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

Final Evidence Report and Meeting Summary

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Prepared for

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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 https://icer.org/.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being Arnold Ventures. 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 https://icer.org/who-we-are/independent-funding/.

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.org/who-we-are/people/independent-appraisal-committees/midwest-comparative-effectiveness-public-advisory-council-m-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 experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/assessment/opioids-digital-apps-2020/#overview.

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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.

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Table of Contents

Executive Summary ES1

1. Introduction 1

1.1 Background 1

1.2 Scope of the Assessment 3

1.3 Definitions 5

1.4 Potential Cost-Saving Measures in Opioid Use Disorder 6

2. Patient Perspectives 7

2.1 Methods 7

2.2 Impact on Patients 7

2.3 Impact on Caregivers and Families 7

3. Summary of Coverage Policies and Clinical Guidelines 8

3.1 Coverage Policies 8

3.2 Clinical Guidelines 11

4. Comparative Clinical Effectiveness 12

4.1 Overview 12

4.2 Methods 12

4.3 Results 14

4.4 Summary and Comment 21

5. Long-Term Cost Effectiveness 23

5.1 Overview 23

5.2 Methods 23

5.3 Results 38

5.4 Summary and Comment 44

6. Potential Other Benefits and Contextual Considerations 46

6.1 Potential Other Benefits and Contextual Considerations 47

7. Health-Benefit Price Benchmarks 49

8. Potential Budget Impact 50

8.1 Overview 50

8.2 Methods 50

8.3 Results 51
9. Summary of the Votes and Considerations for Policy 53
9.1 About the Midwest CEPAC Process 53
9.2 Voting Results 55
9.3 Roundtable Discussion and Key Policy Implications 59
References 63
Appendix A. Search Strategic Results A1
Appendix B. Previous Systematic Reviews and Technology Assessments B1
Appendix C. Ongoing Studies C1
Appendix D. Comparative Clinical Effectiveness Supplemental Information D1
Appendix E. Comparative Value Supplemental Information E1
Appendix F. Public Comments F1
Appendix G. Conflict of Interest Disclosures G1

List of Acronyms and Abbreviations 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
DHT	Digital Health Technology
DSM-4	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
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
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

Executive Summary

Background

Opioid use disorder (OUD) is a public health crisis in the United States. The number of drug overdose deaths in the US increased continuously from 1999 to mid-2017[1] when it reached a plateau of approximately 70,000 deaths over the previous 12 months of which approximately 50,000 were from opioids.[2,3] The number of deaths resumed its increase over the past two years. 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.[4]

Medication assisted treatment (MAT) is the most effective treatment for OUD, but more than half of patients starting MAT drop out of treatment within three to six months. Behavioral therapies increase retention in some studies, but they are resource intensive. Digital health technologies (DHTs) offer the potential to expand the availability of behavioral therapies and to reduce cost. We examine the evidence for three such promising digital health technologies (DHTs) in this review: reSET-O, Connections, and DynamiCare.

Patient Perspectives

As part of our review, we spoke with organizations working with individuals and families affected by OUD. There was consensus that MAT is often difficult to access, in part because of the stigma attached to OUD. Supportive therapy as an adjunct to MAT that is delivered through DHTs on smart phones can also expand access without stigma.

There was consensus that better daily functioning and 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. 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.

Comparative Clinical Effectiveness

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.[5-7] None of the studies of these apps has any data on the outcomes that matter to patients and the studies of the precursor elements implemented in the DHTs do not show improvements in long-term retention.

Clinical Benefits

We found no randomized trials, cohort studies or case series that evaluated the DHTs reviewed in this report until after the draft report was released. Recently, two uncontrolled studies suggested potential benefits with reSET-O, but there was a high risk of bias for both studies.[8,9]

The key study supporting the 510(k) application to the FDA of reSET-O (Christensen 2014) included participants who met the DSM-4 criteria for opioid dependence and the FDA qualification criteria for buprenorphine treatment.[10] There was no significant difference in the primary outcome: number of days of continuous abstinence. Any other significant findings should be considered hypothesis generating. The study did find 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 contingency management (CM) in addition to MAT. However, a study of the same intervention with one-year follow-up found no difference in drop-out rates (38.8% versus 38.8%).

There were less data supporting the Connections and DynamiCare apps.

Harms

The studies of the precursor elements implemented in the DHTs did not report on adverse events (AEs), serious adverse events (SAEs), or AEs related to use of the DHTs.[10-13] A secondary analysis of the Christensen 2014 trial published after the draft report was released found no increase in AEs with reSET-O compared with standard therapy.[14]

Controversies and Uncertainties

The primary source of uncertainty in the clinical evidence for these DHTs 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 behavioral components implemented in the DHTs did not measure outcomes with long enough follow-up. The minimum follow-up to demonstrate a meaningful impact on adherence would be six 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.

Summary and Comment

There is no direct, peer-reviewed evidence on the efficacy of any of the DHTs in the population of interest. All three DHTs 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.[15] The use of the DHTs is unlikely to be harmful to patients. Thus, there is moderate certainty that the outcomes with MAT plus use of the DHTs are

comparable to MAT alone (due to no identified harms). There may be incremental benefits, but evidence is lacking to date.

Long-Term Cost Effectiveness

The primary aim of this analysis is to estimate the cost effectiveness of DHTs as an adjunct to MAT for OUD. Where data allowed, the model compared a DHT 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. If a lifetime time horizon were modeled, the results would be very similar to the base-case five-year time horizon, given unlikely separation between the intervention and comparator in clinical outcomes or cost after a period of five years as suggested by currently available evidence.

As data permitted, productivity impacts and other indirect costs were included in a modified societal perspective scenario analysis. The modified societal perspective is not presented as a co-base case because we interpreted the impact of the DHTs on indirect costs to not be substantial (See Section 5.2). The target population consisted of adults 18 years and older with OUD receiving outpatient MAT.

We developed a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models,[16-20] including ICER's previous review of MAT completed in 2018.[21] Our model included two phases, with Phase 1 modeling the time using the DHT as an adjunct to outpatient MAT and its associated clinical and economic outcomes, and Phase 2 capturing continued MAT use beyond the completion of the DHT 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), years 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 three percent per year. Incremental costs per LY gained, incremental costs per QALY gained, incremental costs per evLYG, and incremental costs per additional year on MAT were calculated for all relevant pairwise comparisons.

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 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. The comparator was outpatient MAT (i.e., counseling plus pharmacological therapy) without the use of a DHT.

The average wholesale price and the wholesale acquisition cost for reSET-O are provided in Table ES1. Also provided in Table ES1 is the net price for reSET-O. The net price was the price used in the model to approximate the cost to download the DHT.

Table ES1. Intervention Cost per Download

Intervention	AWP per Download	WAC per Download	Net Price* per Download
reSET-O	$1,998[22]	$1,665[22]	$1,219

AWP: average wholesale price, WAC: wholesale acquisition cost

*Net price was provided to us by the manufacturer and was described as "net of rebates, discounts, allowances and warranty payments where applicable."

Base-Case Results

The addition of reSET-O to outpatient MAT resulted in approximately $800 more total payer costs over a five-year time horizon. The addition of reSET-O to outpatient MAT alone resulted in additional costs to download the DHT and additional MAT costs from increased retention; however, health care utilization costs were slightly lower due to the higher percent of individuals retained on MAT. Clinical outcomes of life years, QALYs, evLYGs, and MAT years with reSET-O were slightly higher than standard of care resulting from the higher number of abstinent days over the first 12 weeks and from the higher percent of individuals retained on MAT treatment over the five-year time horizon. Table ES2 presents the model outputs for the base-case analysis comparing reSET-O to standard of care.

Table ES2. Results for the Base Case for reSET-O Compared to Standard of Care, Five-Year Time Horizon

Intervention	Digital Health Technology Download Cost	Total Health System Costs	Life Years*	QALYs*	evLYGs*	On MAT Years
reSET-O	$1,219	$83,332	4.61821	3.152809	3.152812	0.54
SoC	$0	$82,558	4.61820	3.146440	3.146440	0.46
Incremental	$1,219	$774	0.00002	0.006369	0.006371	0.08

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 $121,500 per QALY gained. Results were similar when compared to outcomes of evLYG due to the very small mortality benefit indirectly associated with reSET-O given the fewer days of illicit use while using the DHT. Table ES3 presents the incremental findings for the base case.

Table ES3. Incremental Cost-Effectiveness Ratios for the Base Case

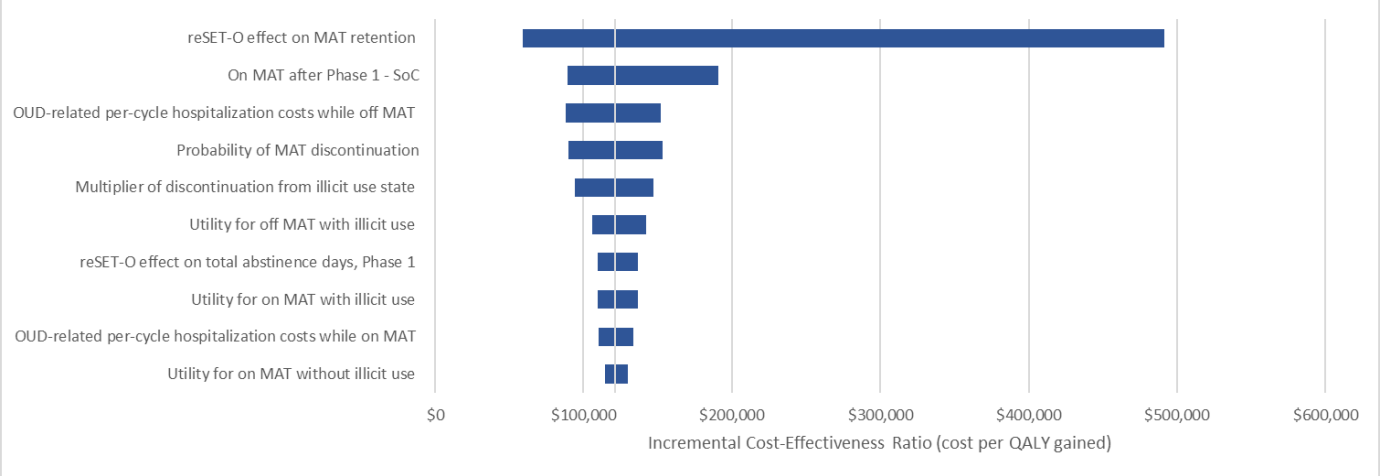
Intervention	Incremental Cost per Life Year Gained	Incremental Cost per QALY Gained	Incremental Cost per evLYG	Incremental Cost per Additional MAT Year
reSET-O vs. SoC	$48,449,000	$121,500	$121,400	$10,000

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

Sensitivity Analyses

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. The primary driver of the cost-effectiveness findings is the reSET-O effect on MAT retention. Figure ES1 presents the tornado diagram resulting from the one-way sensitivity analysis. This figure suggests that if there is only a small improvement in retention associated with reSET-O, reSET-O is no longer cost effective at commonly used thresholds. The odds ratio of retention used in the cost-effectiveness model from the reSET-O pivotal trial was 2.3 (95% CI: 1.15 to 4.60). If the odds ratio is 2.0 or less, reSET-O exceeds a threshold of $150,000 per QALY. Additional supporting information for the one-way sensitivity analysis can be found in the appendix. Probabilistic sensitivity analyses suggested that nearly 40% of iterations produced cost-effectiveness ratios above $150,000 per QALY. Consistent with the clinical evidence review, considerable uncertainty exists within the cost-effectiveness findings that are conditioned on the assumptions and inputs.

Figure ES1. Tornado Diagram for One-Way Sensitivity Analysis of reSET-O versus Standard of Care



Threshold Analyses

Table ES4 presents the results of the threshold analysis for reSET-O as compared to standard of care.

Table ES4. Threshold Analysis Results

Intervention	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	$1,219	$760	$1,080	$1,400

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.

Summary and Comment

Our base-case results suggest that the use of reSET-O as an adjunct 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 net pricing, and given evidence-based assumptions, these potential cost offsets and clinical gains may be enough to generate incremental cost-effectiveness estimates within higher commonly cited cost-effectiveness thresholds.

The cost effectiveness of reSET-O is extremely sensitive to the effect of the DHT on retention, which there is still uncertainty around in the clinical evidence. Despite no evidence available after time on DHT (i.e., after 12 weeks), our model extrapolates the potential downstream benefits of having a higher percentage of individuals retained on MAT over a five-year time horizon. We assumed discontinuation probabilities over time were the same between reSET-O and standard of care after 12 weeks. Therefore, a higher percentage of individuals retained on MAT at 12 weeks in the reSET-O arm as compared to standard of care resulted in 0.08 more MAT years or nearly one added month on MAT over five years.

Finally, the added costs and the added health benefits are modest and uncertain leading to large potential swings in incremental cost effectiveness. The base-case findings should be interpreted with caution alongside the characterization of assumptions and uncertainty as well as the other benefits and contextual considerations.

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.

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 reSET-O.

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 computer based in a clinic) has the potential to increase real-world adherence, but it could also decrease adherence. There are no data yet.

There is the possibility that these DHTs 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 (five 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 DHTs 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.

Health Benefit Price Benchmarks

The health benefit price benchmarks for reSET-O range from $1,080 to $1,400. A discount of 16-35% off WAC would be needed to reach these discounts. The manufacturer-provided net price is $1,219, which is a 27% discount from WAC.

Potential Budget Impact

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), net price ($1,219), 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. 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.[23] 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).[24,25] 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. 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).

Figure ES2 illustrates the cumulative per-patient budget impact calculations for reSET-O compared to SoC, based on the net price of $1,219 for one-time treatment. The average potential budgetary impact for reSET-O was an additional per-patient cost of approximately $819 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 $768 by year five. (Additional net costs per year are presented along with cumulative net costs in Appendix Table E7.)

Figure ES2. Cumulative Net Cost Per Patient Treated with reSET-O at WAC Over a Five-Year Time Horizon

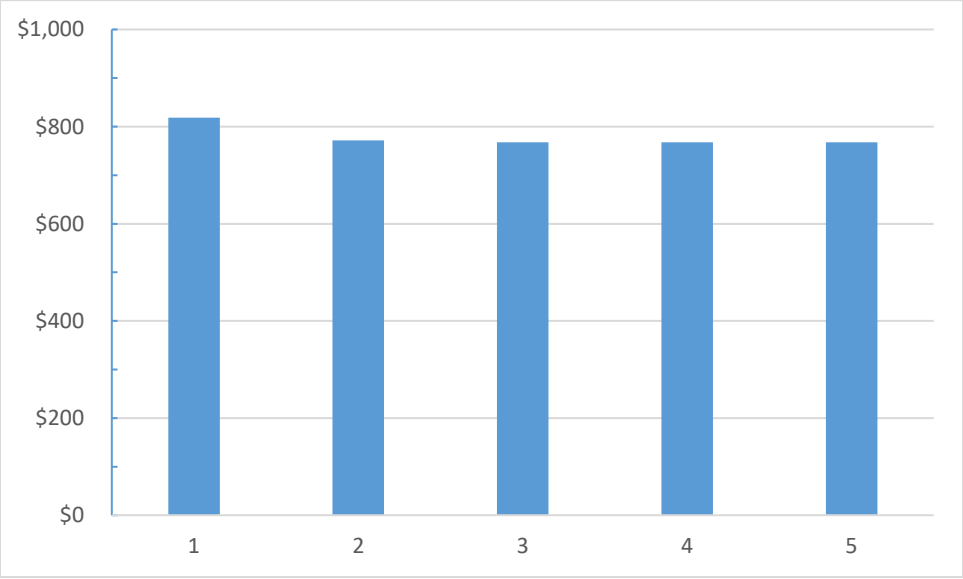


Table ES5 illustrates the potential budget impact of treatment of the eligible population with reSET-O, based on the WAC ($1,665 per download), net price ($1,219), and the threshold prices to reach $150,000, $100,000, and $50,000 per QALY compared to SoC ($1,400, $1,082, and $764, respectively). For reSET-O, the annual potential budgetary impact of treating 20% of the entire eligible population each year (95,656 per year) was $117.2 million, assuming the WAC download price. This was largely due to assumption of one-time download cost with the DHT and the slight savings with no additional costs in subsequent years.

Table ES5. Estimated Total Potential Budget Impact of One-Time Download with reSET-O Using WAC, Net, and Threshold Prices Over a Five-Year Time Horizon (N=95,656 per Year)

	Annual PBI (millions)	Total 5-Year PBI (millions)
WAC	$117.2	$585.8
Net Price	$74.5	$372.4
$150,000/QALY Threshold Price	$91.9	$459.3
$100,000/QALY Threshold Price	$61.4	$307.0
$50,000/QALY Threshold Price	$30.9	$154.7

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

Midwest CEPAC Votes

The Midwest CEPAC Panel deliberated on key questions raised by ICER's report at a public meeting on November 18, 2020. The results of these votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

Patient population for all questions: Adult patients with OUD who are receiving MAT (buprenorphine, methadone)

Clinical Evidence: *Standard of care includes MAT, but not contingency management*

1. Given the currently available evidence, is the evidence adequate to demonstrate a net health benefit for the **reSET-O** app added to standard of care compared to standard of care alone?

Yes: 3 votes	***No: 10 votes***

2. Given the currently available evidence, is the evidence adequate to demonstrate a net health benefit for treatment with the **Connections** app added to standard of care compared to standard of care alone?

Yes: 0 votes	***No: 13 votes***

3. Given the currently available evidence, is the evidence adequate to demonstrate a net health benefit for the **DynamiCare** app added to standard of care compared to standard of care alone?

Yes: 0 votes	***No: 13 votes***

4. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to the **reSET-O** app. Refer to the table below.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
This intervention will not differentially benefit a historically disadvantaged or underserved community		This intervention will differentially benefit a historically disadvantaged or underserved community
1 vote	***6 votes***	***6 votes***

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
5 votes	***8 votes***	0 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Very similar mechanism of action to that of other active treatments		New mechanism of action compared to that of other active treatments
1 vote	***7 votes***	4 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
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
2 votes	***9 votes***	2 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
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
1 vote	***9 votes***	3 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
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
1 vote	***10 votes***	2 votes

5. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment **at current pricing** with **reSET-O** versus standard of care?

Low Long-Term Value for Money	Intermediate Value for Money	High Long-Term Value for Money
8 votes	5 votes	0 votes

Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on digital health technologies as an adjunct to MAT for OUD to policy and practice. The policy roundtable members included two patient advocates, two clinical experts, two payers, and representatives from Pear Therapeutics and CHESS Health. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in the full report.

General

1. Medication-assisted treatment (MAT) saves lives and money, both inside the health system and outside of it. New interventions should be developed, tested, and implemented that can augment the number of individuals who can access MAT, reduce stigma, and ensure that individuals receive care in a format that helps them achieve their goals. DHTs may be important aids in improving care for many individuals, but it is vital that adequate evidence be generated to evaluate the relative effectiveness of different options so that each person can receive effective treatment tailored to maximize their health. Poor evidence that leads to ineffective use of DHTs represents a health risk to individuals, a financial risk to the health system, and a moral risk for us all that society will fail in its responsibility to use its resources to the greatest effect in combatting an ongoing national epidemic.

Researchers / Manufacturers

2. Manufacturers should provide robust evidence of the clinical effectiveness and broader impact of new DHTs. For DHTs like those featured in this report that have a function of guiding or enhancing treatment outcomes, a minimum evidence requirement is high-quality observational or quasi-experimental studies with an appropriate comparator and relevant patient outcomes. However, many DHTs should undergo formal evaluation through randomized controlled trials to minimize the risk of bias in trial results.

3. In addition to evidence on relative safety and effectiveness in the short term, manufacturers should be prepared to provide a full dossier of evidence to payers and providers that includes robust information on 1) the durability of beneficial clinical effects; 2) the impact on health care utilization; 3) the impact on clinician productivity; 4) the usability as measured by clinician and patient experience; 5) the security of IT components; 6) the generalizability of results to diverse patient populations and health systems; and 7) the scalability to larger populations.

4. Manufacturers and researchers should design trials of DHTs to be able to identify potential subgroups of patients who benefit most from a DHT and those who are less likely to benefit. Existing evidence may also be reanalyzed for this purpose.

Payers

5. Given the limited evidence supporting the efficacy of DHTs for OUD, alternative payment models may be appropriate if coverage is provided.

Regulators

6. The FDA should develop a clear taxonomy of DHTs, with different levels of risk and other factors, and clarify evidence requirements that are robust enough to inform patients, clinicians, health systems, and payers regarding the safety and comparative effectiveness of their use in representative patient populations.

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.[26,27] Most experts believe that it is a chronic disease that requires long-term maintenance treatment.[28]

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[1] when it reached a plateau of approximately 70,000 deaths over the previous 12 months of which approximately 50,000 were from opioids.[2,3] Approximately two million people 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.[29] However, there is evidence that this significantly underestimates the true prevalence of OUD.[30,31] 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.[4]

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.[32,33] Treatment of OUD with MAT has been shown to be effective,[28,34] and three types of medications are approved by the FDA: the full opioid agonist methadone, the partial agonist buprenorphine, and the opioid antagonist naltrexone.[35,36]

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 (SUD), including OUD when added to MAT.[15,37] 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.[21] 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 Health Technologies

There is a tremendous amount of interest and innovation in digital health technologies (DHTs), which is reflected in a growing number of National Institutes of Health (NIH) supported grants in this area.[38] 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 SUD. Stakeholders directed us to three digitally implemented health technologies 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. Digital therapeutics represent a subset of DHTs that are intended to prevent, manage, or treat a medical condition and require FDA approval. The FDA cleared reSET-O, because it was found to be substantially similar to its predicate device reSET, which is used to treat substance use disorders other than OUD.[39] 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.[37] 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. In reSET-O, patients earn on average $110 in Amazon or Starbucks gift cards throughout the 12-week treatment program.

Connections

The Connections app brings together two different digital programs: A CHESS[40-42] with CBT4CBT.[43-48] 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 seven-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.[49] 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
- Infections (HIV, hepatitis), injection site reactions, and other complications from continued use of injectable opioids
- Functional outcomes (cognitive, occupational, social/behavioral)[50]
- 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., four weeks), usually at the end of the study.[10]

Addiction

Addiction is a term that had previously been used to refer to people with OUD who were not in recovery or remission and engaged "in behaviors that become compulsive and often continue despite harmful consequences." However, because OUD is recognized to be a biologically-based disease, and the terms "addiction" and "addict" carry societal stigma, they are not preferred and not used in this report.

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.[37]

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 on a scale (mild, moderate, or severe) by the DSM-5, based 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-4 termed "opioid abuse" and "opioid dependence."[51]

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.[52] 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

Relapse is the 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 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.[28]

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.[28]

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.[5-7,53]

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.org/our-approach/methods-process/value-assessment-framework/). 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.[33]

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.[54] 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 people in a partnership or between parent and child, whether it is the parent or child who suffers from OUD. 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 DHTs 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 NCDS, LCDS, or coverage policies from these plans were available for DHTs for OUD at the time this report was written. 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 DHTs 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.[55] RemedyOne will be providing this benefit to its 2.5 million customers. This marks the first PBM to cover prescription DHTs for the treatment of SUD and/or OUD.

The following health plans, PBMs, and treatment centers also provide access to reSET-O for their members: Wellpath Community Care Centers, PreferredOne Health Plan (Minnesota), Serve You Rx, The Hartford Employee Health Plan, ChristianaCare Employee Health Plan, and RemedyOne.[56]

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.[57]

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 DHTs

Public Payers

Currently, CMS does not cover prescription DHTs 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 DHTs for mental health and substance use disorder treatment under Medicare and Medicaid.[58] DHTs 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."[58] 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

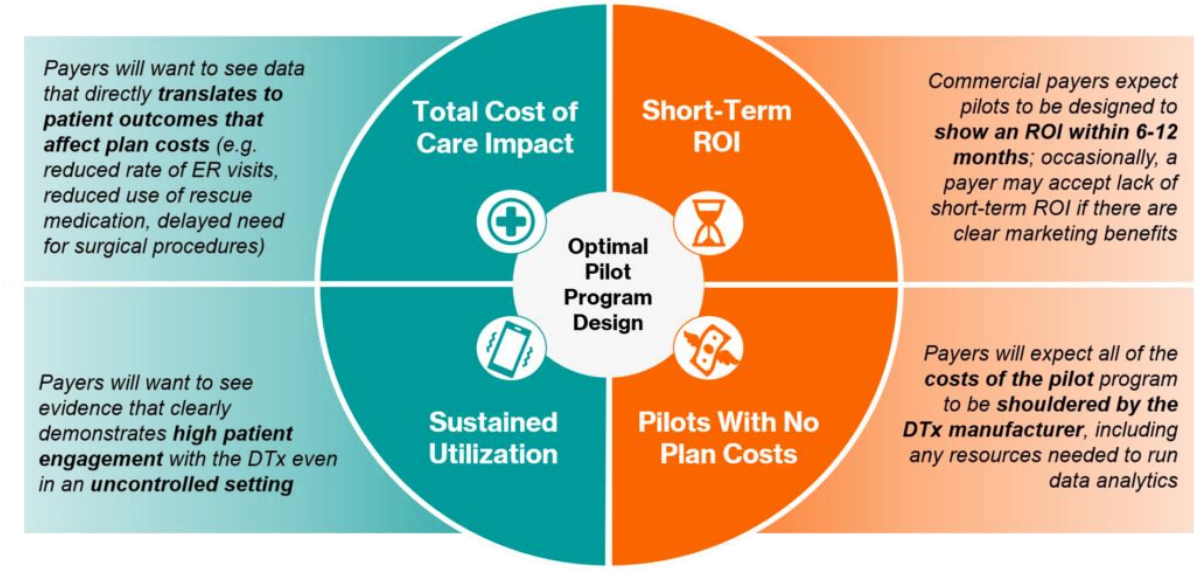
The general approach to evaluating coverage for DHTs varies across payer types. Managed Care Organizations (MCOs) are more likely to focus on business needs first before considering adding on a digital health product to their formulary, PBMs have demonstrated more proactive engagement with manufacturers of DHTs, but tend to focus on products in disease areas that are most relevant or have higher potential for cost savings.[59]

Additionally, a key area of uncertainty is whether DHTs 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 DHTs 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.[59] For example, Express Scripts launched in May 2020 their first ever digital formulary ranging from remote monitoring services and DHTs 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 DHT. 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 DHTs, 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 DHT Uptake[59]



All in all, there is great diversity in the approaches across payer groups regarding DHTs 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 DHTs 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., white papers). 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.[60,61] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[62] 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

Following 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."[63] 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)[64].

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 DHTs 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 D1-D11) 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 1,119 references and one additional reference was identified through a company's website (Appendix Figure A1). In addition, a manufacturer provided us with three additional peer-reviewed publications after our draft report was posted. 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 14 publications describing six randomized trials.

Key Studies

reSET-O

The key randomized trial that formed the basis of the FDA clearance of reSET-O was published in 2014.[10] It built on several prior randomized trials of computerized versions of the TES added to MAT for OUD.[11-13] 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 DHT. There is a small pilot study with published results for CBT4CBT [48], but the larger randomized trial of the combination of CBT4CBT with A CHESS has only recently been funded.[65]

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.[49] 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.[10] It was neither double-blinded nor were the groups comparable at baseline. The other studies were either of fair[11,13] or poor quality.[12]

Connections

The study of the CBT4CBT portion for the Connections app[48] 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[49] 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.[5-7]

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.[10,66] However, during the last week in October, one post-hoc analysis and two new uncontrolled, observational studies were published electronically.[8,9,14]

The key study (Christensen 2014) included participants who met the DSM-4 criteria for opioid dependence and the FDA qualification criteria for buprenorphine treatment (Appendix Table D1).[10,66] 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% vs. 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 D6-D8). 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 ($1,000 vs. $1,808), sex (48% male vs. 62% male), prior treatment (40% vs. 53%), and years of regular opioid use (5 vs. 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 CM 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 six 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.[11,12] 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.

Late Breaking Data

One new publication provided additional safety and efficacy analyses of the Christensen 2014 study described above.[14] They also provided additional baseline characteristic data, which showed that patients in the control group were twice as likely to be also using methamphetamines (12.7% vs. 6.6%, p=0.20) and more likely to be using cocaine as well (21.5% vs. 15.4%, p=0.34). This is potentially important as those patients may be more challenging to treat and to retain in the study.

Finally, they report that the total abstinence rate during the last four weeks of the study using an unusual generalized estimating equations (GEE) analysis was 60.6% in the control group and 75.9% in the active group (p=0.03).[14] Usually in clinical trials, standard statistics would be used – in this case a simple chi-squared test comparing the proportion of patients abstinent in the control group to the same proportion in the active group. Other data in the publication suggest that the true abstinence rate is much lower than that reported in the GEE analysis. Namely, that the proportion of tests that indicated abstinence was 24.06% in the control group and 27.97% in the active treatment group over the entire 12-week study period (p=0.02). Since patients who drop out of the study no longer provide urine samples and missed urine samples are considered positive, the proportion of tests indicating abstinence during the final four weeks of the study should be even lower than 27.97%.

The second study was a real-world observational study describing the 12-week experience of 3,142 patients who redeemed their prescription for reSET-O and completed at least one module.[9] There were no data for 873 patients (28%) during the final four weeks of the study. The authors did not provide the total number of prescriptions for reSET-O that were written so we do not know what proportion of patients prescribed the app actually downloaded it and completed at least one module. Self-report of abstinence as well as urine drug tests were combined to determine abstinence. The statistical methods were not described but were likely the same GEE analysis described in the prior paragraph. They found that 66% of patients completed half of the modules and 49% completed all of the modules. The authors report that 66% of patients were abstinent during the last four weeks of the study.

The final study was a retrospective study using claims data to compare resource utilization for 351 patients in the six months prior to using reSET-O with the six months following initial use of reSET-O.[8] The only inclusion criteria described was that patients had to be enrolled in the health plan for at least four weeks in both the pre and post-initiation time periods. While all of the patients were supposed to be on buprenorphine, only 76.7% had a prescription claim before reSET-O initiation and 72.8% post initiation. They estimated that there were 72 hospitalizations in the pre-initiation period and 27 in the post-initiation period (p=0.024). The also estimated the number of emergency room visits (84 vs. 38, p=0.247). The biggest challenge in interpreting these results is the lack of a control group. It may be that high utilizing patients were chosen to receive reSET-O and that the estimated reduction in resource utilization reflects regression to the mean rather than a true effect of the DHT.

Table 4.1. Outcomes of the Computerized CBT Trials

Study	Arms	N	Length of Follow-Up	Retention (%)
Christensen 2014[10]	– Computer CBT + CM + BUP – CM + BUP	92 78	12 weeks	80.4 64.1
Bickel 2008[11]	– Computer CBT + CM + BUP – Therapist CBT + CM + BUP – BUP	45 45 45	23 weeks	62.2 53.3 57.7
Chopra 2009[12]	– Computer CBT + CM + BUP – Computer CBT + CM* + BUP – BUP	41 42 37	12 weeks	85.4 59.5 75.7
Marsch 2014[13]	– 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

It is important to note that in Marsch 2014, there were no differences in retention rates at 52 weeks between patients who were randomized to the interventions included in reSET-O and those who received MAT alone.[13] Similarly, in Bickel 2008, the differences in retention rate at 23 weeks was lower than that observed in Christensen 2014 even though the intervention was the same.[10,11] This is not surprising. 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.[67] 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).[11]

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 patients ages 18 years and older with OUD to 12 weeks of a web based CBT program known as CBT4CBT plus buprenorphine or buprenorphine alone.[48] 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.[48] 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 D2), 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 vs. 68.6 days, p=0.19) and provided more urine samples (9.3 vs. 8.4, p=0.48). They had significantly more urine tests that were free of all illicit drugs (7.3 vs. 2.3, p=0.01) and a higher percentage free of illicit drugs (81.6% vs. 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.[49] 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% vs. 21%), 60 days (28% vs. 14%), and 90 days (25% vs. 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

In newly published re-analysis of the Christensen 2014 study of the precursor to reSET-O, use of the computer program was not associated with an increase in adverse events (AEs).[14] The overall AE rate was 69.6% in the control group and 62.6% in the intervention group and no AEs were ascribed to use of the computer program.

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 D2-D5), but subgroup analyses were rarely reported.

Uncertainties and Controversies

The primary source of uncertainty in the clinical evidence for these DHTs 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 six 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 DHTs 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 DHTs for Patients with Opioid Use Disorder Treated with MAT

DHT	ICER Evidence Rating
reSET-O	C+
Connections	C+
DynamiCare	C+

The evidence rating is the same for all three DHTs: comparable or incremental. There is no direct, peer-reviewed evidence on the efficacy of any of the DHTs in the population of interest. All three DHTs 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.[15] The use of the DHTs is unlikely to be harmful to patients. Thus, there is moderate

certainty that the DHTs 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 DHTs as an adjunct to MAT for OUD using a decision analytic model. Where data allowed, the model compared a DHT 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. If a lifetime time horizon were modeled, the results would be very similar to the base-case five-year time horizon given unlikely separation between the intervention and comparator in clinical outcomes or cost after a period of five years.

As data permitted, productivity impacts and other indirect costs were included in a modified societal perspective scenario analysis. The modified societal perspective is not presented as a co-base case because we interpreted the impact of the DHTs on indirect costs to not be substantial (See Section 5.2). The target population consisted of adults 18 years and older with OUD receiving outpatient MAT.

We developed a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models,[16-20] including ICER's previous review of MAT completed in 2018.[21] Our model included two phases, with Phase 1 modeling the time using the DHT and its associated clinical and economic outcomes, and Phase 2 capturing continued MAT use beyond the completion of the DHT and its associated clinical and economic outcomes.

Model outcomes included total LYs gained, QALYs gained, evLYGs, years 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 MAT year 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 DHT as an adjunct to outpatient MAT or outpatient 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).

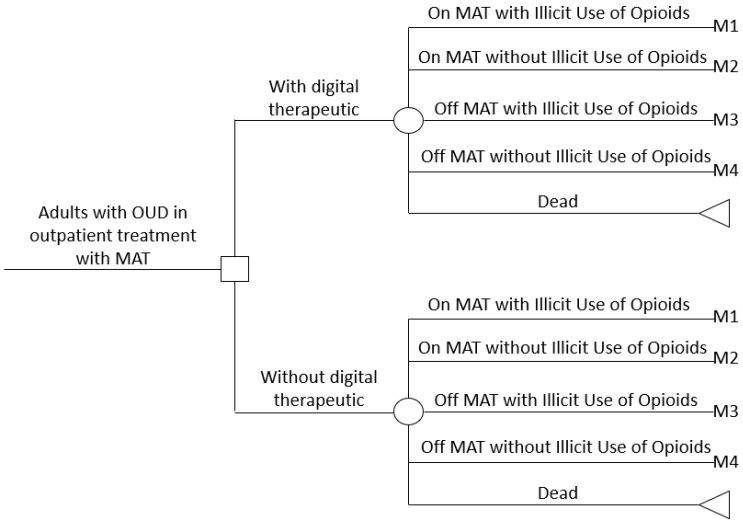
Model Structure

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 DHT. While using the DHT, 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 DHT use. Discontinuation was defined as leaving the trial at will or failing to attend three clinic visits in a row.[10] Illicit use of opioids was defined as testing positive for opioids during a urine drug screening test or missing a urine drug screening test.[10]

DHT 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 DHT use occupied the On MAT without Illicit Use of Opioids health state. The last four weeks of DHT use was selected as the assessment duration for the On MAT without Illicit Use of Opioids health state to align with the DHT evidence and the FDA's recommendation to allow a grace period prior to assessing an intervention's effect. This health state definition was based on all urine drug screening tests over the last four weeks of DHT use to capture those individuals with a period of continuous abstinence. 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 DHT) 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



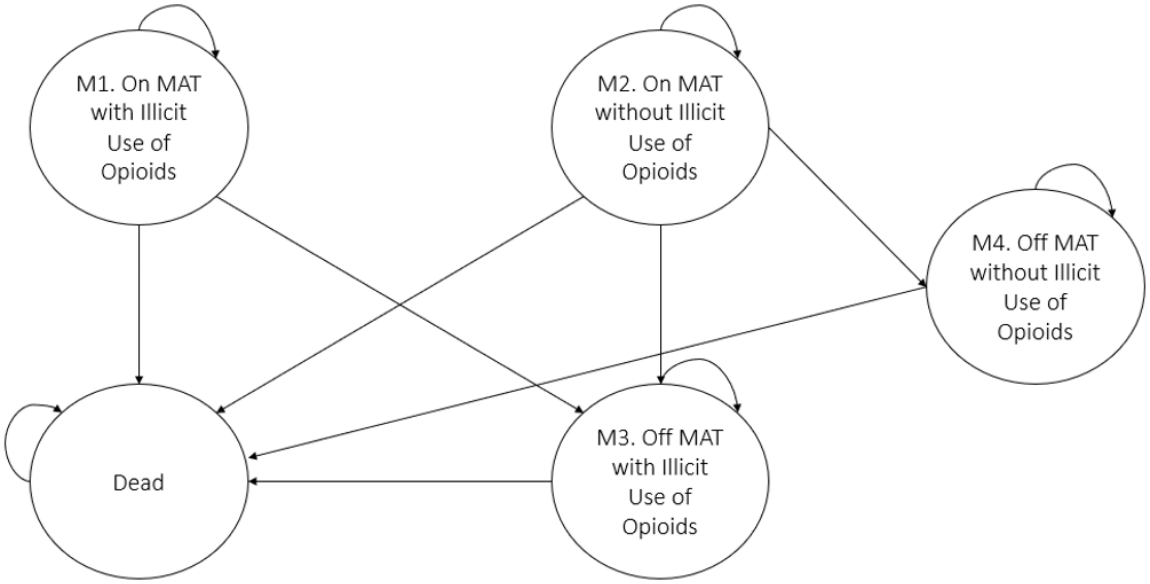
Phase 2 of the model (Figure 5.2) was a Markov model that consisted of the same five health states: 1) On MAT with Illicit Use of Opioids, 2) On MAT without Illicit Use of Opioids, 3) Off MAT with Illicit Use of Opioids, 4) Off MAT without Illicit Use of Opioids, and 5) Dead. Patients entered the Markov 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.[21]

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 DHT (during the Phase 1 decision tree). There was no evidence to suggest a residual effect of a DHT on abstinence after the use of the health technology completed; therefore, any transitions from illicit use to without illicit use that would occur outside of DHT use were 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 mirrored the population characteristics from the pivotal trial used to inform the clinical evidence. Age and sex factored into mortality, and age also influenced utility estimates. Injection as the preferred route of illicit use administration influenced the comorbidities associated with OUD. 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[10]
Female (%)	46%	Weighted average from Christensen et al., 2014[10]
Injection as preferred route of illicit use administration (%)	14%	Weighted average from Christensen et al., 2014[10]
Employed full time (%)	37%	Weighted average from Christensen et al., 2014[10]

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 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.

The comparator was outpatient MAT (i.e., counseling and pharmacological therapy) without the use of a DHT. 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 CM). 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 DHT use entered the On MAT without Illicit Use of Opioids health state in the Markov model.	The final four weeks of DHT use aligned with the DHT evidence and the FDA's recommendation to allow a grace period prior to assessing an intervention's effect. A period of continuous abstinence was required to enter this health state.
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 DHT and while on MAT treatment during Model Phase 1 only.	Any transitions from illicit use to without illicit use that occurred after the DHT were considered to be the same across treatment arms and were not included in Model Phase 2. There is no evidence that suggests a residual effect of reSET-O on abstinence after use.
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 DHT 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 DHT clinical evidence.	No robust data exist on long-term discontinuation/relapse for the DHT 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.[68]
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.[21]	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.

Model Choice or Assumption	Rationale
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 Health Technology Efficacy

DHT efficacy was measured primarily by abstinence and MAT treatment retention and was derived from relevant trial evidence.[10] Efficacy for the standard of care comparator was derived based on the contingency management comparator efficacy[10] and published literature.[68] A study by Gross and colleagues[68] 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 DHT 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 DHT use. Four weeks was used to capture a period of continuous abstinence that was required to enter Phase 2 in an abstinence health state. 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.[10] Abstinence data are presented in Table 5.3. The difference in total days abstinent over Phase 1 assigns a benefit to reSET-O by way of increasing abstinent days. Due to the lack of statistical significance in longest continuous abstinence over the first 12 weeks, and no evidence to suggest an increase in abstinence after 12 weeks, we assigned no difference between reSET-O and standard of care in the percent of the population that entered the On MAT without Illicit Use of Opioids health state in Phase 2 of the model.

Table 5.3. Abstinence from Illicit Opioid Use at Completion of DHT

Abstinence	reSET-O	SoC/CM Comparator	Source
Total Days Abstinent Over Phase 1	67.1 days	57.4 days	Christensen et al., 2014[10]
Percent of Population That Enters the On MAT Without Illicit Use of Opioids Health State in Phase 2	22.8%	22.8%	Data on file

CM: contingency management, SoC: standard of care

MAT Treatment Retention

Over the duration of the DHT (Phase 1), MAT retention data from the DHT pivotal evidence informed the percent of the population who started Phase 2 in the Off MAT with Illicit Use of Opioids health state. Table 5.4 presents the MAT retention evidence from the pivotal trial for reSET-O. MAT discontinuation was gradual over the time of DHT use; thus, for the purposes of assigning outcomes (LYs, QALYs, etc.) in Phase 1 of the model, we assumed discontinuation occurred halfway through the DHT 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 (1.15, 4.60)	Christensen et al., 2014[10]

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

MAT discontinuation after the duration of the DHT was extrapolated from the comparator MAT retention curve (discontinuation=1-retention) from the DHT pivotal trial.[10] 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.[69] 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 DHT 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[10]

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 DHT. 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% CI: 0.042% to 0.080%) and 26.7%, respectively. These rates were converted to per-cycle probabilities in the model.[70,71] 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)[72] and those who were not successfully treated with direct-acting antiviral therapy (98% of treated cases are effectively cured of HCV).[73] 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.[74] We had no evidence to suggest a survival benefit specific to the use of the DHT; however, an increased risk of death was assigned to those illicitly using opioids in addition to all-cause mortality.[75] 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[75]
All-Cause Mortality	U.S. Life Tables[74]	

Health State Utilities

There was no evidence to suggest a utility benefit or decrement associated with time on the DHT. Health state utilities were derived from a study that used an online US cross-sectional survey.[76] 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. Table 5.7 presents the health state utilities used in the model.

Table 5.7. Health State Utilities

Parameter	Value	Source
Off MAT without Illicit Use of Opioids	0.852	Wittenberg et al., 2016[76]
On MAT without Illicit Use of Opioids	0.766	Wittenberg et al., 2016[76]
On MAT with Illicit Use of Opioids – Not Injected	0.761	Wittenberg et al., 2016[76]
Off MAT with Illicit Use of Opioids – Not Injected	0.694	Wittenberg et al., 2016[76]
On MAT with Illicit Use of Opioids – Injected	0.689	Wittenberg et al., 2016[76]
Off MAT with Illicit Use of Opioids – Injected	0.574	Wittenberg et al., 2016[76]

MAT: medication assisted treatment

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.[77] 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.[78] 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.[10] Therefore, HCV-specific disutilities are not anticipated to be a key driver of the model.

Intervention Utilization

Table 5.8 details additional specifics of the DHT utilization. The DHT 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 5.8. Intervention Recommended Utilization

	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 DHT costs, MAT costs, other intervention-related costs, and health care resource utilization costs.

Intervention Costs

The average wholesale price and the wholesale acquisition cost for reSET-O are provided in Table 5.9. Also provided in Table 5.9 is the net price provided to us by Pear Therapeutics that was described as "net of rebates, discounts, allowances and warranty payments where applicable." The net price was the price used in the model to approximate the cost per patient to download the DHT in this evidence report. In the previous draft report of this review, the net price was not provided and thus the WAC was used in those findings.

Table 5.9. Intervention Cost per Download

Digital Health Technology	AWP per Download	WAC per Download	Net Price*
reSET-O	$1,998[22]	$1,665[22]	$1,219

AWP: average wholesale price, WAC: wholesale acquisition cost

*Net price was provided to us by the manufacturer and was described as "net of rebates, discounts, allowances and warranty payments where applicable."

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 16 mg generic sublingual buprenorphine/naloxone. Table 5.10 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 5.10. 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[22]

N/A: not applicable, WAC: wholesale acquisition cost

Non-Drug Costs

Administration Costs

Because the DHT did 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 DHT, not including MAT and the cost of the DHT, was sourced from evidence specific to each DHT and from published literature. Table 5.11 presents the other intervention-related health care utilization over the duration of the DHT for reSET-O.

Table 5.11. Intervention-Related Health Care Utilization while On DHT (Phase 1 of Model)

	reSET-O	SoC Comparator	CM Comparator
Therapist Counseling	6 visits	6 visits	6 visits
Contingency Management	12 weeks*	0 weeks	12 weeks

CM: contingency management, SoC: standard of care

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

Table 5.12 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 5.12. Intervention-Related Health Care Utilization Unit Costs

	Value	Notes/Source
Therapist Counseling	$128	Average commercial reimbursement for CPT code 90834[79]
Contingency Management*	$326 (over 12 weeks)	Sindelar et al., 2007[80]

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 scenario analysis 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.[81] 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 5.13 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 5.12. For the Off MAT without Illicit Use of Opioids health state, we assigned age-adjusted health care costs based on the general population.[82] Estimates while on MAT were not stratified by abstinence status; however, given no difference in continuous abstinence between reSET-O and standard of care, this does not influence the results. Further, the health care utilization costs while on MAT are quite similar to the age-adjusted health care costs for the general population.

Table 5.13. Average Health Care Utilization Costs, per Model Cycle

Per Cycle Costs (4 weeks)	On MAT[81]	Off MAT with Illicit Use of Opioids [81]
Hospitalizations	$379	$1,033
Emergency Department Visits	$55	$101
Outpatient Visits	$136	$159

MAT: medication assisted treatment

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.[83,84] The per-cycle costs of HIV and HCV are reported in Table 5.14 and are based on model inputs used in the 2018 ICER MAT review.[21] 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 5.14 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 5.14. HIV and HCV Treatment Costs per Cycle (4-Week Duration) per Case

	HIV[77]	HCV[73,83]
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

DHT 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,[21] 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.[10] 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.[85] These estimates were combined with SAMHSA data[86] to calculate the productivity loss costs per person (Table 5.15). Additional detail is described elsewhere.[21] These productivity costs were applied to approximately 37% of the modeled cohort[10] 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.[87] 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,[21] 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 5.15). Details of these calculations can be found in the 2018 ICER MAT review appendix.[21]

Table 5.15. 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¥

MAT: medication assisted treatment

*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 zero to one 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. Model outcomes and incremental comparisons at a trial time horizon.
2. Modified societal perspective that included components such as productivity losses, criminal justice and incarceration, or others as applicable.
3. A comparator that included contingency management.

5.3 Results

Base-Case Results

The addition of reSET-O to outpatient MAT resulted in approximately $800 more total payer costs over a five-year time horizon. The addition of reSET-O to outpatient MAT alone resulted in additional costs to download the DHT and additional MAT costs; however, health care utilization costs were slightly reduced due to the higher percent of individuals retained on MAT. Clinical outcomes of life years, QALYs, evLYGs, and MAT years with reSET-O were slightly higher than standard of care resulting from the larger number of abstinent days over Phase 1 and mostly from the higher percent of individuals retained on MAT treatment. The higher percent of individuals

retained on MAT treatment yielded 0.08 additional MAT years over the five years. Table 5.16 presents the model outputs for the base-case analysis comparing reSET-O to standard of care.

Table 5.16. Results for the Base Case for reSET-O Compared to Standard of Care

Intervention	Digital Health Technology Download Cost	Total Health System Costs	Life Years*	QALYs*	evLYGs*	On MAT Years
reSET-O	$1,219	$83,332	4.61821	3.152809	3.152812	0.54
SoC	$0	$82,558	4.61820	3.146440	3.146440	0.46
Incremental	$1,219	$774	0.00002	0.006369	0.006371	0.08

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 $121,500 per QALY gained. Results were similar when compared to outcomes of evLYG due to the very small mortality benefit associated with reSET-O given the fewer days of illicit use while using the DHT. Table 5.17 presents the incremental findings for the base case.

Table 5.17. Incremental Cost-Effectiveness Ratios for the Base Case

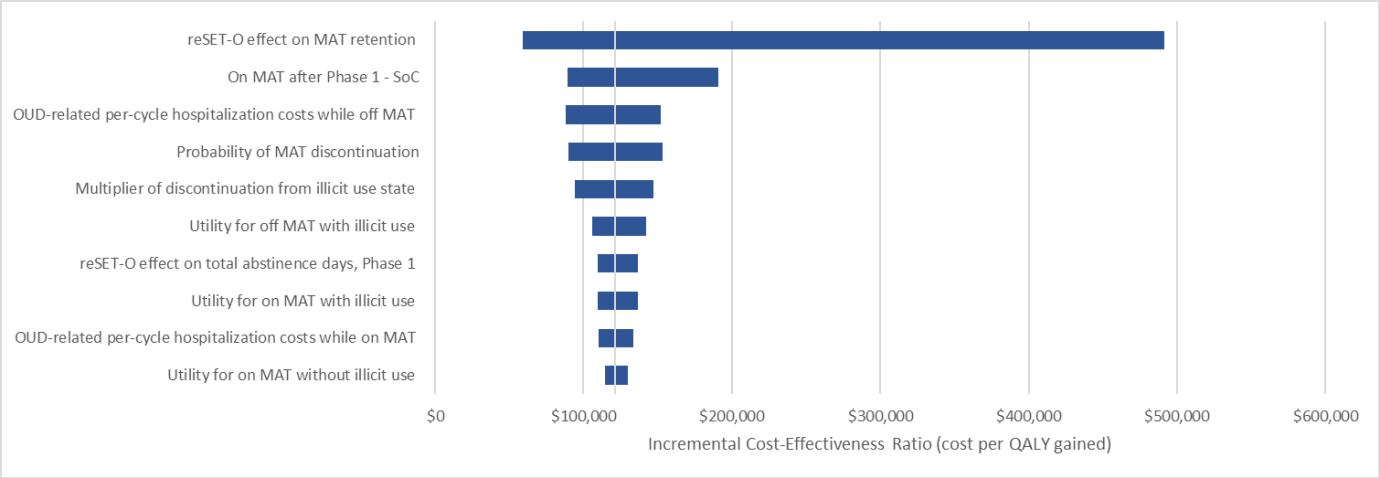
Treatment	Incremental Cost per Life Year Gained	Incremental Cost per QALY Gained	Incremental Cost per evLYG	Incremental Cost per Additional MAT Year
reSET-O vs. SoC	$48,449,000	$121,500	$121,400	$10,000

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. The primary driver of the cost-effectiveness findings is the reSET-O effect on MAT retention. Figure 5.3 presents the tornado diagram resulting from the one-way sensitivity analysis. This figure suggests that if there is only a small improvement in retention associated with reSET-O, reSET-O is no longer cost-effective at commonly used thresholds. The odds ratio of retention used in the cost-effectiveness model from the reSET-O pivotal trial was 2.3 (95% CI: 1.15 to 4.60). If the odds ratio is 2.0 or less, reSET-O exceeds a threshold of $150,000 per QALY. 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. Nearly 40% of the iterations produced cost-effectiveness ratios above $150,000 per QALY. Table 5.18 presents the results from the probabilistic sensitivity analysis, with additional supporting information presented in the appendix.

Table 5.18. 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	4.2%	26.9%	62.0%	79.9%	89.5%

QALY: quality-adjusted life year, SoC: standard of care

Scenario Analyses Results

Trial Time Horizon

A scenario analysis using the trial time horizon of 12 weeks was also conducted. Table 5.19 presents the model outputs and Table 5.20 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. The base-case findings (using a five-year time horizon) differ from these scenario analysis findings (using a 12-week time horizon) due to the higher percent retained on MAT after 12 weeks in the reSET-O arm. The base-case analysis therefore generates a higher estimate for MAT years as compared to the 12-week scenario analysis. The 12-week time horizon scenario analysis generated an incremental 0.02 MAT years between reSET-O and standard of care, whereas the five-year time horizon base-case analysis generated an incremental 0.08 MAT years between reSET-O and standard of care. The additional 0.06 MAT years gained over the longer time horizon, and the associated utility and cost benefits while on MAT, drive the differences in this scenario with the base-case estimates.

Table 5.19. Results for reSET-O Compared to Standard of Care, Trial Time Horizon

Intervention	Digital Health Technology Download Cost	Total Health System Cost	Life Years*	QALYs*	evLYGs*	On MAT Years
reSET-O	$1,219	$4,540	0.2307043	0.1751523	0.1729891	0.21
SoC	$0	$3,425	0.2307039	0.1731145	0.1706734	0.19
Incremental	$1,219	$1,115	0.0000004	0.0020379	0.0020379	0.02

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 5.20. Incremental Cost-Effectiveness Ratios, Trial Time Horizon

Treatment	Incremental Cost per Life Year Gained	Incremental Cost per QALY Gained	Incremental Cost per evLYG	Incremental Cost per Additional MAT Year
reSET-O vs. SoC	$2,725,721,000	$547,000	$547,000	$59,200

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

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 5.21 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 5.21. 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	$83,332	$113,912
SoC	$28,155	$2,638	$82,558	$113,351
Incremental	-$174	-$39	$774	$561

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 5.22) are slightly more favorable.

Table 5.22. 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 MAT Year
reSET-O vs. SoC	$35,133,000	$88,000	$88,000	$7,300

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

The evidence suggesting a direct impact of reSET-O on indirect costs is unknown. If reSET-O improves time on MAT as estimated in the cost-effectiveness model, a potential savings due to indirect costs was estimated as $213 per person over five years. Given the uncertainty in improvement of time on MAT that also suggests uncertainty in potential savings due to indirect costs, we interpreted the impact of reSET-O on indirect costs to not be substantial. Therefore, we presented the modified societal perspective as a scenario analysis and not as a co-base case.

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 5.23 presents the model outputs from this comparison.

Table 5.23. Results for reSET-O Compared to Contingency Management

Intervention	Digital Health Technology Download Cost	Total Health System Cost	Life Years*	QALYs*	evLYGs*	On MAT Years
reSET-O	$1,219	$83,332	4.61821	3.152809	3.152812	0.54
CM Comparator	$0	$82,884	4.61820	3.146440	3.146440	0.46
Incremental	$1,219	$448	0.00002	0.006369	0.006371	0.08

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 5.24 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 5.24. 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 MAT Year
reSET-O vs. CM Comparator	$28,033,000	$70,300	$70,300	$5,800

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

Threshold Analyses Results

Table 5.25 presents the results of the threshold analysis for reSET-O as compared to standard of care. A threshold analysis from the societal perspective is available in the appendix.

Table 5.25. 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	$1,219	$760	$1,080	$1,400

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.[88] 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-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 not cost-effective as compared to standard of care. Similar to our analysis, when a short time horizon (i.e. 12 weeks) is used, the intervention is not cost-effective. The cost effectiveness of reSET-O is dependent on a prolonged benefit of reSET-O that exceeds the 12-week time horizon. Our model includes this in a higher percent retained at the end of DHT use.

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 net pricing, and given evidence-based assumptions, these potential cost offsets and clinical gains may be enough to generate incremental cost-effectiveness estimates within higher commonly cited cost-effectiveness thresholds. The cost effectiveness of reSET-O is extremely sensitive to the effect of the DHT on retention. Despite no evidence available after time on DHT (i.e., after 12 weeks), our model extrapolates the potential downstream benefits of having a higher percentage of individuals retained on MAT over a five-year time horizon. The model assumes discontinuation over time is the same between reSET-O and standard of care after 12 weeks, but there was a higher percentage of individuals retained on MAT at 12 weeks in the reSET-O arm as compared to standard of care, and thus the reSET-O arm had a higher starting point at 12 weeks. The higher percentage of individuals retained on MAT at 12 weeks in the reSET-O arm as compared to standard of care resulted in 0.08 more MAT years or nearly one added month on MAT over five years. This is a model assumption that benefits the DHT and is an important area for clinical evidence generation.

Following public comment on the draft report, three updates were made to the cost-effectiveness model, including reducing the reSET-O price in the cost-effectiveness model to the manufacturer-provided net price, including provider interactions with the reSET-O platform within the counseling sessions rather than as separate sessions, and updating utility values for on MAT with illicit use health states to a US population reference. The first two changes reduced the incremental costs of reSET-O as compared to standard of care. The third change increased the incremental QALYs of reSET-O as compared to standard of care. These three changes made the cost effectiveness of reSET-O more favorable.

Limitations

Only one DHT (reSET-O) had sufficient peer-reviewed evidence to support inclusion in a cost-effectiveness model. The reSET-O cost-effectiveness evaluation is primarily limited by the evidence gaps, resulting from no published comparative evidence after an individual has stopped using the

DHT, despite publications of this evidence dating back to 2014. The effect of reSET-O on MAT retention is a key input on the cost effectiveness, and thus additional clinical evidence on the effect of reSET-O on retention while using reSET-O and after reSET-O is necessary to reduce the uncertainty in the cost effectiveness. 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

The cost effectiveness of reSET-O is within commonly used thresholds of $100,000-$150,000 per QALY gained given a significant impact on MAT retention that is prolonged after completion of the use of reSET-O. If individuals immediately revert to outcomes characteristic of standard of care after using the DHT for 12 weeks, the scenario analysis findings from the 12-week time horizon are more indicative of the cost-effectiveness for reSET-O, which would suggest reSET-O is not cost-effective. Clinical evidence on MAT retention and abstinence after one's use of reSET-O is essential to reduce the uncertainty in the cost-effectiveness findings.

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 DHTs 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 DHTs.

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 DHTs 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 (five 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 DHT 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

The reSET-O price that would achieve incremental cost-effectiveness ratios of $100,000 and $150,000 per QALY or evLYG are presented in Table 7.1. Due to the miniscule gains in life extension associated with reSET-O, the health-benefit price benchmarks are the same for outcomes of either QALY or evLYG.

The ICER health benefit price benchmark (HBPB) is a price range suggesting the highest price a manufacturer should charge for a treatment, based on the amount of improvement in overall health patients receive from that treatment, when a higher price would cause disproportionately greater losses in health among other patients due to rising overall costs of health care and health insurance. In short, it is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good.

Table 7.1. Cost-Effectiveness Threshold Prices for reSET-O

	WAC*	Net Price¥	Price at $100,000 Threshold	Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
reSET-O	$1,665	$1,219	$1,080	$1,400	16%-35%

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*WAC as of October 27th, 2020

¥Net price provided to us by Pear Therapeutics on October 15th, 2020 is "net of rebates, discounts, and allowances".

The health benefit price benchmarks for reSET-O range from $1,080 to $1,400. A discount of 16-35% off WAC would be needed to reach these discounts. The manufacturer-provided net price is $1,219, which is a 27% discount from WAC.

8. Potential Budget Impact

8.1 Overview

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), net price ($1,219), 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.[23] 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).[24,25] 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[89] and in this update.

8.3 Results

Figure 8.1 illustrates the cumulative per-patient budget impact calculations for reSET-O compared to SoC, based on the net price of $1,219 for one-time treatment. The average potential budgetary impact for reSET-O was an additional per-patient cost of approximately $819 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 $768 by year five (additional net costs per year are presented along with cumulative net costs in Appendix Table E7).

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

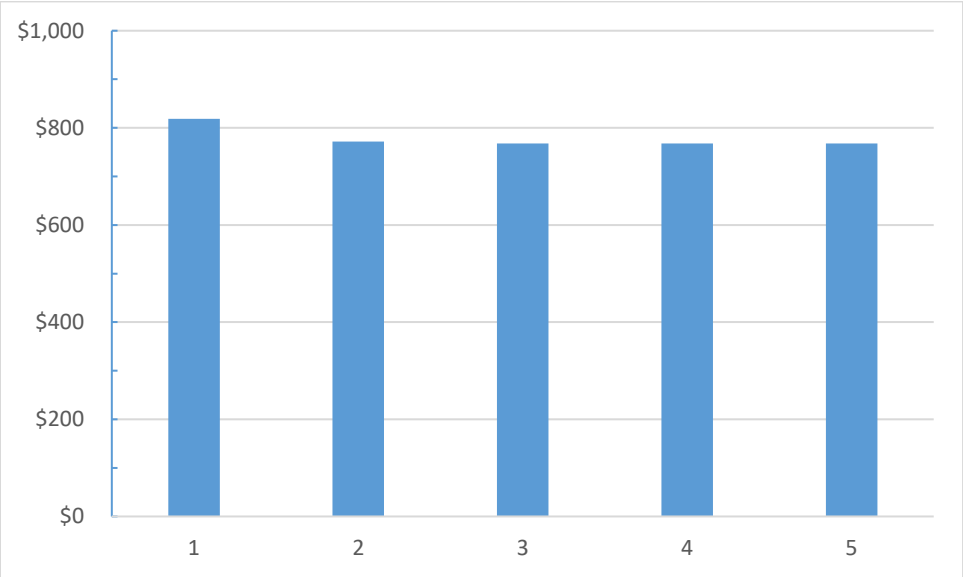


Table 8.1 illustrates the potential budget impact of treatment of the eligible population with reSET-O, based on the WAC ($1,665 per download), net price ($1,219), and the threshold prices to reach $150,000, $100,000, and $50,000 per QALY compared to SoC ($1,400, $1,082, and $764, respectively). For reSET-O, the annual potential budgetary impact of treating 20% of the entire eligible population each year (95,656 per year) was $117.2 million, assuming the WAC download price. This was largely due to assumption of one-time download cost with the DHT 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, Net, and Threshold Prices Over a Five-Year Time Horizon (N = 95,656 per Year)

	Annual PBI (millions)	Total 5-Year PBI (millions)
WAC	$117.2	$585.8
Net Price	$74.5	$372.4
$150,000/QALY Threshold Price	$91.9	$459.3
$100,000/QALY Threshold Price	$61.4	$307.0
$50,000/QALY Threshold Price	$30.9	$154.7

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

9. Summary of the Votes and Considerations for Policy

9.1 About the Midwest CEPAC Process

During Midwest CEPAC public meetings, the Midwest CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to Midwest CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Midwest CEPAC Panel during their deliberation, and help to shape recommendations on ways the evidence can apply to policy and practice.

After the Midwest CEPAC Panel votes, a policy roundtable discussion is held with the Midwest CEPAC Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the November 18, 2020 meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of digital health technologies as an adjunct to MAT for OUD. Following the evidence presentation and public comments (public comments from the meeting can be accessed here), the Midwest CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to digital health technologies as an adjunct to MAT for OUD. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by Midwest CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the Midwest CEPAC Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 9.1 below):

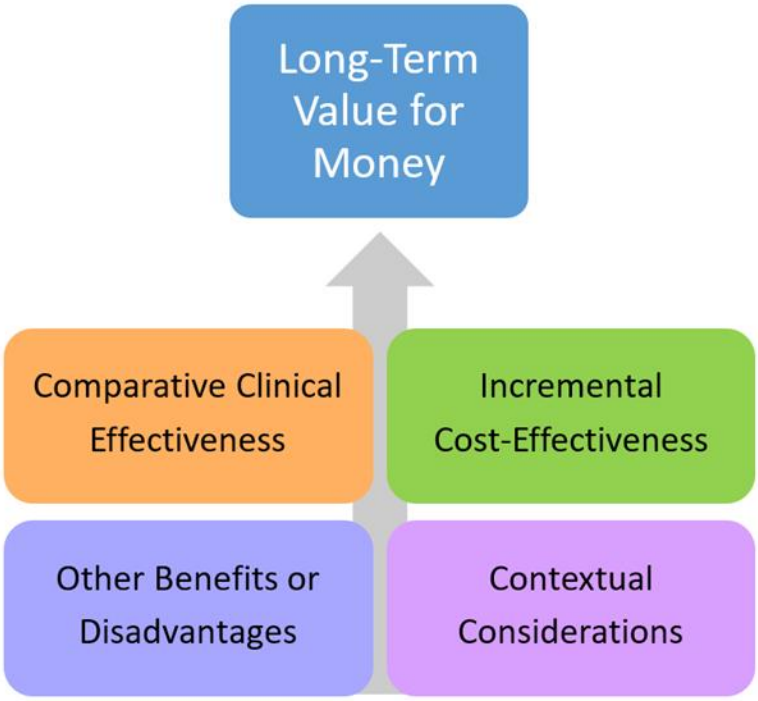
1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the Midwest CEPAC voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

3. Potential other benefits refer to any significant benefits or disadvantages 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. Examples of potential other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether potential other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for potential other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 9.1. Conceptual Structure of Long-Term Value for Money



9.2 Voting Results

Patient population for all questions: Adult patients with OUD who are receiving MAT (buprenorphine, methadone)

Clinical Evidence: *Standard of care includes MAT, but not contingency management*

1. Given the currently available evidence, is the evidence adequate to demonstrate a net health benefit for the **reSET-O** app added to standard of care compared to standard of care alone?

Yes: 3 votes	***No: 10 votes***

Comments: While it was noted that the development of digital therapeutics is promising in treating substance use disorders, clinical experts and CEPAC members expressed concern about the lack of data on the impact of reSET-O on retention beyond the 12-week period

observed in the Christensen study, and on outcomes that are important to patients. For these reasons, the majority of the Midwest CEPAC judged that the evidence for reSET-O was not sufficient to demonstrate a net health benefit for the app added to standard of care compared to standard of care alone.

2. Given the currently available evidence, is the evidence adequate to demonstrate a net health benefit for treatment with the **Connections** app added to standard of care compared to standard of care alone?

Yes: 0 votes	***No: 13 votes***

Comments: The Midwest CEPAC unanimously judged that the evidence was not adequate to demonstrate that the Connections app paired with standard of care provided a net health benefit compared to standard of care alone. This was largely due to the absence of randomized trial evidence for the Connections app.

3. Given the currently available evidence, is the evidence adequate to demonstrate a net health benefit for the **DynamiCare** app added to standard of care compared to standard of care alone?

Yes: 0 votes	***No: 13 votes***

Comments: The Midwest CEPAC's vote was driven by the same considerations highlighted during the discussion of the previous two questions. The CEPAC unanimously voted that there was not enough evidence to demonstrate a net health benefit of using the DynamiCare app with standard of care, as compared to standard of care alone.

4. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to the **reSET-O** app. Refer to the table below.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
This intervention will not differentially benefit a historically disadvantaged or underserved community		This intervention will differentially benefit a historically disadvantaged or underserved community
1 vote	***6 votes***	***6 votes***

Comments: Patient experts noted that the apps have not been rolled out specifically to historically underserved communities, but there is potential to expand access due to the delivery through smartphones. They also highlighted that the target population of patients with OUD is historically stigmatized. For these reasons, the vote was mainly split between "2" and "3."

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
5 votes	***8 votes***	0 votes

Comments: The majority of Council members voted that the model assumptions were neither overly optimistic nor pessimistic. Council members who voted that the model assumptions were overly favorable noted that the model was based on the Christensen study, which did not directly observe reSET-O. They also highlighted the key assumption that the effect of reSET-O on retention persisted beyond the 12-week study period, which could have led to overly optimistic base-case estimates.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Very similar mechanism of action to that of other active treatments		New mechanism of action compared to that of other active treatments
1 vote	***7 votes***	4 votes

Comments: One clinical expert pointed out that digital apps are available to patients regardless of provider availability, differentiating the mechanism from telehealth or virtual appointments. One Council member also discussed how the anonymity provided by a digital app is a potential benefit of the delivery mechanism. However, because this technology must be treated as an add-on to existing therapies, rather than a replacement, the majority of Council members voted "2."

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
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
2 votes	***9 votes***	2 votes

Comments: Votes on this question varied, though the majority of Council members voted "2," meaning that the delivery mechanism is unlikely to impact real-world adherence to MAT and patient outcomes. CEPAC members noted that it was difficult to judge whether there would be an impact of the delivery mechanism on adherence because of the lack of randomized trial data for the app itself, though one Council member highlighted that its impact on reducing stigma could potentially result in higher real-world adherence.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
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
1 vote	***9 votes***	3 votes

Comments: The majority of Council members voted that the app would have an intermediate impact on family and caregivers because of the uncertainty surrounding the effectiveness of the reSET-O app. However, Council members also noted that if the app were shown to be effective, it could dramatically reduce the negative impact on family and caregivers due to the nature of the disease.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
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
1 vote	***10 votes***	2 votes

Comments: Like the previous question, most Council members voted that reSET-O would have an intermediate impact on productivity and return to work, due to the uncertainty in the evidence around its effectiveness.

5. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment **at current pricing** with **reSET-O** versus standard care?

Low Long-Term Value for Money	Intermediate Value for Money	High Long-Term Value for Money
8 votes	5 votes	0 votes

Comments: All Council members judged that the long-term value for money of reSET-O is either "low" or "intermediate" at current pricing. Like the votes on comparative clinical effectiveness and potential other benefits and contextual considerations, these votes were primarily driven by the limited evidence on the reSET-O app itself. CEPAC members who voted "intermediate" highlighted that the incremental cost-effectiveness ratio that was calculated for reSET-O is within commonly cited thresholds, and that there are no demonstrated harms of using the app.

9.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on digital health technologies as an adjunct to MAT for OUD to policy and practice. The policy roundtable members included two patient representatives, two clinical experts, two payers, and two representatives from pharmaceutical manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix G.

Table 9.1 Policy Roundtable Members

Name	Title and Affiliation
Kelcey Blair, PharmD	Vice President, Clinical Solutions at Express Scripts
Anita Ju	Innovation Manager, Blue Shield of California
Miriam Komaromy, MD, FACP, DFASAM	Medical Director, Grayken Center for Addiction, Boston Medical Center, Boston University
Hans Morefield	Chief Executive Officer, CHESS Health
Jake Nichols, PharmD, MBA	President and Chief Executive Officer, Professional Recovery Associates
Mike Pace, MBA	Vice President and Global Head of Market Access, Value, and Evidence, Pear Therapeutics
Kevin Roy, MBA	Chief Public Policy Officer, Shatterproof
Scott Steiger, MD, FACP, FASAM	Associate Clinical Professor of Medicine and Psychiatry, University of California San Francisco

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

General

1. **Medication-assisted treatment (MAT) saves lives and money, both inside the health system and outside of it. New interventions should be developed, tested, and implemented that can augment the number of individuals who can access MAT, reduce stigma, and ensure that individuals receive care in a format that helps them achieve their goals. DHTs may be important aids in improving care for many individuals, but it is vital that adequate evidence be generated to evaluate the relative effectiveness of different options so that each person can receive effective treatment tailored to maximize their health. Poor evidence that leads to ineffective use of DHTs represents a health risk to individuals, a financial risk to the health system, and a moral risk for us all that society will fail in its responsibility to use its resources to the greatest effect in combatting an ongoing national epidemic.**

Researchers / Manufacturers

2. **Manufacturers should provide robust evidence of the clinical effectiveness and broader impact of new DHTs. For DHTs like those featured in this report that have a function of guiding or enhancing treatment outcomes, a minimum evidence requirement is high-quality observational or quasi-experimental studies with an appropriate comparator and relevant patient outcomes. However, many DHTs should undergo formal evaluation through randomized controlled trials to minimize the risk of bias in trial results.**

   Some DHTs, such as those with purely administrative or simple health management functions, pose no clinical risk to patients nor a significant financial risk to health systems. But for DHTs that inform clinicians or that seek to augment existing care, a basic minimum requirement for adequate evidence should include multiple high-quality observational or quasi-experimental studies. These studies should always include an appropriate control arm, such as "usual care" among patients who are waitlisted for a new intervention. Historical controls or pre-post evaluations are frequently vulnerable to confounders, such as regression to the mean, or selection bias, that greatly limits the confidence that can be ascribed to research results. And thus, for many DHTs, it will ultimately be impossible to reach a reasonable judgment without high-quality randomized trial evidence.

   For the DHTs in this report, the current evidence comes from older randomized trials of psychosocial interventions (TES, CBT4CBT, A CHESS, peer support, contingency management), but not the actual implementation of one or more of these interventions on a smart phone. The trials should be sham controlled (another DHT providing informational modules alone for example) and of sufficient duration (minimum six months, one to two years preferred) to assess not only ongoing retention in MAT treatment and abstinence from illicit use of opioids, but also outcomes that matter to patients such as ER visits, hospitalizations, obtaining housing and/or employment, and quality of life.

3. **In addition to evidence on relative safety and effectiveness in the short term, manufacturers should be prepared to provide a full dossier of evidence to payers and providers that includes robust information on 1) the durability of beneficial clinical effects; 2) the impact on health care utilization; 3) the impact on clinician productivity; 4) the usability as measured by clinician and patient experience; 5) the security of IT components; 6) the generalizability of results to diverse patient populations and health systems; and 7) the scalability to larger populations.**

   The evidentiary requirements for FDA approval of DHTs are not well established. When regulatory pathways such as 510k are used, a new DHT may be approved with very little evidence of comparative clinical effectiveness. But even if manufacturers produce more robust

evidence on clinical effectiveness, the broader impact of DHTs cannot be assessed without information and evidence on a wide range of factors, as listed above. Manufacturers seeking success in the marketplace should be aware that payers and providers are inundated with requests to consider new DHTs, and that those with a robust evidence package are far more likely to be adopted. To get this evidence, it is often necessary to pilot test a DHT with one or more provider groups. Surveys of patients and clinicians will be needed to assess usability. And clinical trials will need to be designed to last long enough to demonstrate stability of clinical benefit over an intermediate to long term, and they must capture important potential health care utilization effects. Only with a well-developed evidence dossier including all these components will a payer or health system have the information needed to make a prudent judgement about adoption.

4. **Manufacturers and researchers should design trials of DHTs to be able to identify potential subgroups of patients who benefit most from a DHT and those who are less likely to benefit. Existing evidence may also be reanalyzed for this purpose.**

   For example, in Christensen 2014, the subgroup of patients who had previously undergone MAT treatment seemed to derive a large benefit from TES, while treatment-naïve patients experienced minimal benefit. There is significant heterogeneity in the characteristics of patients suffering from OUD (age, sex, route of administration, treatment setting, housing, employment, urban/rural, co-existing mental health disease, multiple substance use disorders, etc.) that could be explored to identify those patients most likely to benefit from a DHT. This information could then be tested in future studies and allow for more efficient use of DHTs in clinical practice.

Payers

5. **Given the limited evidence supporting the efficacy of DHTs for OUD, alternative payment models may be appropriate if coverage is provided. For instance:**

   - Guaranteed outcomes: payment only if certain metrics are obtained, that could include rates of engagement with the DHT or retention rates in MAT at three, six, and/or twelve months.

   - Pilot projects/co-development to facilitate outreach and education of providers about the availability of the DHT, helping with implementation in specific clinics, along with measurement of the impact of the availability of the DHT on retention in MAT, ER visits, and hospitalization rates.

- Subscription model where the payer pays a certain amount per month based on the number of identified patients with OUD in their covered lives, but with no limit on the number of prescriptions that their providers can write for the DHT.

Regulators

6. **The FDA should develop a clear taxonomy of DHTs, with different levels of risk and other factors, and clarify evidence requirements that are robust enough to inform patients, clinicians, health systems, and payers regarding the safety and comparative effectiveness of their use in representative patient populations.**

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Appendix A. Search Strategic Results

Table A1. 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).

		Checklist Items
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

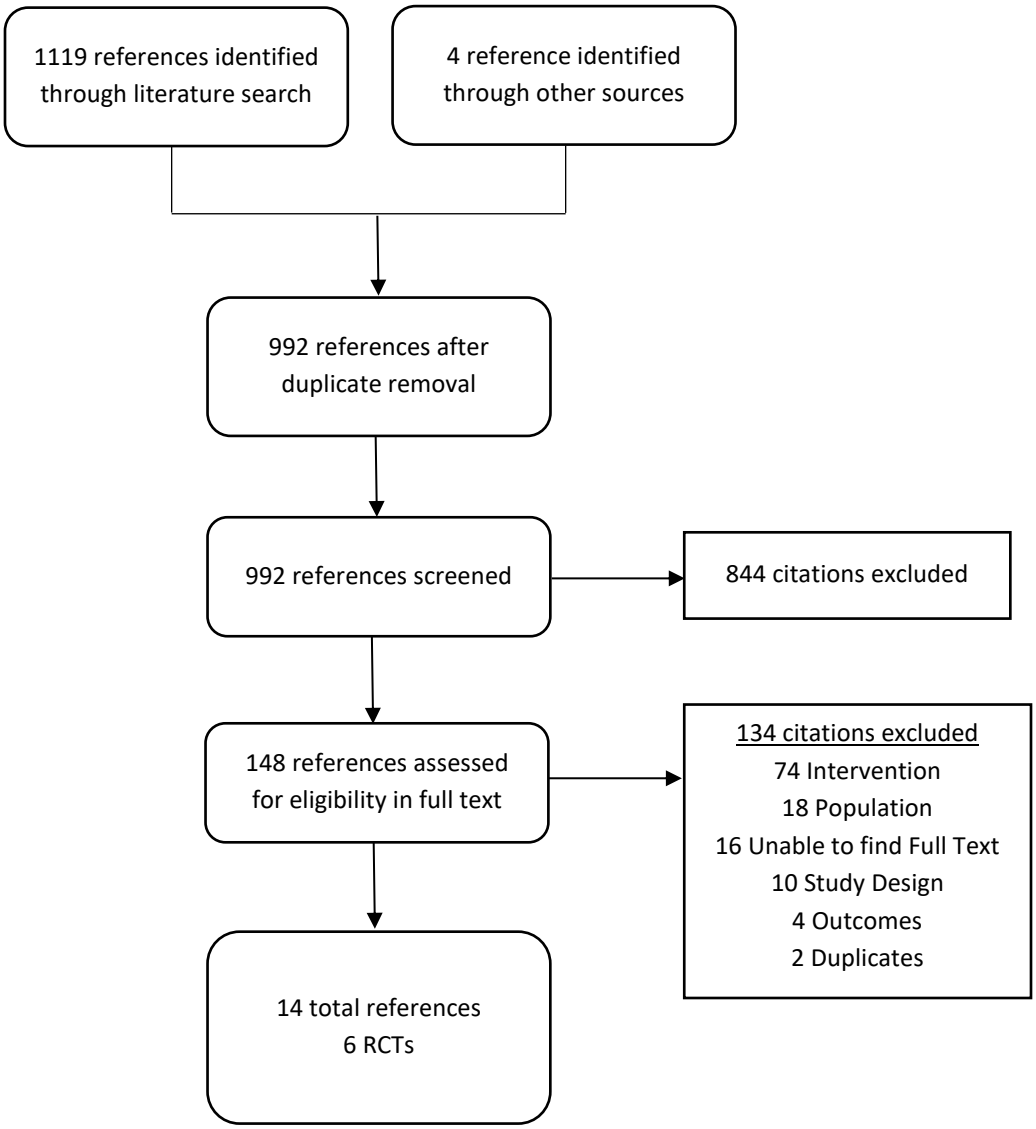
Table A2.1. Search Strategy of Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present and APA PsycInfo

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 A2.2. 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 A1. PRISMA flow Chart Showing Results of Literature Search for Digital Health Technologies 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 C1. 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
Optimizing Retention, Duration and Discontinuation	Phase 4, randomized, open label, factorial assignment, two phase study	**Experimental (Drug):** – Sublingual BUP (standard dose)	**Inclusion Criteria:** – ≥18 years of age	**Primary Outcome**: – Continuous retention in treatment at 26 weeks	July 2025

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion Date
Strategies for Opioid Use Disorder Pharmacotherapy (RDD) **NCT04464980** **Sponsor: NYU Langone Health**	**Phase 1**: Retention **Phase 2**: Discontinuation Estimated N: 1630	– 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	– 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	– 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 – Relapse – Withdrawal symptoms	
Connections					
A Method to Increase Buprenorphine Treatment Capacity	Phase I/II, randomized, open label, parallel assignment study	**Experimental:** – CBT4CBT + BUP	**Inclusion Criteria:** – 18-65 years of age	**Primary Outcome:** *[Time Frame: 12 weeks]*	January, 2021

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion Date
NCT03580902 **Sponsor:** **CBT4CBT, LLC**	Estimated N: 100	**Comparator:** – BUP / NLX	– 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.	– Percent of urine toxicology screens negative for opioids	
DynamiCare					
Encouraging Opioid Abstinence Behavior: Incentivizing Inputs and Outcomes – Pilot **NCT04235582** **Sponsor:** **Aurora Health Care**	Randomized, parallel assignment interventional study Estimated N: 30	**Experimental:** – Outcomes Group (DynamiCare App + Outcomes CM) – Inputs Group (DynamiCare App + Inputs CM) – Combination Group (DynamiCare App + Outputs and Inputs CM)	**Inclusion Criteria:** – ≥18 years of age – 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	**Primary Outcomes:** – 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	July 2021

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion Date
			– Currently using non-medical opioids – Regularly missing scheduled AODA appointments – Understands English **Exclusion Criteria:** – Evidence of active non-substance related psychosis – Significant cognitive impairment	– Quality of Life (at 4, 8, 12 weeks)	

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).[63] 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.

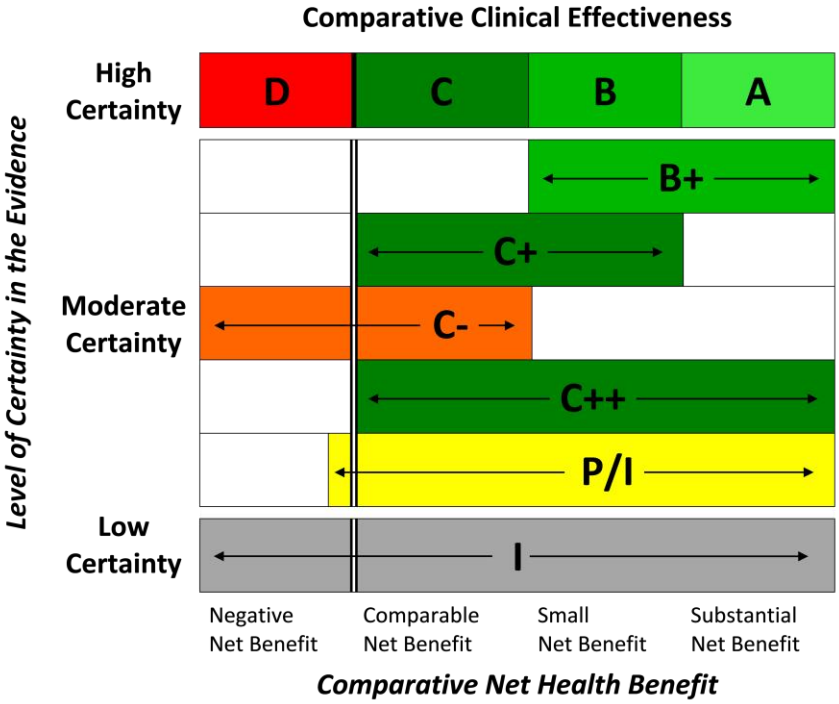
ICER Evidence Rating

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:

1. The magnitude of the difference between a digital health technology agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects; and

2. The level of certainty in the best point estimate of net health benefit.[64,90]

Figure D1. 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 likelihood of a negative net health benefit*
***I = "Insufficient"** – Any situation in which the level of certainty in the evidence is low*

Table D1. 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[10] **Nunes 2019**[66]	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[11]	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[12]	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.

Author	Design, Location, and Duration of Follow-up	N	Inclusion Criteria	Exclusion Criteria	Definitions of Key Outcomes	Interventions Defined
Marsch 2014[13] **Acosta 2012[91]** **Kim 2016[92]**	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[48]	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[49]	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 D2. 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[10] Nunes 2019[66]	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[11]	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[12]	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)
	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)

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	
Marsch 2014[13] Acosta 2012[91] Kim 2016[92]	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[48]	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[49]	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 D3. 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[10] Nunes 2019[66]	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[11]	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[12]	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[13] Acosta 2012[91] Kim 2016[92]	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[48]	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
DynamiCare													

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	
Ryan 2020[49]	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 D4. 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[10] Nunes 2019[66]	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[11]	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[12]	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
	Computer-CBT + CM	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

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	
	(medication) + BUP											
	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[13] Acosta 2012[91] Kim 2016[92]	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[48]	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[49]	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 D5. 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[10] Nunes 2019[66]	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[11]	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[12]	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
Marsch 2014[13] Acosta 2012[91] Kim 2016[92]	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)
	Methadone	80									
Connections											

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
Shi 2019[48]	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[49]	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 D6. 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[10] Nunes 2019[66]	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[11]	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	---
Chopra 2009[12]	Computer-CBT + CM (voucher) + BUP	41	12 Weeks	NR	35 (85.4)	NR; p=0.009	NR	NR	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
	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[13] Acosta 2012[91] Kim 2016[92]	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[48]	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[49]	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 D7. 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[10] Nunes 2019[66]	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[11]	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 (SEM: 6.2)	---	---	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)
Chopra 2009[12]	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[13] Acosta 2012[91] Kim 2016[92]	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[48]	CBT4CBT + BUP	10	12 Weeks	NR	NR	NR	NR	NR	NR
	BUP	10		NR			NR		
DynamiCare									
Ryan 2020[49]	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 D8. 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[10] Nunes 2019[66]	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[11]	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[12]	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[13] Acosta 2012[91] Kim 2016[92]	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[48]	CBT4CBT + BUP	10	12 Weeks	9.3 (1.7)	p=0.48	NR	NR	91.3 (20.8)	p=0.05	NR	NR	NR
	BUP	10		8.4 (3.3)		NR		63.9 (36.6)		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
DynamiCare												
Ryan 2020[49]	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 D9. 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[10] Nunes 2019[66]	Computer-CBT + CM + BUP	92	Non-sign. Improvement; p>0.16	Improvement; p<0.01	Improvement; p<0.01	Improvement; p<0.01	Improvement; p<0.01	Non-sign. Improvement; p>0.16	NR (NR); p<0.01	Non-sign. Improvement; p=0.74	Improvement; p<0.01	NR
	CM + BUP	78										NR
Bickel 2008[11]	Computer-CBT + CM + BUP	45	Improvement; p<0.05	Improvement; p<0.05	Non-sign. Improvement; NR	Improvement; p<0.05	Improvement; p<0.05	Improvement; p<0.05	Improvement; p<0.05	Improvement; p<0.05	Improvement; p<0.05	4.86 (0.05)
	Therapist-CBT + CM + BUP	45	Improvement; p<0.05	Improvement; p<0.05	Non-sign. Improvement; NR	Improvement; p<0.05	Improvement; p<0.05	Improvement; p<0.05	Improvement; p<0.05	Improvement; p<0.05	Improvement; 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[12]	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.	Improvement; p<0.012	NR
	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

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	
	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[13] Acosta 2012[91] Kim 2016[92]	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[48]	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[49]	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 D10. 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[10] **Nunes 2019[66]**	CRA + CM + BUP	92	57 (62.0)	NR	0 (0)	NR	NR
	CM + BUP	78	55 (70.5)	NR	NR	NR	NR
Bickel 2008[11]	Computer-CRA + CM + BUP	45	No Safety Data Reported				
	Therapist-CRA + CM + BUP	45					
	BUP	45					
Chopra 2009[12]	CRA + CM (voucher) + BP	41	No Safety Data Reported				
	CRA + CM (medication) + BP	42					
	BUP	37					
Marsch 2014[13] **Acosta 2012[91]** **Kim 2016[92]**	TES + Methadone	80	No Safety Data Reported				
	Methadone	80					
Connections							
Shi 2019[48]	CBT4CBT + BUP	10	No Safety Data Reported				
	BUP alone	10					
DynamiCare							
Ryan 2020[49]	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 D11. 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[10]	No	Yes	No	Yes	Yes	No	Yes	ITT	Imputation	fair
Bickel 2008[11]	No	Yes	No	Yes	Yes	No	Yes	ITT	Imputation	fair
Chopra 2009[12]	No	Yes	No	Yes	Yes	No	Yes	mITT	Imputation	poor
Marsch 2014[13]	Yes	Yes	No	Yes	Yes	No	Yes	ITT	Imputation	fair
Shi 2019[13]	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 E1. 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	X	X	
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 [93]

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.[94]
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 E2 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 MAT retention was the single input with the most influence on the cost-effectiveness findings, ranging from the lowest cost-effectiveness ratio of approximately $59,000 per QALY gained to the highest cost-effectiveness ratio of nearly $500,000 per QALY gained. The second most influential input was proportion of the cohort on MAT in standard of care.

Table E2. 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 MAT retention	$491,231	$59,083	1.15	4.60
On MAT after Phase 1 – Standard of Care	$89,289	$190,680	0.51	0.76
OUD-related per-cycle hospitalization costs while off MAT	$151,879	$87,977	840.49	1,245.06
Probability of MAT discontinuation	$89,926	$153,391	0.12	0.17
Multiplier of discontinuation from illicit use state	$94,290	$147,143	1.00	1.40
Utility for off MAT with illicit use	$105,721	$142,435	0.68	0.71
reSET-O effect on total abstinence days, Phase 1	$136,478	$109,299	2.30	17.20
Utility for on MAT with illicit use	$136,475	$109,669	0.75	0.78
OUD-related per-cycle hospitalization costs while on MAT	$110,314	$133,764	308.37	456.80
Utility for on MAT without illicit use	$129,707	$114,369	0.75	0.78

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

Probabilistic Sensitivity Analysis Supporting Information

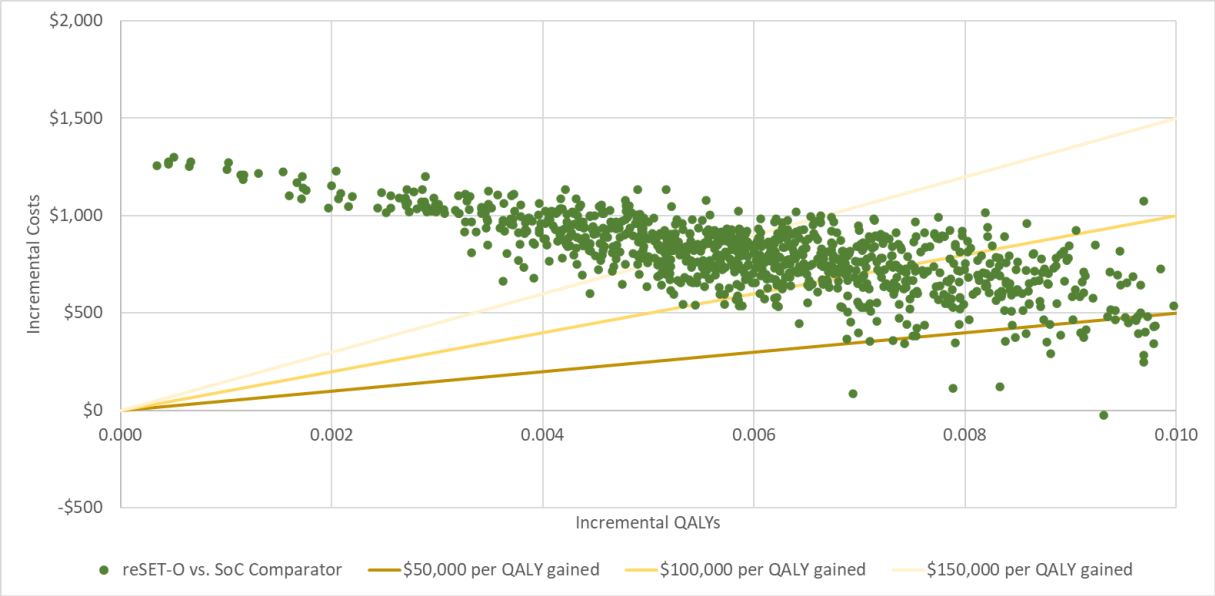
Table E3 provides the results of the probabilistic sensitivity analysis. Figure E1 includes a scatterplot, with each point representing one of the iterations. The range in quality-adjusted life years is larger than the range in costs, suggesting the impact of reSET-O on the clinical outcomes is a key driver of the cost-effectiveness findings. Nearly 40% of the iterations are above a threshold of $150,000 per QALY gained.

Table E3. 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	$83,300	($72,800, $94,800)	$82,500	($71,800, $94,200)
Total QALYs	3.1535	(3.1011, 3.2036)	3.1475	(3.0935, 3.1988)
ICER ($/QALY)	$132,500 ($44,100, $484,800)			

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

Figure E1. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Cloud



QALY: quality-adjusted life year

Threshold Analyses from the Societal Perspective

Table E4 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.

Table E4. 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	$1,219	$970	$1,290	$1,610

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

Undiscounted Base-Case Outcomes

Tables E5 and E6 present the undiscounted model outcomes and incremental findings for the base case.

Table E5. Results for the Base Case for reSET-O Compared to Standard of Care, Undiscounted

Intervention	Digital Health Technology Download Cost	Total Payer Cost	Life Years	QALYs	evLYGs	MAT Years
reSET-O	$1,219	$89,602	4.96062	3.383075	3.383078	0.55
SoC	$0	$88,835	4.96060	3.376629	3.376629	0.47
Incremental	$1,219	$768	0.00002	0.006447	0.006450	0.08

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

Table E6. 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	$44,675,000	$119,000	$119,000	$9,800

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

Table E7. Cumulative Net Cost Per Patient Treated with reSET-O at Net Price Over a Five-Year Time Horizon

	Cumulative Cost	Additional Costs per Year (Non-Cumulative)
Year 1	$819	$819
Year 2	$772	-$47
Year 3	$768	-$4
Year 4	$768	$0
Year 5	$768	$0

Appendix F. Public Comments

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on November 18, 2020. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Three speakers did not submit summaries of their public comments.

A video recording of all comments can be found here. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Dr. Andrea Barthwell, MD, DFASAM
Founder, Encounter Medical Group and Two Dreams
Dr. Barthwell consults for Ideal Option, the Manor, and Pocket Naloxone.

Introduction

Good morning. I am Andrea G. Barthwell, a practicing physician ASAM-certified in addiction medicine. I have over 40 years of experience in treating opioid use disorder (OUD) and am a person in recovery.

I have administrative, policy, scientific, and drug approval experience. I've had an interest in computer-assisted treatment and digital therapies since the 1980s. I have no conflicts to disclose.

Thanks for the opportunity to comment on digital health technologies' value as an adjunct to MAT, particularly reSET-O, the only app considered today that is supported by NIH-funded RCTs and the only app out of 619 opioid-related apps to meet all of the American Psychiatric Association's criteria in a recently published quality review of mental health apps.

Today, I will explain why CEPAC should favorably vote on reSET-O's net health benefit, high long-term value, and other benefits.

Experience

FDA and SAMHSA define MAT as the use of medications in combination with counseling and behavioral therapies; evidence shows that neither alone is sufficient. While medications can arrest withdrawal and allow patients a pause before using, behavioral therapy is needed to retain patients in treatment and train patients in recovery management. Most prescribers are academically and clinically prepared for a focus on medication management; disease management in the area of OUD is much more challenging. Fewer than 10% of patients receiving MAT receive such care.

ReSET-O is designed to close the gap and provides standardized, high-quality, evidence-based therapies that are beneficial to both patients and providers. reSET-O provides access to three of the therapies shown in randomized, clinical trials that promote recovery: CBT, fluency training, and CM. They help in the acquisition, practice, and application of recovery skills in order to manage the triad of withdrawal symptomatology, stress, and cues which precedes and is predictive of return to use or relapse.

Clinical Benefits

reSET-O serves as a consistent companion and support away from the provider. Patients can access reSET-O in real-time and from any location; it provides remote, real-time information sharing with clinicians. It is valuable for patients who lack transportation, are immobile, and live in rural areas and provider deserts like the Robert Taylor Public Housing Authority in Chicago

where I began my practice. By using reSET-O in these settings, stigma of entering an addiction treatment facility is reduced. These qualities are even more relevant in the face of COVID-19 social distancing requirements.

Retention Rates and Data

According to NIDA, the lead NIH agency supporting scientific research on drug use and consequences, a minimum of three months is needed for most individuals with OUD to significantly reduce or eliminate substance use. NIDA had its scientists design, conduct, and sponsor multiple comparative studies involving reSET-O. The data coming out of these studies demonstrated reSET-O's safety and effectiveness relative to standard endpoints.

FDA based its decision to grant reSET-O clearance on data from a multi-site, unblinded, controlled 12-week clinical trial. FDA noted a statistically significant increase in retention for patients who used reSET-O as compared to those who received treatment as usual. Therefore, reSET-O met FDA's high safety and efficacy standards. These same studies that led to FDA's conclusion that reSET-O is clinically safe and effective were shared with ICER, and their existence should be reflected in reSET-O's ratings.

reSET-O's benefits to clinicians and patients is buttressed by real-world evidence in outcomes research on over 3,000 patients who used the app. These patients experienced increased treatment retention and abstinence from illicit use as evidenced by claims data analysis: patients prescribed reSET-O saw reductions in ED visits, inpatient hospitalization, and total health care utilization costs ($2,150 per patient) over a six-month follow-up period.

Conclusion

In sum, clear and compelling evidence shows that to do well on MAT, patients must have access to neurobehavioral treatments like reSET-O, not just medicine. To meet this goal, it is important to accurately identify that reSET-O provides a net benefit AND increases access – which is critical now, when traditional approaches alone are not working and drug overdose is the leading cause of injury-related death in the U.S.; overdoses involving opioids take 128 lives every day. Therefore, payers should be discouraged from denying coverage of reSET-O. Such denials limit clinicians' ability to exercise their medical judgment and further perpetuate the lack of mental health parity.

I encourage CEPAC to validate the existing evidence by voting in support of reSET-O's net health, long-term economic, and other clinical benefits.

Appendix G. Conflict of Interest Disclosures

Tables G1 through G3 contain conflict of interest (COI) disclosures for all participants at the November 18, 2020 public meeting of the Midwest CEPAC.

Table G1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Pamela Bradt, MD, MPH,* Chief Scientific Officer, ICER	**Maggie O'Grady, BS,*** Program Manager, ICER
Jon Campbell, PhD, MS,* Senior Vice President for Health Economics, ICER	**Steven D. Pearson, MD, MSc,*** President, ICER
Rick Chapman, PhD, MS,* Director of Health Economics, ICER	**Jeffrey A. Tice, MD,*** Professor of Medicine, University of California, San Francisco
Noemi Fluetsch, MPH,* Research Assistant, ICER	**Melanie Whittington, PhD, MS**,* Associate Director of Health Economics, ICER
Maggie Houle, BS,* Program and Event Coordinator, ICER	**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	

*No conflicts of interest to disclose, defined as individual health care stock ownership in any health plan or pharmaceutical, biotechnology, or medical device manufacturers, or any health care consultant income or honoraria from health plans or manufacturers.

Table G2. Midwest CEPAC Panel Member Participants and COI Disclosures

Participating Members of Midwest CEPAC	
Eric Armbrecht, PhD (Chair),* Associate Professor, Saint Louis Center for Health Outcomes Research, School of Medicine and College for Public Health and Social Justice	**Jill Johnson, PharmD,*** Professor, University of Arkansas for Medical Sciences
Angela Brown, MPH,* Chief Executive Officer, St. Louis Regional Health Commission	**Chris Jones, PhD ǂ,** Network Director, Venture Investments, University of Vermont Health Network
Donald Casey, MD, MPH, MBA,* President, American College of Medical Quality	**Greg Low, RPh, PhD,*** Director, Massachusetts General Physicians Organization Pharmacy Quality and Utilization Program
Greg Curfman, MD,* Deputy Editor, JAMA	**Tim McBride, PhD,*** Co-Director, Center for Health Economics and Policy; Professor, Washington University in St. Louis
Stacie Dusetzina, PhD,* Associate Professor of Health Policy, Vanderbilt University School of Medicine	**Jeanne Ryer, MSc, EdD,*** Director of Delivery System and Payment Reform, University of New Hampshire Institute for Health Policy and Practice
Megan Golden, JD,* Co-Director, Mission: Cure	**Timothy Wilt, MD, MPH*,** Professor of Medicine; Director, Minnesota Evidence-based Synthesis Program, Minneapolis VA Center for Chronic Disease Outcomes Research
Elbert Huang, MD, MPH,* Professor of Medicine; Director, Center for Chronic Disease Research and Policy, University of Chicago	**Stuart Winston, DO,*** Physician Lead, Professional Enhancement Program, Integrated Health Associates

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

ǂ Chris Jones is a founder of TRUSX Inc., which has clients such as Sanofi, founder of ForMyOdds.com, and a board member of portfolio companies in which UVMHN Ventures is invested. He is also an institutional investor (on behalf of UVMHealth Network Ventures) in Aspenti Health, a drug testing facility.

Table G3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Kelcey Blair, PharmD, Vice President, Clinical Solutions at Express Scripts	Kelcey is a full-time employee of Express Scripts.
Anita Ju, Innovation Manager, Blue Shield of California	Anita is a full-time employee of Blue Shield of California.
Miriam Komaromy, MD, FACP, DFASAM, Medical Director, Grayken Center for Addiction, Boston Medical Center, Boston University	No financial conflicts of interest to disclose.
Hans Morefield, Chief Executive Officer, CHESS Health	Hans is a full-time employee of CHESS Health.
Jake Nichols, PharmD, MBA, President and Chief Executive Officer, Professional Recovery Associates	Jake Nichols was previously employed by Pear Therapeutics.
Mike Pace, MBA, Vice President and Global Head of Market Access, Value, and Evidence, Pear Therapeutics	Mike is a full-time employee of Pear Therapeutics.
Kevin Roy, MBA, Chief Public Policy Officer, Shatterproof	No financial conflicts of interest to disclose.
Scott Steiger, MD, FACP, FASAM, Associate Clinical Professor of Medicine and Psychiatry, University of California San Francisco	No financial conflicts of interest to disclose.