: number, NR: not reported, OR: odds ratio, SD: standard deviation, sign.: significant

*: Appointment attendance 91-120 days

†: after 90 days

‡: urine tests positive for prescribed medications, e.g., buprenorphine, and negative for illicit substances

Table D.7. Efficacy Outcomes II

Trial	Arms	N	Follow-Up	Longest Continuous Abstinence			Total Abstinence		
				Mean Days (SD)	Between Group Diff. (95% CI); p-value	Effect Size (95% CI)	Mean Days (SD)	Between Group Diff. (95% CI); p-value	Effect Size (95% CI)
reSET-O									
Christensen 2014[32] Nunes 2019[53]	Computer-CBT + CM + BUP	92	12 Weeks	55 (26.2)	5.5 (-3.2, 14.2); p=0.214	0.01 (0, 0.069)	67.1 (19.3)	9.7 (2.3, 17.2); p=0.011	0.048 (0.004, 0.147)
	CM + BUP	78		49.5 (30.6)			57.3 (28.0)		
	Computer-CBT + CM + BUP (Treatment Naïve)	55		51 (27.5)	-2.5 (-15.3, 10.3); p=0.7	0.002 (0, 0.088)	63.4 (22.5)	3.2 (-7.7, 14.2); p=0.558	0.005 (0, 0.107)
	CM + BUP (Treatment Naïve)	37		53.5 (31.8)			60.1 (27.7)		
	Computer-CBT + CM + BUP (Treatment Experienced)	37		61.1 (23.1)	15.1 (3.2, 27.0); p=0.014	0.079 (0.002, 0.0245)	72.6 (11.4)	17.8 (8.2, 27.4); p=0.001	0.203 (0.052, 0.3940
	CM + BUP (Treatment Experienced)	41		46 (29.5)			54.8 (28.3)		
Bickel 2008[50]	Computer-CBT + CM + BUP	45	23 Weeks	54.5 (SEM: 8.2)	NR (NR); p=0.04	0.18 (0.01, 0.34)	NR	NR	NR
	Therapist-CBT + CM + BUP	45		55.9 (SEM: 7.6)	NR (NR); p=0.03	0.19 (0.02, 0.35)	NR	NR	NR
	BUP	45		32.8	---	---	NR	---	NR

Trial	Arms	N	Follow-Up	Longest Continuous Abstinence			Total Abstinence		
				Mean Days (SD)	Between Group Diff. (95% CI); p-value	Effect Size (95% CI)	Mean Days (SD)	Between Group Diff. (95% CI); p-value	Effect Size (95% CI)
				(SEM: 6.2)					
Chopra 2009[49]	Computer-CBT + CM (voucher) + BUP	41	12 Weeks	Median (IQR): 28 (7, 77)	NR; p=0.086	NR	Median (IQR): 63 (14, 77)	28 (NR); p=0.043	NR
	Computer-CBT + CM (medication) + BUP	42		Median (IQR): 42 (14, 63)	NR; p=0.029	1.5 (NR)	Median (IQR): 56 (21, 70)	21 (NR); p=0.180	NR
	BUP	37		Median (IQR): 28 (7, 70)	---	---	Median (IQR): 35 (7, 77)	---	---
Marsch 2014[51] Acosta 2012[89] Kim 2016[90]	Computer-CBT + Methadone	80	12 Months	80.1 (NR)	18.2 (NR); p=0.069	NR	174.7 (NR)	40.0 (NR); p<0.05	1.66 (1.48. 1.85); p<0.01
	Methadone	80		61.9 (NR)			134.7 (NR)		
Connections									
Shi 2019[29]	CBT4CBT + BUP	10	12 Weeks	NR	NR	NR	NR	NR	NR
	BUP	10		NR			NR		
DynamiCare									
Ryan 2020[30]	DynamiCare App	108	4 months	NR	NR	NR	NR	NR	NR

BUP: buprenorphine, CBT: cognitive behavioral therapy, CBT4CBT: Computer Based Training for Cognitive Behavioral Therapy, CM: contingency management, diff.: difference, IQR: interquartile range, N: total number of participants, n: number, NR: not reported, OR: odds ratio, SD: standard deviation, SEM: standard error of the mean

Table D.8. Efficacy Outcomes III

Trial	Arms	N	Follow-Up	Number of Urine Specimens Collected		Urine Specimens Free of Opioids and Cocaine		Urine Specimens Free of Opioids		Median Voucher Value Earned, USD (IQR)	Impact of MicroCog Indices Scores	
				Mean (SD)	p-value	Mean % (SD)	p-value	Mean % (SD)	p-value		Retention	Opioid Abstinence
reSET-O												
Christensen 2014[32] Nunes 2019[53]	Computer-CBT + CM + BUP	92	12 Weeks	35.0 (NR)	p=0.590	82.8 (NR)	NR	NR	NR	730.63 (345.00, 997.50)	NR	NR
	CM + BUP	78		34.8 (NR)		70.9 (NR)		NR		736.88 (128.75, 997.50)	NR	NR
	Computer-CBT + CM + BUP (Treatment Naïve)	55		NR	NR	78.3 (NR)	NR	NR	NR	NR	NR	NR
	CM + BUP (Treatment Naïve)	37		NR		74.2 (NR)		NR		NR	NR	NR
	Computer-CBT + CM + BUP (Treatment Experienced)	37		NR	NR	89.6 (NR)	NR	NR	NR	NR	NR	NR
	CM + BUP (Prior Treatment)	41		NR		67.7 (NR)		NR		NR	NR	NR
Bickel 2008[50]	Computer-CBT + CM + BUP	45	23 Weeks	48.3 (70)	n.s.	70 (NR)	0.08	NR	NR	NR	NR	NR
	Therapist-CBT + CM + BUP	45		48.3 (70)	n.s.	73 (NR)		NR	NR	NR	NR	NR
	BUP	45		49 (71)	---	57 (NR)		NR	---	NR	NR	NR

Trial	Arms	N	Follow-Up	Number of Urine Specimens Collected		Urine Specimens Free of Opioids and Cocaine		Urine Specimens Free of Opioids		Median Voucher Value Earned, USD (IQR)	Impact of MicroCog Indices Scores	
				Mean (SD)	p-value	Mean % (SD)	p-value	Mean % (SD)	p-value		Retention	Opioid Abstinence
Chopra 2009[49]	Computer-CBT + CM (voucher) + BUP	41	12 Weeks	36.0 (35.0, 36.0)	n.s.	76 (NR)	p=0.144	84 (NR)	p=0.010	Mean (SD): 479.30 (382.33)	NR	NR
	Computer-CBT + CM (medication) + BUP	42		35.5 (33.0, 36.0)	n.s.	79 (NR)	p=0.067	81 (NR)	p=0.055	N/A	NR	NR
	BUP	37		35.0 (33.0, 36.0)	---	69 (NR)	---	72 (NR)	---	N/A	NR	NR
Marsch 2014[51] Acosta 2012[89] Kim 2016[90]	Computer-CBT + Methadone	80	12 Months	30.7 (NR)	p<0.01	NR	NR	NR	NR	NR	Higher General Cognitive Proficiency scores increased the chance of drop out by approx.. 2%; HR=1.016	MicroCog Indices significant predictors for weeks of cont. abstinence, but not for total weeks of opioid abstinence.
	Methadone	80		2.4 (NR)		NR	NR	NR		NR		
Connections												
Shi 2019[29]	CBT4CBT + BUP	10	12 Weeks	9.3 (1.7)	p=0.48	NR	NR	91.3 (20.8)	p=0.05	NR	NR	NR

Trial	Arms	N	Follow-Up	Number of Urine Specimens Collected		Urine Specimens Free of Opioids and Cocaine		Urine Specimens Free of Opioids		Median Voucher Value Earned, USD (IQR)	Impact of MicroCog Indices Scores	
				Mean (SD)	p-value	Mean % (SD)	p-value	Mean % (SD)	p-value		Retention	Opioid Abstinence
	BUP	10		8.4 (3.3)		NR		63.9 (36.6)		NR	NR	NR
DynamiCare												
Ryan 2020[30]	DynamiCare App	108	4 Months	NR	NR	NR	NR	NR	NR	NR	NR	NR

BUP: buprenorphine, CBT: cognitive behavioral therapy, CBT4CBT: Computer Based Training for Cognitive Behavioral Therapy, CM: contingency management, Cont.: continuous, diff.: difference, IQR: interquartile range, N: total number of participants, n: number, N/A: not available, NR: not reported, SD: standard deviation

Table D.9. Patient Reported Outcomes

Trial	Arms	N	ASI Composite Scale, Change From Baseline; p-value									HAQ, Mean Scores (SEM)
			Medical	Employment	Alcohol	Drug	Psychiatric	Legal	Family / Social	Cocaine	Opioids	
reSET-O												
Christensen 2014[32] Nunes 2019[53]	Computer-CBT + CM + BUP	92	Non-sign. Improve-ment; p>0.16	Improvement; p<0.01	Improve-ment; p<0.01	Improve-ment; p<0.01	Improve-ment; p<0.01	Non-sign. Improve-ment; p>0.16	NR (NR); p<0.01	Non-sign. Improve-ment; p=0.74	Improve-ment; p<0.01	NR
	CM + BUP	78										NR
Bickel 2008[50]	Computer-CBT + CM + BUP	45	Improve-ment; p<0.05	Improvement; p<0.05	Non-sign. Improve-ment; NR	Improve-ment; p<0.05	Improve-ment; p<0.05	Improve-ment; p<0.05	Improve-ment; p<0.05	Improve-ment; p<0.05	Improve-ment; p<0.05	4.86 (0.05)
	Therapist-CBT + CM + BUP	45	Improve-ment; p<0.05	Improvement; p<0.05	Non-sign. Improve-ment; NR	Improve-ment; p<0.05	Improve-ment; p<0.05	Improve-ment; p<0.05	Improve-ment; p<0.05	Improve-ment; p<0.05	Improve-ment; p<0.05	4.84 (0.04)
	BUP	45	↑; p<0.05	↑; p<0.05	↑; non-sign.	↑; p<0.05	↑; p<0.05	↑; p<0.05	↑; p<0.05	↑; p<0.05	↑; p<0.05	4.74 (0.05)
Chopra 2009[49]	Computer-CBT + CM (voucher) + BP	41	↑; non-sign.	↑; p<0.012	↑; non-sign.	↑; p<0.012	↑; p<0.012	↑; p<0.012	↑; non-sign.	↑; non-sign.	Improve-ment; p<0.012	NR

Trial	Arms	N	ASI Composite Scale, Change From Baseline; p-value									HAQ, Mean Scores (SEM)
			Medical	Employment	Alcohol	Drug	Psychiatric	Legal	Family / Social	Cocaine	Opioids	
	Computer-CBT + CM (medication) + BP	42	↑; non-sign.	↑; p<0.012	↑; non-sign.	↑; p<0.012	↑; p<0.012	↑; p<0.012	↑; non-sign.	↑; non-sign.	↑; p<0.012	NR
	BUP	37	↑; non-sign.	↑; p<0.012	↑; non-sign.	↑; p<0.012	↑; p<0.012	↑; p<0.012	↑; non-sign.	↑; non-sign.	↑; p<0.012	NR
Marsch 2014[51] Acosta 2012[89] Kim 2016[90]	Computer-CBT + Methadone	80	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Methadone	80	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Connections												
Shi 2019[29]	CBT4CBT + BUP	10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	BUP	10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
DynamiCare												
Ryan 2020[30]	DynamiCare App	108	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

ASI: addiction severity index, BUP: buprenorphine, CBT: cognitive behavioral therapy, CBT4CBT: Computer Based Training for Cognitive Behavioral Therapy, CM: contingency management, HAQ: Helping Alliance Questionnaire, N: total number of participants, NR: not reported, SEM: standard error of means
↑: Improvement

Table D.10. Safety

Author	Arms	N	Any AEs, n (%)	Any SAEs, n (%)	Any TAEs, n (%)	AEs leading to D/C, n (%)	Mortality, n (%)
reSET-O							
Christensen 2014[32] **Nunes 2019[53]**	CRA + CM + BUP	92	57 (62.0)	NR	0 (0)	NR	NR
	CM + BUP	78	55 (70.5)	NR	NR	NR	NR
Bickel 2008[50]	Computer-CRA + CM + BUP	45	No Safety Data Reported				
	Therapist-CRA + CM + BUP	45					
	BUP	45					
Chopra 2009[49]	CRA + CM (voucher) + BP	41	No Safety Data Reported				
	CRA + CM (medication) + BP	42					
	BUP	37					
Marsch 2014[51] **Acosta 2012[89]** **Kim 2016[90]**	TES + Methadone	80	No Safety Data Reported				
	Methadone	80					
Connections							
Shi 2019[29]	CBT4CBT + BUP	10	No Safety Data Reported				
	BUP alone	10					
DynamiCare							
Ryan 2020[30]	DynamiCare App	108	No Safety Data Reported				

AE: adverse event, BUP: buprenorphine, CBT: cognitive behavioral therapy, CBT4CBT: Computer Based Training for Cognitive Behavioral Therapy, CM: contingency management, D/C: discontinuation, N: total number of participants, n: number, NR: not reported

Table D.11. Study Quality

Trial	Comp. Groups	Non-diff. Follow-up*	Patient/ Investigator Blinding (Double-Blind)	Clear Def. of Intervention	Clear Def. of Outcomes	Selective outcome reporting	Measure-ments Valid	ITT analysis	Approach to Missing Data	USPSTF Rating
Christensen 2014[32]	No	Yes	No	Yes	Yes	No	Yes	ITT	Imputation	fair
Bickel 2008[50]	No	Yes	No	Yes	Yes	No	Yes	ITT	Imputation	fair
Chopra 2009[49]	No	Yes	No	Yes	Yes	No	Yes	mITT	Imputation	poor
Marsch 2014[51]	Yes	Yes	No	Yes	Yes	No	Yes	ITT	Imputation	fair
Shi 2019[51]	No	Yes	No	Yes	Yes	No	Yes	ITT	Imputation	fair

Comp.: comparable, def.: definition, diff.: differential, ITT: intention-to-treat, USPSTF: United States Preventive Services Taskforce

* Participants who dropped out were considered treatment failures

Appendix E. Comparative Value Supplemental Information

Table E.1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	☐	☐	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	☐	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	X	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al [91]

Description of evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy. [92]
2. For each cycle (Cycle I) in the model where using the intervention results in different years of life gained, we multiply this general population utility by the incremental life years (ΔLYs).
3. If no life years were gained or lost using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.
4. If life years were higher in the intervention versus comparator, the intervention Cycle I evLY is equal to the product of the comparator life years and intervention average utility plus the value derived in Step 2.
5. The total evLY is then calculated as the cumulative sum of Cycle I evLYs using the above calculations for each arm.
6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

One-Way Sensitivity Analysis Supporting Information

Table E.2. presents the lower and upper inputs used to generate the tornado diagram, along with their corresponding incremental cost-effectiveness ratios. The effect of reSET-O on total abstinence days was the single input with the most influence on the cost-effectiveness findings, ranging from the lowest cost-effectiveness ratio of approximately $309,000 per QALY gained for an additional 17.2 days of abstinence as compared to standard of care to the highest cost-effectiveness ratio of greater than $1,000,000 per QALY gained for an additional 2.3 days of abstinence as compared to standard of care. The second most influential input was the effect of reSET-O on MAT retention.

Table E.2. Tornado Diagram Inputs and Results for reSET-O versus Standard of Care

	Lower Input ICER	Upper Input ICER	Lower Input	Upper Input
reSET-O effect on total abstinence days, Phase 1	$1,070,000	$309,000	2.3	17.2
reSET-O effect on MAT retention, Phase 1	$758,000	$352,000	1.15	4.60
Utility for off MAT with illicit use	$365,000	$699,000	0.68	0.71
On MAT after Phase 1, Standard of Care	$402,000	$685,000	37%	87%
Utility for on MAT with illicit use	$611,000	$397,000	0.69	0.71
OUD-related per-cycle hospitalization costs while off MAT	$545,000	$409,000	$840	$1,245
Utility for on MAT without illicit use	$555,000	$425,000	0.75	0.78
Per-cycle probability of MAT discontinuation, Phase 2	$423,000	$527,000	12%	17%
Multiplier of discontinuation from illicit use state	$432,000	$519,000	1.00	1.40
OUD-related per-cycle hospitalization costs while on MAT	$457,000	$507,000	$308	$457

ICER: incremental cost-effectiveness ratio, MAT: medication assisted treatment, OUD: opioid use disorder

Probabilistic Sensitivity Analysis Supporting Information

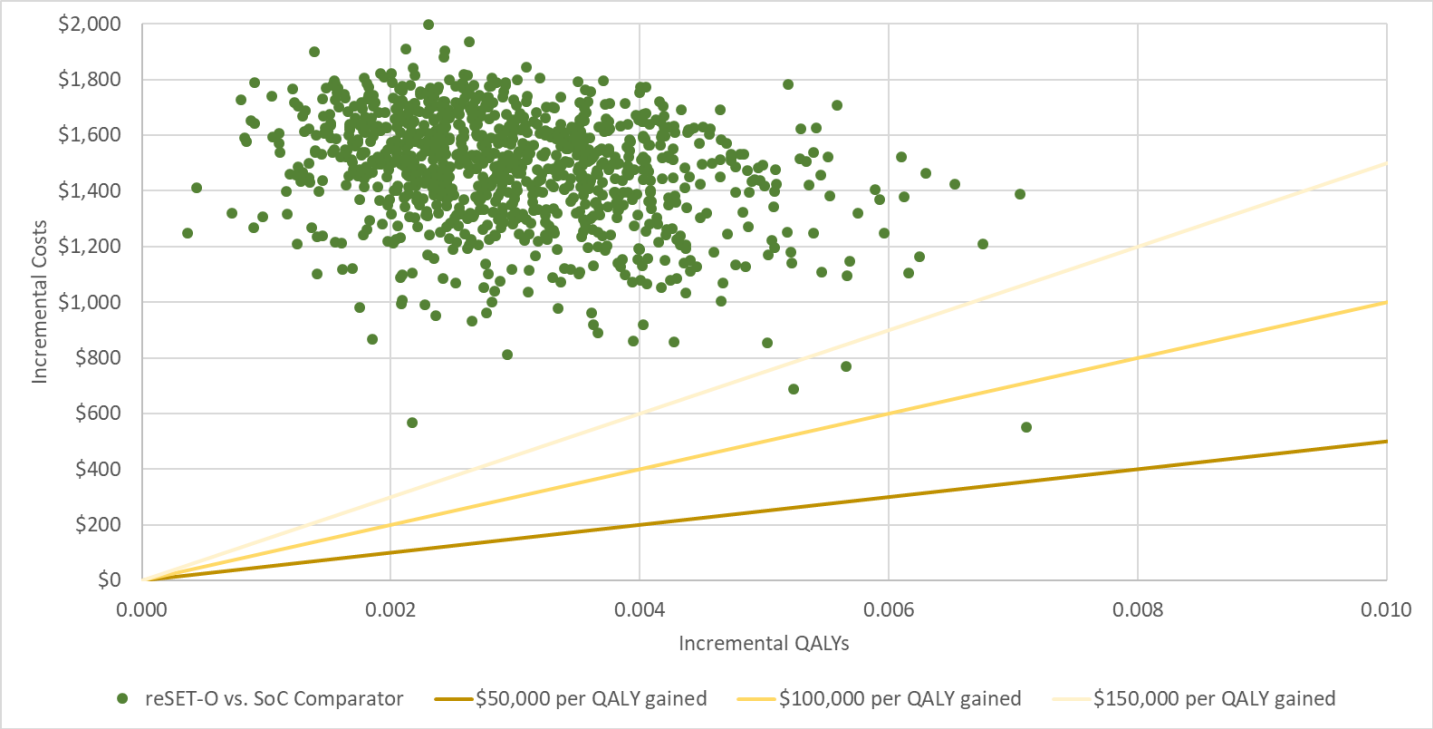
Table E.3 provides the results of the probabilistic sensitivity analysis. Figure E.X includes a scatterplot, with each point representing one of the iterations. None of the iterations produced cost-effectiveness estimates less than $150,000 per QALY gained.

Table E.3. Results of Probabilistic Sensitivity Analysis for reSET-O versus Standard of Care

	reSET-O		Standard of Care	
	Mean	95% Credible Range	Mean	95% Credible Range
Total Costs	$84,000	($73,000, $96,000)	$82,000	($71,000, $95,000)
Total QALYs	3.1366	(3.0814, 3.1881)	3.1336	(3.0778, 3.1861)
ICER ($/QALY)	$501,000 ($232,000, $1,237,000)			

ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year

Figure E.1. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Cloud



QALY: quality-adjusted life year

Threshold Analyses from the Societal Perspective

Table E.4. provides the results of the threshold analysis results assuming a societal perspective. Similar to the estimates in the draft report, reSET-O is compared to standard of care to generate these estimates. Note that these results are preliminary and for reasons discussed in Section 6 of the draft report should not be assumed to reflect the health-benefit price benchmarks that will be provided in the next version of this Report.

Table E.4. Threshold Analysis Results

	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY
reSET-O	$1,665	N/A	$580	$730	$880

N/A: not available, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Undiscounted Base-Case Outcomes

Tables E.5 and E.6 present the undiscounted model outcomes and incremental findings for the base case.

Table E.5. Results for the Base Case for reSET-O Compared to Standard of Care, Undiscounted

Intervention	Digital Therapeutic Download Cost	Total Payer Cost	Life Years	QALYs	evLYGs	On MAT at 12 Weeks (%)
reSET-O	$1,665	$90,270	4.96062	3.367798	3.367801	80.4%
SoC	$0	$88,835	4.96060	3.364787	3.364787	64.1%

evLYG: equal value life year gained, MAT: medication-assisted treatment, QALY=quality-adjusted life year, SoC: standard of care

Table E.6. Incremental Cost-Effectiveness Ratios for the Base Case, Undiscounted

Treatment	Incremental Cost per Life Year Gained	Incremental Cost per QALY Gained	Incremental Cost per evLYG	Incremental Cost per Additional Person on MAT at 12 Weeks
reSET-O vs. SoC	$83,510,000	$476,000	$476,000	$8,800

evLYG: equal value life year gained, MAT: medication-assisted treatment, QALY: quality-adjusted life year, SoC: standard of care

Table E.7. Cumulative Net Cost Per Patient Treated with reSET-O at WAC Over a Five-year Time Horizon

	Cumulative Cost	Additional Costs per Year (Non-Cumulative)
Year 1	$1,486	$1,486
Year 2	$1,439	-$47
Year 3	$1,435	-$4
Year 4	$1,435	$0
Year 5	$1,435	$0