MIDWEST CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL

AN ICER PROGRAM

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

Modeling Analysis Plan

August 3rd, 2020

Institute for Clinical and Economic Review

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Table of Contents

1. Approach

This analysis plan details our modeling approach and outcomes to be assessed for the economic evaluation of digital therapeutics as an adjunct to medication assisted treatment for opioid use disorder (OUD). Refer to the Research Protocol for details on the systematic review of the clinical evidence on this topic.

The primary aim of this analysis is to estimate the cost-effectiveness of digital therapeutics as an adjunct to medication assisted treatment (MAT) for OUD using a decision analytic model. Where data allow, the model will compare each digital therapeutic as an adjunct to outpatient MAT to outpatient MAT without the use of a digital therapeutic. The base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only) and a five-year time horizon. We deviated from the ICER Reference Case lifetime time horizon because of relatively high rates of treatment discontinuation and restart in the MAT environment. Although some models in this disease area have modeled even shorter time horizons, we selected five years as our base case to capture potential downstream effects of MAT that result from potential gains in abstinence and treatment retention associated with the use of a digital therapeutic. As data permit, productivity impacts and other indirect costs will be included in a modified societal perspective scenario analysis, which will be considered as a co-base case when the societal costs of care are large relative to the direct health care costs and the impact of the digital therapeutic on these costs is substantial. The target population will consist of adults 18 years or older with OUD receiving outpatient MAT. As data allow, we may model two sub-populations consisting of individuals who had previously received a treatment for opioid dependence and separately individuals who were treatment naïve prior to initiating the digital therapeutic. The model will be developed in Microsoft Excel Version 16, with some components of the model, including discontinuation over time, developed in RStudio (version 1.1.442).

2. Methods: Long-Term Cost Effectiveness

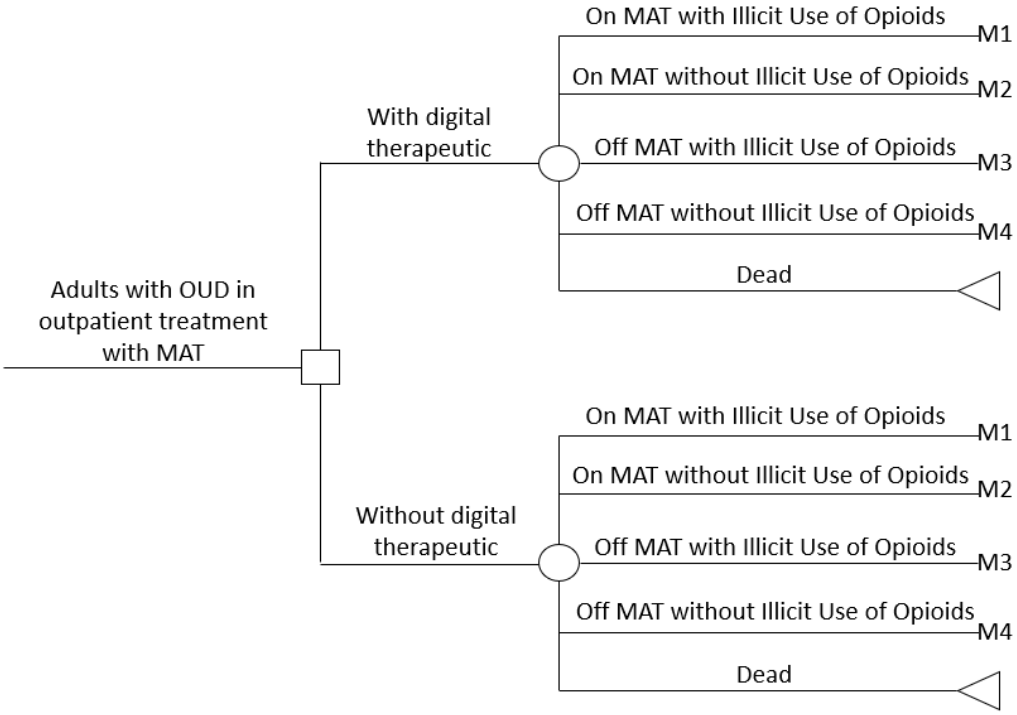
2.1 Overview and Model Structure

We will develop a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models,[1-5] including ICER's previous review of MAT completed in 2018.[6] The model will have two phases, with Phase 1 modeling the time using the digital therapeutic and its associated clinical and economic outcomes, and Phase 2 capturing continued MAT use following the digital therapeutic and its associated clinical and economic outcomes.

The model will use intention-to-treat analyses from trials and other sources, with a hypothetical cohort of patients entering the model with OUD being treated with either a digital therapeutic as an adjunct to MAT or MAT without the use of a digital therapeutic. Costs and outcomes will be discounted at 3% per year.

The model schematic for this assessment is depicted in Figures 2.1 and 2.2. Phase 1 of the model (Figure 2.1) will follow a decision tree and will mirror the duration of the time on digital therapeutic. While using the digital therapeutic, there are five potential health states an individual could occupy, including: 1) On MAT with Illicit Use of Opioids, defined as those who have not discontinued MAT, have not died, and are illicitly using opioids; 2) On MAT without Illicit Use of Opioids, defined as those who have not discontinued MAT, have not died, and are not illicitly using opioids (i.e. abstinence); 3) Off MAT with Illicit Use of Opioids, defined as those who have discontinued MAT and are illicitly using opioids; 4) Off MAT without Illicit Use of Opioids, defined as those who have discontinued MAT due to persistent abstinence that has lasted longer than 12 months; and 5) dead, defined as those who die over the duration of digital therapeutic use.

Figure 2.1. Phase 1 Decision Tree Schematic



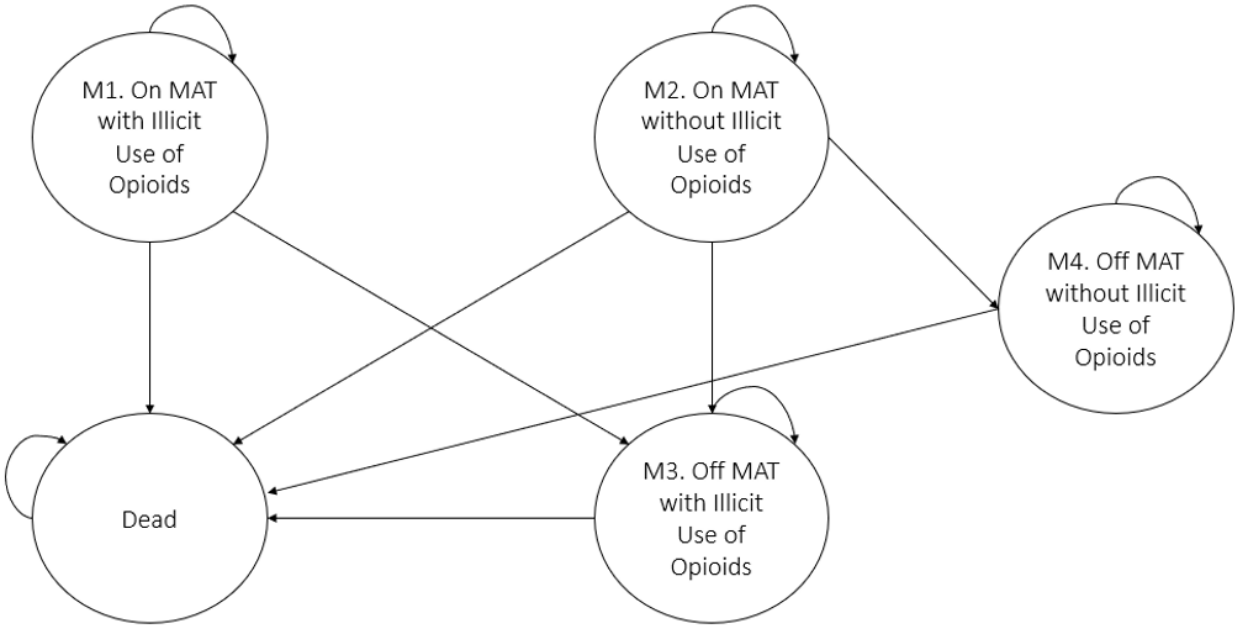
Phase 2 of the model (Figure 2.2) will be a Markov model that will consist of the same five health states: 1) On MAT with Illicit Use of Opioids, 2) On MAT without Illicit Use of Opioids (i.e. abstinence), 3) Off MAT with Illicit Use of Opioids, 4) Off MAT without Illicit Use of Opioids (i.e., persistent abstinence), and 5) Dead. Individuals that have opioid negative urine drug screening tests

for all assessment points over the last four weeks of digital therapeutic use will enter the Markov model in the On MAT without Illicit Use of Opioids health state. The last four weeks of digital therapeutic use was selected as the assessment duration for the On MAT without Illicit Use of Opioids health state to align with the digital therapeutic evidence and the FDA's recommendation to allow a grace period prior to assessing an intervention's effect. Individuals that do not meet this definition but are on MAT at the end of the digital therapeutic will enter the Markov model in the On MAT with Illicit Use of Opioids health state. Individuals that discontinue MAT while using the digital therapeutic will enter the Markov model in the Off MAT with Illicit Use of Opioids health state. Individuals must be abstinent for 12 consecutive months to enter into the Off MAT without Illicit Use of Opioids health state. Because Phase 1 is less than 12 months (the digital therapeutic duration), no one will enter the Markov model in the Off MAT without Illicit Use of Opioids health state. However, we describe how individuals can transition to this health state over the Markov model time horizon below. Patients that die over the duration of the digital therapeutic will enter the Markov model in the dead health state.

Model cycle length will be four weeks, based on outcomes reported in clinical data and previously published economic models. During Phase 2 of the model, patients can transition from On MAT with Illicit use of Opioids to Off MAT with Illicit Use of Opioids due to MAT discontinuation. Patients can transition from On MAT without Illicit use of Opioids to Off MAT with Illicit Use of Opioids, upon which they are considered to have relapsed, or to Off MAT without Illicit Use of Opioids (i.e. persistent abstinence), occurring in an assumed 10% of all patients who remain in the On MAT without Illicit Use of Opioids health state for 12 months.[6]

Once in the Off MAT with Illicit Use of Opioids or in the Off MAT without Illicit Use of Opioids health state, patients cannot 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 health state, patients could not move to an upstream health state. Also, in the Markov model (Phase 2), patients cannot 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 occurs while using the digital therapeutic (during the Phase 1 decision tree). Any transitions from illicit use to without illicit use that would occur outside of digital therapeutic use were considered to be the same across treatment arms. Patients remain in the model until death or until the end of the model time horizon. All patients can transition to death from all causes from any of the alive health states. In addition, patients can die from opioid overdose in health states where they are illicitly using opioids. People who inject drugs (PWID) also have an increased risk of death due to associated comorbidities, including Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) infections.

Figure 2.2. Phase 2 Markov Model Schematic



2.2 Key Model Choices and Assumptions

Our model will be informed by the key choices and assumptions listed in Table 2.1.

Table 2.1. Key Model Choices and Assumptions

Model Choice or Assumption	Rationale
Individuals that have opioid negative urine drug screening tests for all assessment points over the last four weeks of digital therapeutic use will enter the On MAT without Illicit Use of Opioids health state in the Markov model.	The final four weeks of digital therapeutic use aligns with the digital therapeutic evidence and the FDA's recommendation to allow a grace period prior to assessing an intervention's effect.
Missing urine drug screening tests will be assumed to be positive for opioids.	This is an intent to treat analysis and missing data will be considered as a failure (i.e. non-abstinent).
The transition to On MAT without Illicit Use of Opioids from On MAT with Illicit Use of Opioids occurs while using the digital therapeutic and while on MAT treatment.	Any transitions from illicit use to without illicit use that would occur after the digital therapeutic are considered to be the same across treatment arms.
Treatment discontinuation to Off MAT with Illicit Use of Opioids can occur from both On MAT without Illicit Use of Opioids and On MAT with Illicit Use of Opioids. The percent of total discontinuation from each of these health states will be assumed to be	Published evidence on MAT discontinuation based on illicit use status was not identified; therefore, we assumed slightly more individuals that discontinue will discontinue from an illicit use health state.

Model Choice or Assumption	Rationale
40% from On MAT without Illicit Use of Opioids and 60% from On MAT with Illicit Use of Opioids.	
MAT discontinuation after the duration of the digital therapeutic was extrapolated from the MAT retention curve (discontinuation=1-retention) in the digital therapeutic clinical evidence.	No robust data exist on long-term discontinuation/relapse for the digital therapeutics.
Upon relapse to illicit use of opioids, patients are assumed to return to the same opioid use (prescription or injectable) at baseline.	We found no robust published evidence on the illicit use of specific opioids by category in patients who have relapsed.
We assumed that 10% of all 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.[6]	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 overdose 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 overdose among OUD patients.
Serious adverse event (SAE)-related costs or disutilities were not included in the model.	The 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 assume that background health care costs (sourced from a claims analysis) include 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 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 and mortality hazard ratio associated with HIV infection and treatment with anti-retroviral therapy (ART).	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.
Among PWID diagnosed with HCV, clinical consequences of HCV were only assigned for those for whom there was no spontaneous clearance of HCV infection and who fail treatment.	Patients with spontaneous HCV infection clearance or those successfully treated with direct-acting antiviral therapy are assumed to have no HCV-specific disutilities or increased mortality. The proportion of individuals meeting these conditions is expected to be quite small given the high cure rates associated with current treatments.

2.3 Populations

The population of focus for the economic evaluation will consist of adults 18 years or older with OUD in outpatient MAT. As data allow, we may model sub-populations consisting of individuals who had previously received a treatment for opioid dependence and separately individuals who were treatment naïve prior to initiating the digital therapeutic. Table 2.2 provides the baseline population characteristics for the model that mirror the population characteristics from the pivotal trial used to inform the clinical evidence.

Table 2.2. Baseline Population Characteristics

Population Characteristics	Value	Notes/Source
Mean age (years)	34	Weighted average from Christensen et al., 2014[7]
Female (%)	46%	Weighted average from Christensen et al., 2014[7]
Injection as preferred route of administration (%)	14%	Weighted average from Christensen et al., 2014[7]
Prior treatment (%)	46%	Weighted average from Christensen et al., 2014[7]
Employed full time (%)	37%	Weighted average from Christensen et al., 2014[7]

2.4 Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers. The following interventions were considered for potential inclusion in the cost-effectiveness model:

- reSET-O (Pear Therapeutics)
- Connections (CHESS Health)
- DynamiCare (DynamiCare Health)

Data availability dictates the feasibility of each intervention being included in the model. At the posting of this model analysis plan, reSET-O was determined as the only intervention with sufficient peer-reviewed evidence in the OUD population to be included in the cost-effectiveness model. Other interventions may be added to the cost-effectiveness model if appropriate data become available during this review.

Comparators

The comparator will be outpatient MAT without the use of a digital therapeutic. The pivotal evidence for reSET-O included contingency management as part of the outpatient treatment in the comparator group, and thus one comparator for reSET-O will include contingency management for the same duration as the digital therapeutic as part of the outpatient treatment regimen to mirror

the pivotal trial findings. Contingency management is a type of behavioral therapy that provides rewards to patients following positive behaviors, such as negative urine drug screenings. Given that contingency management is not considered standard of care for this population, a comparator for reSET-O will also be outpatient MAT alone (i.e. including counseling but not contingency management). Additional evidence will be sought through the clinical review to identify clinical inputs for this comparator. The comparator inputs presented through the rest of this model analysis plan are for the comparator that includes contingency management as part of the outpatient MAT.

2.5 Input Parameters

Clinical Inputs

Digital Therapeutic Efficacy

Digital therapeutic efficacy will be estimated by synthesizing best available evidence and will be measured primarily by abstinence and MAT treatment duration. Digital therapeutic efficacy will be derived from relevant trial data.[7]

Abstinence

Abstinence data from the digital therapeutic evidence will inform the number of days abstinent during Phase 1 and will inform the percent of the population who start 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 will be used as the number of days abstinent during Phase 1 of the model. Data on file provided from the manufacturer of reSET-O will be used to inform the percent of the population in each arm who will 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 will include those who had urine drug screening tests negative for opioids across all assessment points for the last four weeks of digital therapeutic use. Missing urine drug screenings will be assumed to be positive for opioids. The percent of the population that occupy the On MAT without Illicit Use of Opioids health state will not significantly differ between the intervention and comparator arm(s) due to a non-significant difference in longest continuous abstinence reported in the reSET-O pivotal trial.[7] Abstinence data for reSET-O are presented in Table 2.3.

Table 2.3. Abstinence from Illicit Opioid Use at Completion of Digital Therapeutic

Abstinence	reSET-O	CM Comparator	Source
Total Days Abstinent Over Phase 1	67.1 days	57.4 days	Christensen et al., 2014[7]
Percent of Population That Enters the On MAT Without Illicit Use of Opioids Health State in Phase 2	[redacted]	[redacted]	Data on file

Beyond the digital therapeutic duration, no incidence of abstinence associated with the digital therapeutic will be modeled. Any transitions to abstinence that would occur outside of digital therapeutic use would not be the result of digital therapeutic use and would thus equally influence both the intervention and comparator.

MAT Treatment Discontinuation

Over the duration of the digital therapeutic (Phase 1), MAT discontinuation data from the digital therapeutic pivotal evidence will inform the percent of the population who start Phase 2 in the Off MAT with Illicit Use of Opioids health state. Discontinuation will be equivalent to one minus the MAT retention percent from the pivotal evidence. Table 2.4 presents the MAT retention evidence from the pivotal trial for reSET-O. MAT discontinuation is gradual over the time of digital therapeutic use; thus, for the purposes of assigning outcomes (LYs, QALYs, etc.) in Phase 1 of the model, we will assume discontinuation occurs halfway through the digital therapeutic duration.

MAT discontinuation after the duration of the digital therapeutic will be extrapolated from the MAT retention curve (discontinuation=1-retention) in the digital therapeutic clinical evidence. Table 2.4 provides the source for the Phase 2 MAT discontinuation evidence. To derive per-cycle transition probabilities to health states of off MAT treatment, we will fit parametric survival curves to Kaplan-Meier discontinuation curves utilizing the approach described by Hoyle and Henley.[8] First, we will extract data points from digitized copies of the trial curve, then use 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 will include the distributional forms of exponential, Weibull, log-normal, log-logistic, and gamma. The base-case parametric function will be selected based on best model fit using Akaike information criterion (AIC) values and visual comparison. Beyond trial duration, discontinuation will be extrapolated using the best-fitting curve function observed within the trial period.

In Phase 2, treatment discontinuation to Off MAT with Illicit Use of Opioids can occur from both On MAT without Illicit Use of Opioids and On MAT with Illicit Use of Opioids. The percent of total discontinuation from each of these health states will be assumed to be 40% from On MAT without Illicit Use of Opioids and 60% from On MAT with Illicit Use of Opioids. MAT retention for reSET-O are presented in Table 2.4.

Table 2.4. reSET-O MAT Retention

On MAT	reSET-O	CM Comparator	Intervention Effect	Source/Notes
On MAT at End of Phase 1	80.4%	64.1%	HR=2.12 (1.17, 3.83)	Discontinuation is equivalent to 1 minus the number retained on MAT from Christensen et al., 2014[7]
On MAT Over Phase 2	Figure 2 of Christensen et al., 2014 [7]			Discontinuation is equivalent to 1 minus the number retained on MAT from Christensen et al., 2014[7]

Adverse Events

We had no evidence to suggest adverse events were associated with the use of the digital therapeutic. Further, no MAT-related adverse events will be modeled. Informed by the 2018 ICER MAT review, evidence on serious adverse events from MAT lack specificity on what specific 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 will not be specifically modeled in our analysis.

Comorbidities Associated with OUD

Key OUD-related comorbidities with significant public health impact include HCV and HIV infections among PWID. A cohort study and a meta-analysis based on four US-specific surveys on PWID reported annual incidence of HIV and HCV among PWID as 0.055% (95% Confidence Interval: 0.042% to 0.080%) and 26.7%, respectively. These rates will be converted to per-cycle probabilities in the model.[9,10] Presence of comorbidities will be associated with clinical and economic consequences. However, clinical consequences for HCV will only be assigned to patients with HCV without spontaneous HCV infection clearance (24.4% of HCV cases spontaneously clear)[11] and those who are not successfully treated with direct-acting antiviral therapy (98% of treated cases are effectively cured of HCV).[12] Therefore, the proportion of HCV cases who experience clinical consequences is expected to be quite small (<2%% of HCV cases) given the high potential for spontaneous clearance and high cure rates associated with current treatments.

Mortality

Transition to the dead health state can occur from any of the alive health states and will be based on all-cause gender- and age-specific mortality sourced from the Human Mortality Database's US-specific tables.[13] We have no evidence to suggest a mortality benefit specific to the use of the digital therapeutic; however, an increased risk of death associated with opioid overdose was assigned to those illicitly using opioids in addition to all-cause mortality.[14] An increased risk of mortality associated with HIV and HCV will be attributed to PWID who have HIV or HCV.[15,16] For HCV, only patients without spontaneous HCV infection clearance (24.4% of HCV cases spontaneously clear)[11] and those who are not successfully treated with direct-acting antiviral therapy (98% of treated cases are effectively cured of HCV)[12] have HCV-increased mortality. Therefore, the proportion of individuals meeting these conditions is expected to be 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.[7] Therefore, HCV-specific mortality is not anticipated to be a key driver of the model. Table 2.5 reports the mortality inputs used in the model, all of which will be converted to per-cycle transition probabilities for inclusion in the model.

Table 2.5. Mortality Inputs

Parameter	Value	Source
Illicit use of Opioids	13.3 per 100,000 people who illicitly use opioids	Kaiser Family Foundation, 2016[14]
HR of Death from HIV[128]	3.15 (95% CI: 2.59 to 3.82)	Lappalainen et al., 2015[16]
MRR of Death from HCV[129]	2.37 (95% CI: 1.28 to 4.38)*	El Kamary et al., 2011[15]
All-Cause Mortality	U.S. Life Tables [13]	

HR: hazard ratio, MRR: mortality rate ratio, CI: confidence interval

*The increased mortality risk from HCV is only applied to approximately 1.5% of HCV cases because increased mortality was applied only to those for whom there was no spontaneous clearance of HCV infection and to those for whom were not cured from drug treatment.

Heterogeneity and Subgroups

If data allow, we may provide separate estimates for those that are treatment naïve versus those who had previously received OUD treatment prior to initiating the digital therapeutic. Differences in these sub-groups will be driven by potential differences in abstinence and treatment retention alone; all other model inputs will remain consistent with the base-case analysis. Table 2.6 presents the data elements needed to support these sub-group analyses.

Table 2.6. Heterogeneity and Subgroups

OUD Treatment Naïve	reSET-O	CM Comparator	Intervention Effect	Source
Percent of population that enters the On MAT without Illicit Use of Opioids Health State in Phase 2	[redacted]	[redacted]	[redacted]	Data on file from Pear Therapeutics
On MAT Treatment at Completion of Digital Therapeutic	72.7%	70.3%	HR=1.15 (0.53, 2.51)	Christensen et al., 2014[7]
OUD Treatment Experienced	**reSET-O**	**CM Comparator**	**Intervention Effect**	**Source**
Percent of Population that Enters the On MAT without Illicit Use of Opioids Health State in Phase 2	[redacted]	[redacted]	[redacted]	Data on file from Pear Therapeutics
On MAT Treatment at Completion of Digital Therapeutic	91.9%	58.5%	HR=6.57 (1.92, 22.45)	Christensen et al., 2014[7]

HR=hazard ratio

Health State Utilities

There was no evidence to suggest a utility benefit or decrement associated with time on the digital therapeutic. Health state utilities will be the same as those used in the 2018 ICER MAT review. These health state utilities were derived from a study that used an online US cross-sectional survey.[17] The study comprised hypothetical descriptive vignettes for OUD and associated MAT-related health states that were developed based on inputs from literature, clinical expert opinion, and people diagnosed with OUD. Quality of life assessments were undertaken using the standard gamble technique. For each health state, two sets of vignettes were developed, one including physical/emotional descriptors, and another "expanded" version adding societal factors to the physical/emotional descriptors (i.e., employment, criminal justice, and family relationship-specific aspects). The study excluded comorbidity-associated vignettes because its primary focus was assessing quality of life associated with OUD alone. Health state utilities when on MAT with concurrent use of illicit opioids were calculated by applying the ratio of utilities when illicitly using opioids with and without MAT (from a UK study)[2] to the base utility when illicitly using opioids when off MATs (from the cross-sectional survey).[17] Health state utilities in the Off MAT without Illicit Use of Opioids health state were sourced from a nationally representative survey study conducted in the US.[18] Table 2.7 presents the health state utilities used in the model.

Table 2.7. Health State Utilities

Parameter	Value	Source
Off MAT without Illicit Use of Opioids	0.852 (0.736 – 0.901)	Wittenberg et al., 2016 [17]
On MAT without Illicit Use of Opioids	0.766 (0.738-0.795)	Wittenberg et al., 2016 [17]
On MAT with Illicit Use of Opioids – Not Injected	0.700 (0.660 – 0.727)	Connock et al., 2007[2]
Off MAT with Illicit Use of Opioids – Not Injected	0.694 (0.660 – 0.727)	Wittenberg et al., 2016 [17]
On MAT with Illicit Use of Opioids – Injected	0.618 (0.538-0.727)	Connock et al. 2007 [2]
Off MAT with Illicit Use of Opioids – Injected	0.574 (0.538 – 0.611)	Wittenberg et al., 2016 [17]

For PWID diagnosed with HIV, we applied a 6.9% 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.[19] Multipliers specific to anti-retroviral therapy (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% 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.[20] 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 is expected to be 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.[7] Therefore, HCV-specific disutilities are not anticipated to be a key driver of the model.

Intervention Utilization

Table 2.8 details additional specifics of the digital therapeutic utilization. The digital therapeutic will be modeled as an adjunct to MAT. The MAT regimen that will be modeled will consist of a generic once daily 16mg sublingual buprenorphine/naloxone tablet.

Table 2.8. Intervention Recommended Utilization

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

Cost Inputs

All costs used in the model will be updated to 2020 US dollars. The model will include direct medical costs, including but not limited to intervention (i.e. digital therapeutic) cost, costs associated with MAT acquisition, costs to provide contingency management if applicable, and costs associated with other health care utilization.

Intervention Costs

In lieu of manufacturer-provided net prices, the wholesale acquisition cost for reSET-O will be used to approximate the cost per patient to access the digital therapeutic. Table 2.9 presents the cost for reSET-O per download.

Table 2.9. Intervention Cost per Patient

Digital Therapeutic	AWP per Download	WAC per Download	Source
reSET-O	$1,998	$1,665	Redbook[21]

AWP=average wholesale price, WAC=wholesale acquisition cost

Drug Costs

The only drug costs that will be included in the model will be the wholesale acquisition cost of MAT. The MAT regimen will consist of once daily 16mg generic sublingual buprenorphine/naloxone. Table 2.10 details the average daily and annual cost for generic buprenorphine/naloxone. Costs associated with MAT acquisition will only be assigned to patients in health states that correspond to On MAT.

Table 2.10. Drug Costs

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

Non-Drug Costs

Administration Costs

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

Health Care Utilization Costs

Non-MAT and non-digital therapeutic health care utilization over the duration of the digital therapeutic will be sourced from evidence specific to each digital therapeutic and from published literature. Table 2.11 presents the non-MAT and non-digital therapeutic health care utilization over the duration of the digital therapeutic for reSET-O.

Table 2.11. Intervention-Related Health Care Utilization while On Digital Therapeutic (Phase 1 of Model)

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

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

Table 2.12 provides the unit cost for each health care utilization type. The cost of contingency management is only applied to the comparator that includes contingency management because the cost of contingency management for reSET-O is assumed to be included in the reSET-O price.

Table 2.12. Intervention-Related Health Care Utilization Unit Costs

	Value	Notes/Source
Therapist Counseling	$128	Average commercial reimbursement for CPT code 90834[22]
Provider-Patient Interaction with Digital Therapeutic Platform	$65	Average Commercial Insurance Allowed for CPT Code of 99212 for Level II Office Visit[23]
Contingency Management*	$326 (over 12 weeks)	Sindelar et al., 2007[24]

CPT: Current procedural terminology

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

OUD-related health care costs will be sourced from a retrospective cohort study using claims data from the Truven Health Analytics MarketScan® database.[25] This analysis reports baseline and follow-up costs specific to treatment with buprenorphine (and other pharmacological and non-pharmacological therapy) in patients diagnosed with OUD. Patients were followed for one year and costs included those associated with inpatient admissions, emergency department (ED) visits, outpatient visits, and pharmacy costs. The population-weighted average costs of inpatient, ED, and

outpatient visits among the buprenorphine-treated populations at baseline and follow-up will be attributed to patients in the following health states: Off MAT with Illicit Use of Opioids, On MAT with Illicit Use of Opioids, and the On MAT without Illicit Use of Opioids. Pharmacy costs will be excluded to avoid double-counting of costs of MAT. During Phase 1 of the model, outpatient costs will be excluded to avoid double-counting of costs associated with the utilization reported in Table 2.11. Table 2.13 details the per-cycle (4-week) non-MAT health care costs that will be included in the model. In addition to the costs reported in Table 2.13, we will assign age-adjusted health care costs based on the general population to all health states.[26]

Table 2.13. Average Non-MAT, Non-Intervention Health Care Costs, per Model Cycle

Per Cycle Costs (4 weeks)	On or Off MAT with Illicit Use of Opioids[25]	On MAT without Illicit Use of Opioids[25]
Inpatient Admissions	$392	$339
Emergency Department Visits	$82	$72
Outpatient Visits	$490	$741

Costs reported are per cycle (4 weeks) and are reflective of average health care utilization for patients with OUD. These costs are not unit costs.

Comorbidity Costs

For PWID diagnosed with HIV or HCV, we will attribute drug and other non-drug costs associated with these comorbidities.[27,28] The per-cycle costs of HIV and HCV are reported in Table 2.14 and are based on model inputs used in the 2018 ICER MAT review.[6] 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 2.14 and are only applied for two cycles to correspond with the eight-week HCV treatment duration. Other HCV treatment costs will only be assigned to individuals treated with HCV drug therapy who were not cured, which is only approximately 2% of treated HCV patients.[12]

Table 2.14. HIV and HCV Treatment Costs per Cycle (4-week Duration) per Case

	HIV[19]	HCV[12,27]
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, which is approximately 2%.[12]

Productivity Costs and Other Indirect Costs

Each digital therapeutic can be associated with productivity gains by keeping more people in health states that correspond to abstinence. Similar to the 2018 ICER MAT review,[6] we will include costs associated with lost productivity, criminal justice, and incarceration in a scenario analysis that will take a modified societal perspective. For lost productivity, based on the modeled population characteristics, it was estimated that 37% of the population is employed. Birnbaum et al. reported productivity costs which included lost wages, excess disability, medically-related absenteeism, lost wages from incarceration, and presenteeism associated with opioid abuse, dependence, and misuse in the US.[29] These estimates were combined with SAMHSA data[30] to calculate the productivity loss costs per person (Table 2.15). These productivity costs will be applied to approximately 37% of the modeled cohort 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.[31] 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,[6] we will assume 43% of the population will be involved in criminal justice and incarceration-related events, and will therefore apply these costs to the same percentage within our cohort. 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 2.15). Details of these calculations can be found in the 2018 ICER MAT review appendix.[6]

Table 2.15. 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¥

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

2.6 Model Outcomes

Model outcomes will include total life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal-value life years gained (evLYG), and total costs over a five-year time horizon. The model will also output clinical outcomes, such as on MAT at digital therapeutic completion. Total costs, LYs,

QALYs, and evLYGs will be reported as discounted values, using a discount rate of 3% per annum. Undiscounted results will be presented in an Appendix. Incremental costs per LY gained, incremental costs per QALY gained, incremental costs per evLYG, and incremental costs per additional person on MAT at digital therapeutic completion will be calcaulted for all relevant pairwise comparisons.

2.7 Model Analysis

Cost-effectiveness will be estimated using incremental cost-effectiveness ratios, with incremental analyses comparing each digital therapeutic as an adjunct to MAT to MAT without the use of a digital therapeutic. The base case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only). Productivity impacts and other indirect costs (as data permit) will be considered in a separate scenario analysis. This modified societal perspective 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 treatment 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.

Sensitivity Analyses

We will conduct one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses will also be performed by jointly varying all uncertain model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We will also perform threshold analyses for digital therapeutic costs across a range of incremental cost-effectiveness ratios ($50,000, $100,000, $150,000 and $200,000 per QALY and evLYG).

Scenario Analyses

If data allow, we will consider conducting scenario analyses that include:

1. Modified societal perspective that includes components such as productivity losses, criminal justice and incarceration, or others as applicable.

2. Sub-population of those treatment naïve at digital therapeutic initiation.

3. Sub-population of those treatment experienced at digital therapeutic initiation.

Model Validation

We will use several approaches to validate the model. First, we will provide preliminary model structure, methods and assumptions to innovators, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we will also share the model with the relevant manufacturers for external verification around the time of publishing the draft report for this review. Finally, we will compare results to other cost-effectiveness models in this therapy area. The outputs from the model will be validated against the trial/study data of the interventions and any relevant observational datasets.

References

1. Carter JA, Dammerman R, Frost M. Cost-effectiveness of subdermal implantable buprenorphine versus sublingual buprenorphine to treat opioid use disorder. *J Med Econ.* 2017;20(8):893-901.
2. Connock M, Juarez-Garcia A, Jowett S, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technol Assess.* 2007;11(9):1-171, iii-iv.
3. Jackson H, Mandell K, Johnson K, Chatterjee D, Vanness DJ. Cost-Effectiveness of Injectable Extended-Release Naltrexone Compared With Methadone Maintenance and Buprenorphine Maintenance Treatment for Opioid Dependence. *Subst Abus.* 2015;36(2):226-231.
4. Nosyk B, Guh DP, Bansback NJ, et al. Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment. *CMAJ.* 2012;184(6):E317-328.
5. Schackman BR, Leff JA, Polsky D, Moore BA, Fiellin DA. Cost-effectiveness of long-term outpatient buprenorphine-naloxone treatment for opioid dependence in primary care. *J Gen Intern Med.* 2012;27(6):669-676.
6. Institute for Clinical and Economic Review. Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value. 2018.
7. Christensen DR, Landes RD, Jackson L, et al. Adding an Internet-delivered treatment to an efficacious treatment package for opioid dependence. *Journal of consulting and clinical psychology.* 2014;82(6):964-972.
8. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. *BMC Med Res Methodol.* 2011;11:139.
9. Lansky A, Finlayson T, Johnson C, et al. Estimating the number of persons who inject drugs in the united states by meta-analysis to calculate national rates of HIV and hepatitis C virus infections. *PLoS One.* 2014;9(5):e97596.
10. Page K, Morris MD, Hahn JA, Maher L, Prins M. Injection drug use and hepatitis C virus infection in young adult injectors: using evidence to inform comprehensive prevention. *Clin Infect Dis.* 2013;57 Suppl 2:S32-38.
11. Smith DJ, Jordan AE, Frank M, Hagan H. Spontaneous viral clearance of hepatitis C virus (HCV) infection among people who inject drugs (PWID) and HIV-positive men who have sex with men (HIV+ MSM): a systematic review and meta-analysis. *BMC Infect Dis.* 2016;16:471.
12. Food and Drug Administration. *MAVYRET TM (glecaprevir and pibrentasvir) tablets, for oral use.* 2007.
13. Human Mortality Databases. https://usa.mortality.org/. Published 2016. Accessed 07/15/2018.
14. Opioid Overdose Death Rates and All Drug Overdose Death Rates per 100,000 Population (Age-Adjusted). 2016.
15. El-Kamary SS, Jhaveri R, Shardell MD. All-cause, liver-related, and non-liver-related mortality among HCV-infected individuals in the general US population. *Clin Infect Dis.* 2011;53(2):150-157.
16. Lappalainen L, Hayashi K, Dong H, Milloy MJ, Kerr T, Wood E. Ongoing impact of HIV infection on mortality among people who inject drugs despite free antiretroviral therapy. *Addiction.* 2015;110(1):111-119.

17. Wittenberg E, Bray JW, Aden B, Gebremariam A, Nosyk B, Schackman BR. Measuring benefits of opioid misuse treatment for economic evaluation: health-related quality of life of opioid-dependent individuals and their spouses as assessed by a sample of the US population. *Addiction.* 2016;111(4):675-684.
18. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making.* 2006;26(4):410-420.
19. Bernard CL, Brandeau ML, Humphreys K, et al. Cost-Effectiveness of HIV Preexposure Prophylaxis for People Who Inject Drugs in the United States. *Ann Intern Med.* 2016;165(1):10-19.
20. Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med.* 2015;162(6):397-406.
21. Redbook. Accessed July 23, 2020, 2020.
22. Reifsneider D. Therapy Session Rates by CPT Code. https://www.simplepractice.com/blog/median-therapy-session-rates-by-state-and-city-cpt-codes/. Published 2019. Updated July 10, 2020. Accessed.
23. UNITED HOSPITAL DISTRICT'S TOP 25 PRIMARY CARE CPT CODES AND 2019 PRICING. 2019.
24. Sindelar JL, Olmstead TA, Peirce JM. Cost-effectiveness of prize-based contingency management in methadone maintenance treatment programs. *Addiction.* 2007;102(9):1463-1471.
25. Shah A, Duncan M, Atreja N, Tai KS, Gore M. Healthcare utilization and costs associated with treatment for opioid dependence. *J Med Econ.* 2018;21(4):406-415.
26. Services CfMaM. National Health Expenditure Data. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Age-and-Gender. Published 2019. Accessed.
27. Johnson RL BH, Ferro C. . The burden of hepatitis C virus disease in commercial and managed Medicaid populations. *Milliman.* 2015.
28. Bernard CL, Owens DK, Goldhaber-Fiebert JD, Brandeau ML. Estimation of the cost-effectiveness of HIV prevention portfolios for people who inject drugs in the United States: A model-based analysis. *PLoS Med.* 2017;14(5):e1002312.
29. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Med.* 2011;12(4):657-667.
30. Archive SAMHD. National Survey on Drug Use and Health (NSDUH-2007). 2007.
31. Krebs E, Urada D, Evans E, Huang D, Hser YI, Nosyk B. The costs of crime during and after publicly funded treatment for opioid use disorders: a population-level study for the state of California. *Addiction.* 2017;112(5):838-851.