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

Research Protocol

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Institute for Clinical and Economic Review

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1. Background, Objectives, and Research Questions

1.1 Background

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

In addition to its health and social impacts, OUD can lead to death from drug overdose. The number of drug overdose deaths in the US increased continuously from 1999 to mid-2017 [4] when it reached a plateau of approximately 70,000 deaths over the previous 12 months of which approximately 50,000 were from opioids.[5,6] Approximately 2.4 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.

1.2 Objectives

The scope of this project was previously available for public comment, and has been revised upon further discussions and input from stakeholders. In accordance with the revised scope, this project will assess both the comparative clinical effectiveness and economic impacts of digital therapeutics as an adjunct to medication assisted treatment of opioid use disorder. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, the assessment is informed by two research components: a systematic review of the existing evidence and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). See the model analysis plan (expected publication date August 3, 2020) for details on the proposed methodology and model structure that will be used for the economic evaluation.

1.3 Research Questions

To inform our review of the clinical evidence, we have developed the following research questions:

1. What is the net health benefit of reSET-O in conjunction with best supportive care versus best supportive care alone in the population described below?
2. What is the net health benefit of ACHESS / Connections in conjunction with best supportive care versus best supportive care alone in the population described below?
3. What is the net health benefit of DynamiCare Health in conjunction with best supportive care versus best supportive care alone in the population described below?

Note that best supportive care includes MAT for the three research questions above.

1.4 PICOTS Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Population

The key population of interest for the review will be patients aged 18 years and above with OUD in various treatment settings who are taking MAT. 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
- ACHESS / Connections
- DynamiCare Health

Comparators

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

Outcomes

The outcomes of interest are described in the list below.

- Key Outcomes That Matter to Patients
    - Mortality (overdose deaths, suicide, all-cause)
    - 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)

- Other 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

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.

Setting

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

Study design

Randomized controlled trials and non-randomized controlled trials with any sample size will be included. Comparative observational studies of any sample size will also be included.

2. Evidence Review Methods

2.1 Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on digital therapeutics as an adjunct to medication assisted treatment for opioid use disorder will follow established best methods.[15,16] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, APA PsycInfo, and EMBASE for relevant studies. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include abstracts from conference proceedings identified from the systematic literature search if they provide any additional data not available in peer-reviewed publications. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 1-2 below.

To supplement the database searches, we will perform a manual check of the reference lists of included trials and reviews and invite key stakeholders to share references germane to the scope of this project. We will also supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

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

1	Exp opioid-related disorders/ or analgesics, opioid/ or substance-related disorders/ or narcotic-related disorders/
2	(Opioid OR opioid*related disord* OR opioid addict* OR opioid dependen* OR opioid abus* OR addiction, opioid OR dependence, opioid OR abuse, opioid OR opiate OR opiate addict* OR opiate dependen* OR opiate abus* OR addiction, opiate OR dependence, opiate OR abuse, opiate OR substance abuse).ti,ab.
3	1 OR 2
4	(Exp buprenorphine/ OR buprenorphine, nalaxone 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 Footnotes

Table 2.2. Search Strategy of EMBASE SEARCH

#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 nalaxone'/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

Table Footnotes

2.2 Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will independently screen the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

2.3 Data Extraction Strategy

Data will be extracted into Excel. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (digital therapy, directions for use), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and quality assessment for each study.

The data extraction will be performed in the following steps:

1. One reviewer will extract information from the full articles, and a second reviewer will validate the extracted data.

2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

2.4 Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor." [18]

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 paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *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: *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 or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.*

2.5 Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include reSET-O, ACHESS, Dynamicare, digital therapeutics, and opioid use disorder. We will select studies which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

2.6 Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: (1) a summary of the evidence base, (2) synthesis of outcome results, and (3) heterogeneity and subgroups.

Summary of Evidence Base

The studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. An evidence table shell is presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, patient characteristics, interventions, outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

Synthesis of Results

The results of the studies will be synthesized for each outcome and described narratively in the report. Analyses to be conducted will reflect the nature and quality of the evidence base (see below). Key considerations for interpreting the results will be specified and described in the Evidence Report.

Analyses are expected to be descriptive in nature only, as differences in entry criteria, patient populations, outcome assessments, and other factors are likely to preclude formal quantitative direct or indirect assessments of reSET-O, ACHESS / Connections, and Dynamicare Health. Nevertheless, if studies are sufficiently similar in terms of patient populations, outcomes assessed, interventions, and comparators, we will conduct random effect pairwise meta-analyses and network meta-analyses where feasible. A pairwise meta-analysis quantitatively synthesizes results from multiple studies that assessed the same intervention and comparator. [19] A network meta-analysis extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates

obtained from common comparator(s)). [20,21] The specific approach for any (network) meta-analysis will depend on the available evidence and will be detailed in the report.

Heterogeneity and Subgroups

To explore heterogeneity across studies, we will examine if there are differences in the distribution of key characteristics across studies. For this project, key characteristics include employment status, anxiety, type of medication assisted treatment, prior exposure to treatment, intravenous drug use, and multi-drug use. If studies differ with respect to these characteristics, these differences will be highlighted in the discussion of the evidence.

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009. [17] Additional explanation of each item can be found in Liberati et al. 2009. [22]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) 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 and (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.	

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Appendix B. Data Extraction Summary Table Shell

Table B1. Study Design

Author & Year of Publication (Trial)	Study Design & Duration of Follow-Up	Interventions	Inclusion Criteria	Exclusion Criteria

Table B2. Baseline Characteristics

Author & Year of Publication (Trial)	Study Arms	N	Sex	Age	Employment Status	Primary Opioid Used	Mixed/Multi Substance Use Disorder	Prior SUD Treatment Program

SUD: substance use disorder

Table B3. Efficacy Outcomes

Author & Year of Publication (Trial)	Study Arms	N	Treatment Retention	Opioid/Substance Abstinence	Employment-related Outcomes	Housing-related Outcomes	Relationship-related Outcomes

Table B4. Harms

Author & Year of Publication (Trial)	Study Arms	N	Adverse Events	Serious Adverse Events	Treatment Discontinuation	Mortality