DIGITS Pilot Protocol and Statistical Analysis Plan
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The DIGITS pilot study was conducted to evaluate the feasibility of integrating digital therapeutics into primary care and to prepare for the DIGITS Trial. In this study, we quantitatively examine implementation during the pilot study by describing the proportion of eligible patients reached by the digital therapeutics and fidelity related to ideal use. The pilot study included the enactment of several implementation strategies to be used in the future DIGITS Trial: practice facilitation (PF), health coaching (HC), and standard implementation (SI).

The DIGITS pilot study took place at Kaiser Permanente Washington (KPWA), a large integrated health system in Washington State. We selected two primary care clinics (referred to as Clinics A and B) in Seattle, WA for the pilot based on the presence of highly skilled licensed independent clinical social workers (LICSWs) willing to participate in a pilot study of digital therapeutics. We also intentionally selected clinics of disparate sizes. Clinic A was a large outpatient medical center with approximately 29,000 primary care empaneled patients. Clinic B was a newer and smaller medical center with approximately 2,500 empaneled patients.

Implementation Strategy Interventions

The SI strategy involved a 2-hour training, quality improvement meetings, an implementation toolkit consisting of clinician workflow aids, patient pamphlets, and scripts to help clinicians introduce the digital therapeutic to patients, and electronic health record (EHR) tools including documentation/charting templates and after-visit-summaries, an order set, and a population management workbench (i.e., EHR registry). The PF strategy is an evidence-based clinician-facing implementation strategy designed to support clinicians in overcoming implementation and workflow challenges. HC is a patient-facing strategy designed to support patient self-management and engagement in treatment.

Digital Therapeutic Intervention

Digital therapeutic prescriptions were entered into the EHR by LICSWs and routed to a medical doctor for approval. The digital therapeutics implemented were reSET® and reSET-O®, prescription smartphone apps made by Pear Therapeutics which had been authorized by the United States Food and Drug Administration (FDA) for the treatment of SUDs (not including alcohol use disorders, unless they are accompanied by drug use) and opioid use disorder (OUD; only when accompanied by prescription buprenorphine use), respectively. reSET is a 90-day prescription and reSET-O is an 84-day prescription. Both apps leveraged cognitive-behavioral approaches and are shown to improve patient outcomes in randomized controlled trials conducted in specialty addiction treatment settings.

Timeline and population

Pilot activities involved two distinct three-month periods. During the first period (2/10/21 to 5/5/21), one LICSW from each of the two pilot clinics was trained to offer reSET and reSET-O. During this time, LICSWs offered the apps to patients in the absence of PF or HC. This supported our goal of testing the pilot standard implementation materials. During the second period (5/6/21 to 8/6/21), Clinic A received both PF and HC, and Clinic B received HC only.

The study's quantitative outcome evaluation relied on secondary data sources. We report on two analytic cohorts: 1) a "main analytic cohort" consisted of patients who met pre-defined eligibility criteria, allowing us to calculate reach of the digital therapeutic in a defined patient population (which was consistent with the main trial eligibility criteria), and 2) a secondary "prescribed cohort", which consisted of all patients prescribed the digital therapeutic, regardless of whether they met criteria for the analytic cohort.

The main analytic cohort consisted of patients at least 18 years of age who had a primary care visit at Clinic A or B during the accrual period (defined below) and had a high-scoring screen for drug use the day of the visit or at any time in the prior year. A high-scoring screen was defined as a score of four on the Single Item Screen for Cannabis (SIS-C) (the highest score, indicating daily or almost daily cannabis use) and/or a score greater than zero for other drugs on the Single Item Screen for Drugs (SIS-D) (indicating any past year use of other drugs). Patients who have requested through the health system not to be contacted for research or not to have their chart reviewed for research were excluded. We included patients who had high-scoring substance use screens rather than patients with documentation of an active SUD diagnosis in analyses to avoid the potential for identification bias.

The second cohort, a prescribed cohort, consisted of patients who were prescribed the digital therapeutics. Patients in this cohort did not necessarily meet criteria for the analytic cohort (e.g., they may not have had a high-scoring drug screen or a visit at Clinic A or B during the accrual period or before their prescription) but were determined by clinicians to meet eligibility criteria for one of the digital therapeutics. For example, a patient who indicated on the SIS-C that they used cannabis weekly (as opposed to daily) would not have met criteria for the analytic cohort, but a clinical discussion may have revealed a need for SUD treatment.

Data collection and analysis

Data was collected from the EHR for an accrual period and an outcomes assessment period. The intended launch date was 2/10/21 (see above), but technical problems delayed reSET and reSET-O account creation and prescriptions until 3/2/21. Specifically, clinicians could not access the vendor's website from web browser versions that were installed in clinical offices; to resolve this, the app vendor ultimately modified their website. In addition, the EHR order set did not initially route prescriptions to physicians, which required EHR programmer intervention. We set a patient accrual period of 2/23/21 to 8/6/21, which captures everyone who was prescribed the digital therapeutics, including patients who may have visited clinics slightly before the technical problems were resolved. The outcomes assessment period (2/23/21 to 11/12/21) included the accrual period (since the outcome of reach of the digital therapeutic, defined below, could happen as early as the day of eligibility), a one-week grace period (to allow patients who became eligible on the last day of the accrual period to have at least one week to be reached), and three follow-up months to capture app use for patients who had a 12-week digital therapeutic prescription at any point during the pilot.

Baseline characteristics from the EHR included demographics, address, insurance status, healthcare utilization, and mental health and SUD screening information and diagnoses. For patients having multiple eligible visits (those where they were 18 or older and had a high-scoring screen), we used the first eligible visit as the "qualifying visit" on which to anchor time-varying covariates and outcomes. For patients who were prescribed the digital therapeutics but did not have an eligible visit, we used the prescription date as the qualifying visit. The time-period for constructing baseline clinical characteristics was from two years before until the day before the qualifying visit. Age was measured on the date of the qualifying visit. Sex (binary male/female), race, and ethnicity were from the time of the data pull to get the most current data. Insurance and address (used to classify rurality/urbanity was defined using the 2010 rural-urban commuting area codes and 2010 Census Tract geocoding) were measured on the date of or in the month before the qualifying visit, depending on data availability.

Our primary outcomes were clinic-level measures of reach and fidelity. Reach was defined as the number and proportion of patients who were prescribed reSET or reSET-O, downloaded the app and activated their prescription, and completed at least one module within the app. Fidelity was defined as the average (across patients) of the number of weeks (out of 12 possible weeks) in which patients completed at least four modules per week and had a past-month SUD-related visit. This definition of fidelity is based on Pear Therapeutic's recommendation that patients complete four modules per week (the maximum number of modules per week for which a patient can receive a contingency management reward) and the FDA label requirement and clinical recommendation that patients use the digital therapeutic while under the care of a

clinician (our health system leaders determined monthly SUD-related visits satisfied this requirement). We used a database provided by the vendor to obtain data related to app use such as activations and module completion during the outcomes assessment period.

Additional outcomes were treatment engagement and additional reach and fidelity measures. Treatment engagement was defined as the average (across patients) of the number of months in which patients had at least one visit for SUD treatment. Additional reach measures (which were subcomponents of the primary reach outcome measure) were the number and proportion of patients who were prescribed reSET or reSET-O (regardless of whether they downloaded the app and activated their prescription) and the number and proportion of patients who were prescribed the app and subsequently downloaded it and activated their prescription. Additional fidelity measures were the average number of weeks (out of 12 possible weeks) in which patients completed at least one module per week or completed at least four modules per week. Treatment engagement and fidelity-3 were subcomponents of the primary fidelity outcome measure. Adoption was measured to record if clinicians other than LICSWs completed training to prescribe the digital therapeutics.

Table 1. DIGITS pilot study outcome measures

Measure	Definition
Primary outcomes	
Reach	The number and proportion of patients who were prescribed reSET or reSET-O, downloaded the app and activated their prescription, and completed at least one module within the app.
Fidelity	The average of the sum of number of weeks (out of 12 possible weeks) in which patients completed at least four modules per week and had a past-month SUD-related visit.
Additional pre-specified outcomes	
Treatment engagement	The average of the sum of the number of months in which patients had at least one visit for SUD treatment.
Reach-2	The number and proportion of patients who were prescribed reSET or reSET-O.
Reach-3	The number and proportion of patients who were prescribed reSET or reSET-O, downloaded the app and activated their prescription.
Fidelity-2	The average of the sum of number of weeks (out of 12 possible weeks) in which patients completed at least one module per week.

Fidelity-3	The average of the sum of number of weeks (out of 12 possible weeks) in which patients completed at least four modules per week.
Adoption	The proportion of other healthcare providers initiating a patient on reSET or reSET-O, overall and by provider type.

While both of our primary outcomes required clinician and patient involvement, reach relied more heavily on actions from clinicians and fidelity relied more heavily on actions from patients. For example, PCPs and LICSWs were responsible for identifying patients who were eligible for the digital therapeutics; PCPs would connect potentially eligible patients to the integrated LICSW who would offer the digital therapeutics to patients. If the patient agreed to try the app and the designated medical doctor approved the prescription, that patient would be included in the numerator of reach-2. Downloading the digital therapeutic and activating the prescription (reach-3) was the responsibility of patients, although a motivated clinician with time to do so could assist with this step. Module completion (which was factored into reach, fidelity, fidelity-2 and fidelity-3 [module completion is critical because it is the primary way patients receive treatment from reSET or reSET-O]) required activation from patients, although clinicians were instructed to encourage patients to complete modules. Treatment engagement (a subcomponent of fidelity) was the joint responsibility of clinicians and patients. Many external factors could influence treatment engagement (e.g., appointment/scheduling access, patient ability to pay for SUD-related visits, etc.).

Data analyses were descriptive. Patient characteristics were described among eligible patients in Clinics A and B and in the sample overall. Outcomes were calculated among the eligible sample, overall and separately within each of the two clinics. We additionally calculated outcomes among the secondary sample of patients who were prescribed reSET (including some patients who did not meet eligibility criteria [e.g., were prescribed reSET but did not have a high scoring screen within a year prior to a primary care visit]) within each of the two clinics and in the sample overall.