

Digital Therapeutics as an Adjunct to Medication Assisted Treatment for Opioid Use Disorder: Effectiveness and Value

Revised Scope

June 12, 2020

Background

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

In addition to its health and social impacts, OUD can lead to death from drug overdose. The number of drug overdose deaths in the US increased continuously from 1999 to mid-2017⁴ when it reached a plateau of approximately 70,000 deaths over the previous 12 months of which approximately 50,000 were from opioids.^{5,6} Approximately 2.4 million persons in the US suffer from OUD; two-thirds of this prevalence relates to prescription opioid painkillers and one-third relates to heroin or other illicit opioids.⁷ 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 2018.⁸

Several treatment approaches are available to treat OUD. Medication assisted treatment (MAT) is the most common approach. MAT is defined as the use of medications approved by the Food and Drug Administration (FDA), generally in combination with counseling and behavioral therapies.⁹ Treatment of OUD with MAT has been shown to be effective,^{10,3} and three types of medications are approved by the FDA: the full opioid agonist methadone, the partial agonist buprenorphine, and the opioid antagonist naltrexone.^{11,12}

In 2018, ICER updated its 2014 assessment on MAT for the management of patients with opioid dependence.¹³ The report found that “long-term maintenance treatment approaches using methadone or Suboxone® to reduce the craving 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 opioid dependence treatment.

Digital therapeutics

There is a tremendous amount of interest and innovation in digital therapeutics, which is reflected in a growing number of NIH supported grants in this arena.¹⁴ Digital technologies represent a novel approach to enhance medical 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 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 diseases.

Digital technology has impacted all aspects of modern life including health. Digital therapeutics use both online and smartphone technologies to treat a medical or psychological condition. The first digital therapeutic to be approved by the FDA, reSET, is an app used to assist outpatient treatment for substance use disorders. A separate version of the app, reSET-O, has been approved for use in patients with OUD.

Stakeholder Input

This scoping document was developed with input from diverse stakeholders, including patients, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Stakeholders suggested that telehealth approaches to MAT for OUD were qualitatively different from digital adjuncts to MAT, so we removed them from the final scope. Some stakeholders suggested only including FDA-approved digital therapeutics, but others encouraged us to consider other platforms with evidence supporting their effectiveness and the potential for FDA approval in the future. We elected to go with the larger group of digital therapies in order to give a broader perspective on what is available and to help inform future research. We also heard from stakeholders that we should focus on settings and populations where patients are able to have access to a smart phone or tablet since therapeutic content would be delivered through technology. Thus, we removed prison-based settings given the unlikelihood that patients in these settings would have access to smartphones. Finally, we heard repeatedly that outcomes such as abstinence and treatment retention were primarily useful when evaluated after 12 to 18 months of follow-up. Short-term measures of these outcomes may not reliably translate into improvements that matter to patients or reductions in long-term health care costs.

Report Aim

This project will evaluate the health and economic outcomes of digital therapeutics in addition to MAT in OUD. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms - including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs - are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's [grey literature policy](#)).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided in a research protocol published on the Open Science Framework website (<https://osf.io/7awvd/>).

Populations

The key population of interest for the review will be patients aged 18 years and above with OUD in various treatment settings. Given different patient incentives for seeking treatment and differing mechanisms of action for the treatments themselves, we will focus on a range of patients who are seeking detoxification, maintenance treatment, or long-term recovery from OUD. We will consider subpopulations that focus on young adults (up to 25 years), injection site users, and pregnant women if data are available.

Interventions

We will evaluate interventions used in conjunction with best supportive care, which includes MAT. The interventions include:

- reSET-O
- ACHES / Connections
- DynamiCare Health

Comparators

Data permitting, we intend to compare all the interventions to each other within each population and to best supportive care that includes MAT.

Outcomes

The outcomes of interest are described in the list below.

Intermediate / Short-term outcomes

- Short-term and long-term abstinence from illicit use (misuse and abuse) of opioids
- Retention in treatment
- Engagement with the app
- Diminishing illicit use of opioids
- Opioid withdrawal syndrome
- Infectious (HIV, hepatitis), injection reactions, and other complications through continued use of injectable opioids
- Functional outcomes (cognitive, occupational, social/behavioral)¹⁵
- Craving/desire for opioids
- Accidental pediatric exposure
- Mental 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

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)

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.

Settings

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

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. These general elements (i.e., not specific to a given disease) are listed in the table on the next page.

Table 1.1. Potential Other Benefits or Disadvantages and Contextual Considerations

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 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

ICER encourages stakeholders to provide input on these elements in their public comment submissions. We appreciate the suggestions made by Pear Therapeutics, Blue Shield of California, and the Frost Medical Group. These will be incorporated into the draft report.

Scope of Comparative Value Analyses

As a complement to the evidence review and where data allow, we will develop a *de novo* Markov model to assess the cost-effectiveness of the digital therapeutics of interest in addition to outpatient MAT treatment relative to outpatient MAT treatment alone. The model structure will be based in part on a literature review of prior published models of opioid use disorder and ICER's previous review of MAT completed in 2018.^{13,16-20} The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). As data permits, productivity impacts and other indirect costs will be considered in a modified societal perspective scenario analysis. This modified societal perspective scenario analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs and the impact of the digital therapeutic on these costs is substantial. This will most often occur in cases where the change in incremental cost-effectiveness ratios between the two perspectives is greater than 20%, greater than \$200,000 per QALY, and/or crosses the threshold of \$100,000-\$150,000 per QALY gained. The target population will consist of adults 18 years or older with opioid use disorder in outpatient treatment with medication-assisted treatments. As data allow, we intend to model a more homogeneous sub-population of individuals with a poorer prognosis (e.g., those not abstinent at model entry).

A detailed economic model analysis plan with proposed methodology, model structure, parameters, and assumptions is forthcoming. The model will consist of health states including: on MAT treatment with illicit use of opioids, on MAT treatment without illicit use of opioids (i.e. abstinence), off MAT treatment with illicit use of opioids, off MAT treatment without illicit use of opioids (i.e. abstinence), and death. Similar to ICER's previous review of MAT completed in 2018, a cohort of patients will transition between these health states during predetermined cycles of four weeks over a five-year time horizon. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., duration of digital therapeutic use, 1 year) and longer time horizons (e.g., lifetime). Future costs and outcomes will be discounted 3% per year. Key model inputs will include digital therapeutic effectiveness, health care costs, and MAT-specific inputs (including MAT treatment effectiveness, discontinuation, adverse events, mortality, cost, and quality of life). Probabilities, costs, and other inputs will differ to reflect varying effectiveness between intervention(s) and comparator(s). Digital therapeutic effectiveness will be estimated by synthesizing best-available evidence and will be measured primarily by abstinence and MAT treatment duration.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. Health outcomes will include abstinence at digital therapeutic completion, abstinence duration, on MAT treatment at digital therapeutic completion, MAT duration, life-years gained, quality-adjusted life years (QALYs) gained, and equal-value life

years gained ([evLYG](#)). Quality of life weights will be applied to each health state, including quality of life decrements for adverse events. The model will include direct medical costs, including but not limited to digital therapeutic cost, costs associated with MAT acquisition, administration, and monitoring, condition-related care (including costs to provide contingency management for the comparator if contingency management was provided in the comparator evidence), provider interaction with the patient through the digital therapeutic, and adverse events. In addition, for the modified societal perspective, productivity changes and other indirect costs will be included in a separate analysis as available data allow. Relevant pairwise comparisons will be made between each intervention and its respective comparator, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per additional person abstinent. No head to head comparisons between interventions are expected due to differences in the comparator treatments (including or not including contingency management).

Uncertainty will be assessed through one-way and probabilistic sensitivity analyses. In addition to one-way and probabilistic sensitivity analyses, a two-way sensitivity analysis between digital therapeutic cost and abstinence at intervention completion will be conducted.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found [here](#).

Identification of Low-Value Services

As described in its Value Assessment Framework for 2020-2023, ICER will include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's [Value Assessment Framework](#)). These services are ones that would not be directly affected by reset-O, as these services will be captured in the economic model. Rather, we are seeking services used in the current management of Opioid Use Disorder beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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