Clinical UM Guideline

Subject: Mobile Device-Based Health Management Applications

Guideline #: CG-ANC-08 **Publish Date:** 04/16/2025

Status: Reviewed **Last Review Date:** 02/20/2025

Description

This document addresses the use of practitioner-prescribed software applications for health management purposes when used on a mobile device (e.g., mobile phone, laptop, smartwatch, or tablet) with the intent to evaluate, diagnose or treat an illness, injury, disease or its symptoms. This document does not address mobile-based software applications (MSAs) that are used in the function or control of another FDA-cleared or approved stand-alone hardware medical device. This document also does not address MSAs accessible to the general public for download (including direct-to-consumer [DTC] or over-the-counter [OTC] applications), applications that promote general wellness, or applications operated by a healthcare practitioner in a clinical setting for remote health monitoring.

Note: Over-the-counter (OTC) and consumer wearable devices may be excluded from benefit plan coverage. This may include smart phone, smart watch, or other personal tracking devices, including any software or applications.

Note: Please see the following related document for additional information:

- CG-MED-102 Dichoptic Digital Therapy for Amblyopia

Clinical Indications

Medically Necessary:

Mobile-based health management applications are considered **medically necessary** when *all* of the following criteria in I and II have been met:

I. Criteria to evaluate the mobile software application (MSA):
   A. The MSA has been approved or cleared by the Food and Drug Administration (FDA); **and**
   B. There is credible scientific evidence which permits reasonable conclusions regarding the impact of the MSA on health outcomes; **and**
   C. The MSA has been proven materially to improve the net health outcome or be as beneficial as any established alternative;
   AND

II. Criteria to evaluate the appropriateness of the MSA for the individual:
   A. The MSA has been prescribed by a healthcare practitioner; **and**
   B. There is documentation supporting that the MSA was ordered for a covered purpose such as preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and in accordance with generally accepted standards of medical practice;*** and**
   C. The requested MSA is not primarily for the convenience of the individual, prescribing clinician, caregiver, or other healthcare provider**.**

*****Generally accepted standards of medical practice means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, physician specialty society recommendations and the views of physicians practicing in relevant clinical areas, and any other relevant factors.

Not Medically Necessary:

Mobile-based health management applications are considered **not medically necessary** when the criteria above have not been met.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT	
99199	Unlisted special service, procedure or report [when specified as a mobile-based health management software application]

HCPCS

E1399	Durable medical equipment, miscellaneous [when specified as a mobile-based health management software application]
G0552	Supply of digital mental health treatment device and initial education and onboarding, per course of treatment that augments a behavioral therapy plan
G0553	First 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (DMHT) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing information related to the use of the DMHT device, including patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month
G0554	Each additional 20 minutes of monthly treatment management services directly related to the patient's therapeutic use of the digital mental health treatment (DMHT) device that augments a behavioral therapy plan, physician/other qualified health care professional time reviewing data generated from the DMHT device from patient observations and patient specific inputs in a calendar month and requiring at least one interactive communication with the patient/caregiver during the calendar month
T1505	Electronic medication compliance management device, includes all components and accessories, not otherwise classified [when specified as a mobile-based health management software application]

ICD-10 Diagnosis

All diagnoses

When services are Not Medically Necessary:
For the procedure codes listed above when criteria are not met.

When services are also Not Medically Necessary:

HCPCS

A9291	Prescription digital cognitive and/or behavioral therapy, FDA-cleared, per course of treatment

ICD-10 Diagnosis

All diagnoses

Discussion/General Information

Estimates report over 85% of adults living in the United States (US) own a smartphone (Pew Research Center, 2021). “Health-related mobile applications available to consumers on top app stores worldwide now surpass 350,000, with more than 90,000 digital health apps added in 2020 — an average of more than 250 apps per day.” (Institute for Human Data Science [IQVIA], 2021, 2024). Examples of medical mobile device software applications (MSAs) currently available include applications that purport to perform cognitive behavior therapy, augment weight loss goals, identify a suspicious nevi (mole), or even distinguish between normal cardiac sinus rhythm and potentially dangerous arrhythmias. Transforming a personal mobile device, such as a smartphone, into a medical device has the potential for far-reaching implications on the diagnosis and management of many diseases and disorders in addition to promoting general health and wellness. Despite the enormous effort to develop and disseminate digital health innovations, evidence of efficacy, or even a widely accepted framework for evaluation of efficacy, currently remains lacking. According to IQVIA (2021),

> …independent organizations continue to highlight the need for larger and more robust randomized controlled trials (RCTs) that follow patients for longer times and report between-group differences in benefit, assessments of usability, and user-retention to determine the durability of their clinical effect, and evidence of cost-effectiveness that can be analyzed versus standard of care.

The US Food and Drug Administration (FDA) Center for Devices and Radiologic Health (CDRH) is among one of several groups leading development of a framework for evaluating the burgeoning number of MSAs anticipated to reach market as part of the expanding digital health innovation arena. The framework is detailed in their guideline entitled, “Policy for device software functions and mobile medical applications” (FDA, 2019).

A number of additional MSAs are in the developmental pipeline for FDA approval or clearance, including those developed by Click Therapeutics, Inc., a company developing and seeking FDA approval for several digital software solutions to aid in the

management of diverse conditions including but not limited to insomnia, acute coronary syndrome, migraine and overactive bladder.

The FDA's regulatory oversight of software functions includes the following subsets:

1. **Software functions that are an extension of one or more medical devices by connecting to such device(s) for purposes of controlling the device(s) or analyzing medical device data.**
   Examples of software functions that control medical devices include: software that provides the ability to control inflation and deflation of a blood pressure cuff through a mobile platform and mobile apps that control the delivery of insulin on an insulin pump by transmitting control signals to the pumps from the mobile platform.

Device software functions of these types are considered accessories to the connected device and not addressed by this document.

2. **Software functions (typically, mobile apps) that transform the mobile platform into a regulated medical device by using attachments, display screens, or sensors or by including functionalities similar to those of currently regulated medical devices.**
   Examples of these types of software functions include: a software function that uses a mobile platform for medical device functions, such as attachment of a blood glucose strip reader to a mobile platform to function as a glucose meter; or attachment of electrocardiograph (ECG) electrodes to a mobile platform to measure, store, and display ECG signals; a software function that uses the built-in accelerometer on a mobile platform to collect motion information for monitoring sleep apnea; a software function that uses sensors (internal or external) on a mobile platform for creating electronic stethoscope function is considered to transform the mobile platform into an electronic stethoscope.

Mobile software functions of this type are addressed by this document when the ancillary hardware device is intended to function solely in conjunction with the mobile device application.

3. **Software functions that become a regulated medical device by performing patient-specific analysis and providing patient-specific diagnosis, or treatment recommendations. These types of functions are similar to or perform the same function as those types of software devices that have been previously cleared or approved.**
   Examples of software functions that perform sophisticated analysis or interpret data (electronically collected or manually entered) from another medical device include: software functions that use patient-specific parameters and calculate dosage or create a dosage plan for radiation therapy; Computer Aided Detection software (CAD) image processing software; and radiation therapy treatment planning software.

These types of software are addressed by this document when they operate on a mobile device, have received FDA clearance or approval, are clinician-prescribed, and when the intent of the MSA is to evaluate, diagnose or treat an illness, injury, disease or its symptoms.

In January 2019, the FDA released its publication, "Developing a Software Precertification Program." In it, an innovative plan is described, to reimagine the way the government administers oversight and approval in the digital device arena that is more efficient than the traditional device approval pathway. The FDA is basing the Pre-Cert pilot program's criteria on five principles of excellence: safety, quality, clinical responsibility, cybersecurity responsibility, and proactive culture. The paradigm shift in the FDA approval process for digital innovation lies in the focus on the manufacturer rather than on the device itself, when a product meets the definition of *software as a medical device*. The current Pre-Cert pilot program, has enrolled nine companies, out of over 100 applicants, to test the novel approval pathway (Apple, Fitbit, Johnson & Johnson, Pear Therapeutics, Phosphorus, Roche, Samsung, Tidepool and Verily). The FDA is currently considering two levels of precertification based on how a company meets the excellence principles and whether it has demonstrated a track record in delivering safe and effective software products. The FDA completed a Pilot Pre-Cert program, intended to determine whether the results align with the results of the traditional approval pathway and satisfy the FDA's established regulatory requirements for safety and effectiveness. As a result of challenges faced during the pilot, the FDA determined the approach explored was not practical to implement under current statutory and regulatory authorities and concluded, "the modern medical device landscape could benefit from a new regulatory paradigm, which would require a legislative change" (FDA, 2022).

In addition to the FDA's innovative program underway to evaluate the safety and effectiveness of digital health applications, a number of other organizations, both global and national, have also initiated tandem efforts to develop a framework for evaluation of products in this burgeoning field (Agency for Healthcare Research and Quality [AHRQ], 2022; American Medical Association [AMA], 2018; American Psychiatric Association [APA], 2019; World Health Organization [WHO], 2019). At this time, no single framework has been adopted for evaluation of medical mobile applications by medical or regulatory bodies and a recent study asserts "the need for a more rigorous and inclusive approach to clinical research supporting FDA-authorized prescription digital therapeutics" (Kumar, 2023).

Some MSAs, particularly those that operate with an ancillary hardware medical device, may be intended to replace a service rendered in the healthcare setting. Use of MSAs should not be substantiated primarily for the convenience of the individual, prescribing clinician, caregiver, or other healthcare provider; for example, in cases where appropriate alternatives for the indicated health service(s) are geographically accessible, and/or when the individual has concurrent ambulatory or hospital care

needs. However, use of MSAs may be appropriate when they are in accordance with generally accepted standards of medical practice, the MSA has been proven materially to be as beneficial as the established alternative, and credible scientific evidence permits reasonable conclusions regarding the impact of the MSA on health outcomes.

Practitioner-prescribed, FDA cleared or approved, MSAs (not an all-inclusive list)

AspyreRx™, Better Therapeutics, Inc.

AspyreRx is a prescription-only digital therapeutic device intended to provide cognitive behavioral therapy to individuals 18 years or older with type 2 diabetes. The device targets behavior to aid in the management of type 2 diabetes in individuals who are under the care of a healthcare provider. The application provides cognitive behavioral therapy intended as a treatment for adjunctive use with standard of care.

AspyreRx was evaluated in an RCT which enrolled 669 adults with type 2 diabetes and an HbA1c of 7 to < 11% (Hsia, 2022). Study participants were randomly assigned to receive access to AspyreRx (n=326) or a control application (n=343), both were adjunct to standard of care. After 90 days of access to AspyreRx, change in HbA1c was -0.28% (95% confidence interval [CI], -0.41 to -0.15) in the intervention group and +0.11% (95% CI, -0.02 to 0.23) in the control group (treatment group difference 0.39%; p<0.0001). Though statistically significant, the minimal clinically important difference (MCID) in HbA1c established in the peer-reviewed literature is 0.5%, this study did not attain that difference (Santos, 2023). Hypoglycemia was reported by 2 participants in the AspyreRx group and none in the control group. No adverse events in either group were attributed to AspyreRx use. Further study is warranted.

BlueStar®Rx, WellDoc®

BlueStar is a digital health platform for type 2 diabetes that provides tailored guidance driven by artificial intelligence and is focused on six critical dimensions of chronic disease care, which apply to diabetes as well as many other conditions like high blood pressure, pre-diabetes, and heart failure.

BlueStar was evaluated in a randomized controlled trial (RCT) which enrolled 163 individuals with type 2 diabetes whose HbA1c levels were poorly controlled or abnormal at the time of enrollment. Enrolled primary care practices (PCP) were randomized to one of four study groups: control-usual care (n=56), coach-only (n=23), coach PCP portal (n=22), and coach PCP portal with decision support (n=62). Participants who were randomized to use an MSA to help manage their diabetes in addition to usual care, improved HbA1c by an average 1.9%, compared with a 0.7% improvement in those randomized to usual care alone, a difference of 1.2% (p<0.001) over the 12-month study period (Quinn, 2011). The study's limitations include a small sample size in the study arms and an acknowledged randomization failure ("[coach portal with decision support] patients had higher baseline glycated hemoglobin than [usual care] (9.9 vs. 9.2%, p=0.04") that may have inflated the observed effect size.

Agarwal and colleagues (2020) conducted a multicenter, pragmatic RCT to determine if BlueStar application usage leads to improved HbA1c levels among diverse participants across diverse clinical scenarios. In total, 223 study participants were randomized to either the 'immediate treatment group' (ITG; n=110 [received the BlueStar intervention for 6 months]) or the wait-list control group (WLC; n=113 [received usual care for the first 3 months and then received the intervention for 3 months]). The primary outcome was HbA1c levels at 3-month follow-up. Secondary outcomes assessed disease self-management, experience of care, and self-reported health utilization. At 3 months, the mean difference in HbA1c levels between the ITG and WLC groups was not statistically significant (mean difference = -0.42; 95% CI, -1.05 to 0.21; p=0.19). Similarly, there was no effect on secondary outcomes and BlueStar usage was found to vary significantly across clinical sites (median of 9 versus 36 log-ins over 14 weeks at the lowest, versus highest usage sites, respectively). Evidence of BlueStar's clinical efficacy remains to be established in addition to defining factors that may affect individual and site-specific variations that impact the application's usage as recommended.

Canvas Dx™, Cognoa, Inc.

Canvas Dx is used by healthcare providers as an aid in the diagnosis of Autism Spectrum Disorder (ASD) for individuals ages 18 months through 72 months who are at risk for developmental delay. The device is not intended for use as a stand-alone diagnostic device but as an adjunct to the diagnostic process. In 2022, Megerian and colleagues conducted a double-blinded, cohort study which tested the accuracy of CanvasDx. This study compared the diagnostic agreement of the device to two or more independent specialists in a cohort of 425 children (aged 18-72 months) who had developmental delay concerns (425 study completers, 36% female, 29% ASD prevalence). The PPV was determined to be 80.8% (95% CI, 70.3%-88.8%) and NPV was 98.3% (95% CI, 90.6%-100%). Of those who received a determinate output (ASD positive or negative [31.8%]) sensitivity was 98.4% (95% CI, 91.6%-100%) and specificity was 78.9% (95% CI, 67.6%-87.7%). Of 711 children originally consented to participate in the study, 286 (40%) dropped out. There is insufficient data to help us understand whether use of the Canvas Dx application increases time to diagnosis in a real-world setting, in a manner that is likely to improve clinically relevant ASD outcomes.

DaylightRx

DaylightRx is a digital therapeutic intended to treat generalized anxiety disorder (GAD) using cognitive behavioral therapy (CBT) by improving GAD symptoms as an adjunct to usual care in individuals aged 22 years and older.

In 2020, Carl and colleagues conducted an RCT to evaluate the efficacy of Daylight for treating moderate-to-severe symptoms of GAD. A total of 256 adult participants (18-67 years; mean age=30.9) were enrolled and completed assessments at baseline, mid-intervention (3 weeks), post-intervention (6 weeks), and follow-up (10 weeks); the majority of the sample self-identified as female (68%), White (84%) and having at least some college education (83%). Study participants were randomized to either digital CBT (n=128) or waitlist control (n=128). The primary outcome, anxiety symptoms, was measured using the GAD-7 scale. Authors reported a significant reduction in GAD-7 anxiety scores in the digital CBT group compared with the waitlist control group at all assessment time points. At the 6-week follow-up, participants in the digital CBT group were more likely to experience remission of anxiety (65/107 [61%]) compared with waitlist control (38/122 [31%]) (odds ratio [OR], 3.99; 95% CI, 2.21, 7.21; p<0.001). At final follow-up (Week 10), 73/103 (71%) in the digital CBT group experienced remission compared with 41/ 124 (33%) in the waitlist control (OR, 5.84; 95% CI, 3.15, 10.82; p<0.001). The control group, which was unblinded, experienced a similar trend in significant reduction of symptoms from baseline, albeit less pronounced. While the reduction in self-reported GAD symptoms in this RCT is promising, a trial design including objective measures, in a more diverse sample is warranted.

d-Nav Insulin Guidance System®, Hygieia

The d-Nav Insulin Guidance System was evaluated in a multicenter RCT of 181 individuals with uncontrolled type 2 diabetes. Participants were randomized to either d-Nav and healthcare professional support (intervention group; n=93) or healthcare professional support alone (control group; n=88). The primary outcome of interest was to compare average change in HbA1c from baseline to 6 months. Safety was assessed by the frequency of hypoglycemic events. The mean decrease in HbA1c from baseline to 6 months was 1.0% in the intervention group, and 0.3% in the control group (p<0.0001). The difference in frequency of hypoglycemic events between the groups was not statistically significant (Bergenstal, 2019). Current data is limited to a single study of small sample size and long-term data of net health outcomes is lacking.

Drowzle® Pro, Resonea

Drowzle Pro is a mobile software system that records and analyzes respiratory patterns during sleep to facilitate the in-home screening of obstructive sleep apnea (OSA).

Drowzle was evaluated in a longitudinal cohort study of 59 individuals who were administered a clinically indicated polysomnography (PSG) in a sleep lab where investigators compared the DROWZLE algorithm to PSG results. Investigators found the algorithm provided a sensitivity of 93.7%, specificity of 63.0%, negative predictive value of 89.5%, and positive predictive value of 75.0%, in the detection of moderate and severe OSA among individuals compared to PSG scores (Narayan, 2019). Studies evaluating real-world application are lacking, as is data describing how screening results impact diagnosis and management of OSA as compared to generally accepted standards of medical practice.

EndeavorRx™, Akili Interactive

EndeavorRx is a game-based therapeutic intervention designed to improve cognitive function in children aged 8-12 who have been diagnosed with ADHD through a video game-like interface via at-home play for 25 min per day, 5 days per week for 4 weeks.

EndeavorRx was evaluated in an RCT which enrolled 348 children (8-12 years old) diagnosed with ADHD to receive treatment with either EndeavorRx (n=108) or a digital control intervention (n=168). Enrolled children were ineligible if they were already receiving medical therapy for ADHD. The mean change from baseline on the Test of Variables of Attention (TOVA) Attention Performance Index (API) was 0.93 in the EndeavorRx group and 0.03 in the control group (Adjusted p<0.050); there were no differences between groups on secondary measures. There were no serious adverse events or discontinuations. Treatment-related adverse events were mild and included frustration (3%) and headache (2%). Compliance averaged 83% of expected sessions played (Kollins, 2020). Study limitations included the enrollment of only children with an objective baseline deficit in attentional function and those not currently receiving medical treatment for ADHD, thus representing a small subset of the ADHD population. In addition, the study-period was limited to 28 days of follow-up. It is unclear whether the treatment resulted in the improvement of clinically meaningful outcomes or benefits commensurate to generally accepted standards of medical practice.

In 2021, Kollins and colleagues conducted a multi-center, open-label study of EndeavorRx as an adjunct to pharmacotherapy in a cohort of 8-14-year-old study participants with ADHD on stimulant medication (n=130) and not on any medication for ADHD (n=76). The enrolled participants used EndeavorRx for 4 weeks, followed by a 4-week pause and another 4-week treatment. The primary outcome of interest was change in ADHD-related impairment after 4 weeks as measured by the Impairment Rating Scale (IRS). IRS showed a statistically significant improvement in both cohorts (p<0.001) after 4 weeks. However, it is unclear whether treatment with EndeavorRx generates a clinically meaningful benefit as the minimum clinically important difference (MCID) in childhood ADHD symptoms for the IRS has not been established. Durability of effect also remains to be determined.

FibriCheck®, Qompium, NV

FibriCheck is indicated for self-testing by individuals who have been diagnosed with, or are susceptible to developing, atrial fibrillation and who would like to monitor and record their heart rhythms on an intermittent basis. At present, only a pilot study with limited study participant numbers is published in the peer-reviewed literature (Beerten, 2021). While additional peer-reviewed evidence is available addressing diagnostic validity and performance, there is limited evidence to determine a meaningful impact on clinical outcomes.

Freespira®, PaloAlto Health Sciences, Inc.

Freespira is intended for the treatment of post-traumatic stress disorder (PTSD), panic disorder, panic attacks and other panic symptoms. Treatment entails two 17-minute in home sessions daily for 4 weeks under the supervision of a licensed healthcare provider.

Freespira was evaluated in a multicenter, single arm trial of 69 adults with panic disorder who received 4 weeks of Capnometry Guided Respiratory Intervention (CGRI) using Freespira, which provides feedback of end-tidal CO2 (PETCO2) and respiration rate (RR) via a custom sensor device. This intervention is delivered via home use following initial training by a clinician and provides remote monitoring of client adherence and progress by the clinician. Outcomes were assessed immediately post-treatment and at 2- and 12-month follow-up. CGRI was associated with a response rate of 83% and a remission rate of 54%, in addition to large decreases in panic severity. Similar decreases were found in functional impairment and in global illness severity. Gains were largely sustained at follow-up. PETCO2 moved from the slightly hypocapnic range to the normocapnic range (Tolin, 2017).

In 2020, Kaplan and colleagues evaluated the impact of Freespira over a 12-month period in a cohort of 51 individuals enrolled at a single center. In total, 45 (87%) completed the 4-week, twice-daily Freespira home device treatments and at least 15 of the 56 protocol-specified therapy sessions. By study-end (12 months) just 22 participants were available for complete analysis. Overall, the cohort's Panic Disorder Severity Scale (PDSS) score fell from a baseline median of 14.4 (standard deviation [SD]=3.8) to 4.4 (SD=4.5) at 12 months, and 82% of the cohort reported a PDSS decrease of ≥ 40% (clinically significant) whereas 86% were free from panic attacks.

Currently available evidence evaluation of Freespira lacks comparison to generally accepted standards of medical practice, is limited by small sample sizes despite the prevalence of panic disorder in the general population and is participant to bias from loss to follow-up (Ostacher, 2021).

Halo™ AF Detection System, LIVMOR, Inc.

Halo is a wearable smartwatch device for intermittently monitoring pulse rhythms to detect atrial fibrillation (AF).

While there is no published peer-reviewed evidence at this time evaluating the Halo device, a retrospective propensity-matched cohort study was published in 2021 (Wang) which included 125 individuals with AF using wearables to monitor heart rate and rhythm and 500 with AF who did not use wearables. Study participants were followed for 90 days to compare pulse rate and healthcare use between individuals who wore wearables and those who did not. The study found that prior to propensity matching, those who use wearables were, on average, significantly younger ($p<0.001$) and healthier (composite score of congestive heart failure, hypertension, diabetes, prior ischemic event, vascular disease, age, and gender; $p<0.001$). After matching, study participants using wearables were found to have similar pulse rates, to those who did not, but utilized significantly more healthcare. In particular, there was a significant difference in receipt of a cardiac ablation, with 17.6% (n=22) in the wearables group compared to 7.4% (n=37; $p=0.001$) having received an ablation. The study authors conclude, "Given the increasing use of wearables by patients with AF, prospective, randomized, long-term evaluation of the associations of wearable technology with health outcomes and health care use is needed."

Home Vision Monitor® (HVM; previously myVisionTrack), Vital Art and Science, LLC

Home Vision Monitor is intended for the detection and characterization of central 3 degrees metamorphopsia (visual distortion) in individuals with maculopathy, including age-related macular degeneration and diabetic retinopathy, and as an aid in monitoring progression of disease factors causing metamorphopsia.

Korot and colleagues (2021) studied the Home Vision Monitor in a cohort study of 417 individuals to evaluate uptake and engagement of the application but no published studies have evaluated clinically meaningful outcomes related to use of the software.

Insulia®, Voluntis, Inc.

Insulia (formerly called Diabeo-Basal, Franc, 2019) is a Software program that recommends basal insulin doses for adults with Type 2 diabetes treated with long-acting insulin analogs as an aid in the management of diabetes based on the treatment plan created by a healthcare provider.

Insulia was evaluated in a 13-month RCT which enrolled a total of 191 participants with inadequately controlled type 2 diabetes who were randomized into three groups: group 1 (standard care, n=63), group 2 (interactive voice response system, n=64) and

group 3 (Diabeo-BI app software, n=64). At 4 months follow-up, HbA1c reduction was significantly higher in the telemonitoring groups (p<0.002). Fasting blood glucose was reached by twice as many participants in the telemonitoring groups as in the control group, and insulin doses were also titrated to higher levels. No severe hypoglycemia was observed in the telemonitoring groups and mild hypoglycemia frequency was similar in all groups (Franc, 2019). Current data is limited to a short period of evaluation, and the comparison arms sample sizes were limited.

In 2020, Franc and colleagues published results of a multicenter RCT to investigate the efficacy of the Diabeo app software (Insulia) in a real word study (TELESAGE study). This open-label trial enrolled 665 individuals who were randomized into one of three parallel study arms: standard of care, Diabeo alone, or Diabeo+telemonitoring. The primary outcome was reduction in HbA1c levels at 12-month follow-up. Participants who used Diabeo one or more times a day demonstrated a significant and meaningful reduction in HbA1c levels compared to the standard of care arm after a 12-month follow-up (mean difference -0.41% in Diabeo alone arm [p=0.001] and -0.51% for Diabeo+telemonitoring arm [p≤0.001]). Adherence rates across all three study arms were very low. In the intention-to-treat population, HbA1c changes and incidence of hypoglycemia were comparable between arms. In this trial, intention-to-treat analyses showed no meaningful benefit, despite post-hoc exploratory analyses demonstrating statistical significance.

iSageRx, AmalgamRx, Inc.

iSageRx is indicated for the management of type 2 diabetes by calculating appropriate long-acting basal insulin doses for titrating insulin levels based on a clinician-prescribed, individualized titration plan. Currently, there is no published peer-reviewed evidence evaluating iSageRx, beyond an abstract, which permits reasonable conclusions regarding impact on health outcomes (Grdinovac, 2019).

MamaLift Plus™

MamaLift Plus is a prescription-only digital therapeutic designed to provide components of CBT for use in the treatment of mild to moderate postpartum depression. In 2024, MamaLift Plus received clearance for marketing by the FDA for individuals 22 years of age and older diagnosed with mild to moderate postpartum depression, as an adjunct to clinician-managed outpatient care. The mobile or tablet-based application's self-guided, interactive treatment modules are designed for daily use over a period of 8 to 9 consecutive weeks (FDA, 2024).

MamaLift Plus clearance was based on unpublished results from the SuMMER (Supporting Maternal Mental health & Emotional Regulation) clinical trial (NCT05958095). SuMMER was a sham-controlled, RCT which enrolled 141 participants across 33 states. Study participants were randomized 2:1 to MamaLift Plus and treatment as usual (TAU) or the sham control arm (a digital placebo arm plus TAU). The study was powered to enroll 210 study participants with a planned interim analysis to meet a deadline for FDA input; as a result, the study was stopped at the enrollment of 141 participants. The primary outcome was a 4-point change on the Edinburgh Postnatal Depression Scale (EPDS) scale, which is considered a clinically significant change. Two follow-up assessments were planned for week-4 and week-8 (study-end). Report of study outcomes are pending peer-reviewed publication. Several methodological concerns are worth noting: the study was unblinded, treatment as usual was not tracked, and missing data handled was not mentioned in the protocol (missing rates are higher in the sham arm). The long-term benefit of treatment with MamaLift Plus plus TAU on recurrent depression has not been evaluated in studies lasting beyond 8 weeks. The ability of MamaLift Plus to prevent potential depression relapse or recurrent depressive episodes after treatment discontinuation has not been studied.

Mobile Insulin Dosing System (MIDS), Glooko, Inc.

MIDS is indicated for the management of type 2 diabetes by calculating appropriate long-acting basal insulin doses for titrating insulin levels based on a clinician-prescribed, individualized titration plan. Currently, there is no published peer-reviewed evidence evaluating MIDS which permits reasonable conclusions regarding impact on health outcomes.

My Dose Coach, Sanofi, Inc.

My Dose Coach is a smartphone application designed to help users diagnosed with type 2 diabetes titrate their basal insulin according to a clinician-prescribed individualized titration plan. Unnikrishnan (2022) and colleagues conducted a retrospective analysis included 2517 active users; 85% of users were from India, none resided in the US. Two weeks of data was analyzed. Just under 50% of users had high MDC usage and 44% (irrespective of usage frequency) achieved their individual fasting blood glucose target. High use was associated with significantly better fasting blood glucose target achievement and less time to achieve that target compared to the moderate- and low-usage groups (p<0.01 for all). There was no significant difference in hypoglycemia incidence among usage groups. This relatively brief (2 weeks) retrospective trial did not include participants from the US, had limited usage amongst participants and lacked a comparison group.

In 2023, Hermanns and colleagues published results from an open-label, RCT which enrolled 236 individuals diagnosed with type 2 diabetes with a BMI ≥25.0 kg/m2 who were on basal insulin therapy or were initiating basal insulin therapy, and had suboptimal glycemic control (HbA1c >7.5%; 58.5 mmol/mol). Completing participants in the intervention group (n=117) titrated their basal insulin dose using My Dose Coach for 12 weeks. Control group participants (n=119) titrated their basal insulin dose according to a written titration chart. The primary outcome was the baseline-adjusted change in HbA1c at 12 weeks.

Investigators reported a between-group difference of -0.31% (95% CI: 0.01%-0.69%; p=0.04) in favor of the My Dose Coach group. Study outcomes demonstrated a low-magnitude statistically significant difference but not a clinically significant difference in HbA1c after 12 weeks of My Dose Coach use. Further study is warranted to permit reasonable conclusions regarding My Dose Coach's impact on health outcomes.

NightWare™, Apple Watch®

NightWare is a mobile application that exclusively uses Apple's smartwatch motion and heart rate data to detect the occurrence of nightmares and arouses the wearer by vibrating with the intention of interrupting the nightmare without waking the sleeper. Davenport and colleagues (2022) conducted a 30-day, RCT to determine the efficacy of NightWare in 65 Veterans (n=30 in active arm; n=35 in control arm) with impaired sleep secondary to trauma-related nightmares. The primary outcome was the Pittsburgh Sleep Quality Index (PSQI). Other measures included self-reported sleep quality, PTSD/depression symptoms, and quality of life. Individuals in both the active and control arms demonstrated statistically significant improvement on all measures relative to their own baseline measures. However, none of the comparisons between arms reached a statistically significant difference. A post hoc analysis that excluded participants with low frequency usage (<50% of nights) demonstrated a statistically significant (p=0.016) improvement in perceived sleep quality (based on the Pittsburg Sleep Quality Index) amongst the remaining 21 participants in the active arm, relative to 27 control participants. However, in this exploratory analysis of high utilizers, the relevant difference (2.2 points on the PSQI) did not reach the relevant MCID (2.5 points). This trial was of short duration, users exhibited low app usage and results did not demonstrate a clinically meaningful difference in the intent-to-treat population.

Oleena®, Voluntis, Inc.

Oleena received FDA 510K clearance in 2019 as a prescription mobile app designed to help individuals diagnosed with cancer better manage their symptoms as well as enable remote monitoring by care teams. Currently, there is no published peer-reviewed evidence evaluating Canvas Dx which permits reasonable conclusions regarding impact on health outcomes.

Parallel™, Mahana Therapeutics, Inc.

Parallel (formerly known as Regul8) is a Digital program that uses CBT to reduce the severity of symptoms for irritable bowel syndrome (IBS). It is intended to be used together with other IBS treatments to treat adults, 22 years or older, for up to 3 months.

The premise behind Parallel (web-based CBT) was evaluated in the Assessing Cognitive behavioural Therapy for IBS (ACTIB) trial, a three-arm, RCT in which 558 participants were enrolled into either a telephone-delivered CBT (TCBT; n=186) group, web-based CBT (WCBT; n=185) group with minimal therapist support, or treatment as usual (TAU, n=187) (Everitt 2019a). Both intervention groups continued to also receive treatment as usual. The primary outcomes of interest were IBS Symptom Severity Score (IBS-SSS) and Work and Social Adjustment Scale (WSAS) at 12 months. At study end, 27% of the TCBT arm, 73% of the WCBT arm, and 30% of the TAU group were lost to follow-up. Of the remaining study participants, compared with TAU, IBS-SSS and WSAS scores were significantly lower in the TCBT group (both scores p<0.001) and the WCBT group (p=0.002 and p=0.001, respectively) at 12 months. There were no serious adverse reactions to any interventions. The study was limited by a substantial loss to follow-up and the dissimilarities between the interventions in the study and the Parallel application. Also, comparison to in-person CBT is lacking.

Everitt and colleagues (2019b) conducted a 24-month follow-up to the ACTIB trial, at which time, 58% (n=323 of the original 558 participants remained). At 24 months the IBS-SSS score was significantly lower in the TCBT group (p=0.002) relative to TAU but the differences in the WCBT group were not sustained (p=0.33). Similarly, the mean WSAS score was lower in the TCBT group (p<0.001) but differences in the WCBT group fell to marginal significance (p=0.036) relative to the TAU group. Given the continued substantial loss to follow-up and loss in significance in the WCBT group (more comparable to the Parallel application software design than TCBT), the efficacy of the application as an intervention for refractory IBS, remains to be established.

Regulora®, metaMe Health Inc.

Regulora provides gut-directed hypnotherapy for adults 22 years of age and older who have been diagnosed with IBS. Regulora is indicated as a 3-month treatment for individuals with abdominal pain due to IBS and is intended to be used together with other IBS treatments.

In 2023, Berry and colleagues published results of an open-label RCT in which 362 adults with IBS were enrolled to compare the safety and efficacy of Regulora with that of digital muscle relaxation accessed via a mobile app on a smartphone or tablet. The primary endpoint was reduction in self-reported abdominal pain (defined as ≥ 30% reduction from baseline in average daily abdominal pain intensity) during the 4-week follow-up period. Study authors report an improvement in the Regulora group, however no significant difference between the two study groups was found (p=0.54). Further investigation is warranted.

Rejoyn

Rejoyn is a smartphone-based digital therapeutic designed to be used by individuals diagnosed with major depressive disorder (MDD) to administer 6 weeks of CBT and emotion-focused mindfulness therapy (EFMT). Following the initial 6-week treatment period the CBT modules were available for repeat viewing for up to 4 additional weeks. In 2024, Rejoyn received 510K clearance from the FDA for the treatment of MDD as an adjunct to clinician-managed outpatient care for adults ages 22 years and older who are being treated with antidepressant medication (FDA, 2024).

The FDA clearance of Rejoyn was based on unpublished results from the remotely conducted Mirai trial, a multicenter, double-blinded RCT (NCT04770285). The primary objective of Mirai was to evaluate the effectiveness of Rejoyn in reducing depressive symptoms. The study's primary efficacy endpoint was the change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at week-6. Report of study outcomes are pending peer-reviewed publication.

reSET® and reSET-O®, PursueCare

reSET® and reSET-O are mobile device software applications intended to increase retention of individuals with opioid use disorder (OUD) and substance use disorder in outpatient treatment by providing cognitive behavioral therapy, as an adjunct to outpatient treatment, for individuals 18 years or older who are currently under the supervision of a clinician.

ReSET-O was evaluated in a randomized, unblinded, parallel trial conducted in 170 opioid-dependent adults who received supervised buprenorphine treatment paired with a behavior therapy program, with or without the addition of a desktop-based version of reSET-O, which was accessed at the clinic 3 times a week for 30 minutes per visit. At study-end (12 weeks), participants who used the desktop computer version of reSET-O had an overall retention rate of 80 percent compared with 64 percent overall retention rate for those who did not. Use of reSET-O was not shown to decrease illicit drug use or improve abstinence compared to the control group (Christensen, 2014). A secondary analysis of the pivotal study data reported outcomes of treatment retention and abstinence relative to 'treatment as usual' but was hampered by the same study limitations (Maricich, 2020a).

In 2020, Velez and colleagues reviewed retrospective pharmacy and medical claims data from commercial, Medicare and Medicaid databases (2018-2019). Ultimately, 334 study participants were included who activated reSET-O, and were continuously enrolled in their medical plan for at least 4 weeks of the 6-month pre-activation and post-activation periods. Despite the abundance of clinically significant pre- and post-activation measures reported (including but not limited to, inpatient encounters [45 less; p=0.03], emergency department visits [27 less; p=0.25] psychiatry encounters [349 less; p<0.04], case management encounters [176 additional; p=0.59], behavioral health services [111 additional; p=0.12], alcohol and substance abuse services [96 less; p=0.35], and mental health services [61 additional; p=0.10]), some were only marginally statistically significant while most were not significant (i.e., p-value > 0.05), with the exception of 638 less drug test events recorded post reSET-O activation (p<0.001) an outcome that may not be desirable in this clinical scenario. Claims data also revealed of the 240 participants who had pharmacy claims data, pre-/post- activation medication possession ratios increased from 0.73 to 0.82, respectively (p=0.004); however, possession of buprenorphine is unlikely to be a valid surrogate measure for medication adherence. In this real-world clinical scenario, generalizability is lacking (> 80% Medicaid enrollees), mortality data (a crucial outcome in this setting) is not reported and reSET-O's ability to impact health behaviors or clinically relevant outcomes was not demonstrated.

In another pragmatic, retrospective evaluation, Maricich and colleagues (2020b) enrolled 3144 individuals upon their downloading the reSET-O application to their personal device. Engagement and therapeutic use data were collected and analyzed on a population, versus individual, level. Substance use was evaluated using a composite measure of self-reported data collected by reSET-O and urine drug screens which were nonuniformly administered by different clinic sites. When excluding participants with missing data from analysis, the abstinent rate (defined as abstinent in the last 4 weeks of treatment) was observed to be 91%, when missing data was considered 'positive' the abstinence rate was 66%. Just 29% of the study population used reSET-O appropriately and consistently for the first 4 weeks (completed 4 or more modules per week), thus adherence to reSET-O's proper use was low in this very large, real-world cohort. The study outcomes relied on self-report, lacking clinically meaningful measures beyond urine drug screens which were not routinely measured across study sites.

In 2020, the Institute for Clinical and Economic Review (ICER) published an evidence report which included published data, to date, evaluating the reSET-O. ICER concluded, "We found no randomized trials, cohort studies or case series that evaluated the DHTs [digital health technologies] reviewed in this report until after the draft report was released. Recently, two uncontrolled studies suggested potential benefits with reSET-O, but there was a high risk of bias for both studies."

Current data is limited to short-term follow-up, and impact on net health outcomes has not been demonstrated. Few of the published studies assess the use of the reSET-O when used outside of a clinic (for example, when downloaded directly to a personal device such as a mobile phone or tablet).

SleepCheckRx

SleepCheckRx is a mobile software system that screens adults for the risk of moderate to severe OSA by analyzing breathing and snore sounds recorded on an Apple iPhone. Currently there is no peer-reviewed published data on SleepCheckRx which permits reasonable conclusions regarding impact on health outcomes.

SleepioRx

SleepioRx is a digital therapeutic intended for the improvement of poor sleep and the management of insomnia disorder in adults aged 18 years and older, as an adjunct to their usual medical care.

SleepioRx was evaluated in a pivotal 24-week, single-blind RCT to examine the effect of the website or app version on daytime functioning, mental health, and sleep compared to sleep hygiene education (SHE). The trial enrolled 1711 adults who screened positive on *DSM-5* criteria for chronic insomnia disorder, and randomized participants to either SleepioRx (n=853) or SHE (n=858) for up to 12 weeks of treatment. The self-reported demographics reflected a population sample that was 78% female, 91% White and a mean age of 48 years. The SleepioRx arm received 6 sessions of the program, lasting around 20 minutes each. The control group received a web page and materials that could be downloaded by users at their own pace. At 24 weeks, sleep-related quality of life scores measured by the Glasgow Sleep Impact Index favored SleepioRx ($p<0.01$). Non-response rates at 24 weeks for control and SleepioRx arms were 42% and 52%, respectively, a significant difference ($p<0.01$) that threatens the study's internal validity. Investigators state that non-respondent sensitivity analyses were performed but little detail of these analyses were described. Study limitations include limited external validity of the sample, high non-respondent rates, differential participation by study arm and limited reporting on statistical methods used to account for missing data (Espie, 2018).

Table 1. Examples of Practitioner-prescribed, FDA cleared or approved, MSAs (not an all-inclusive list)

Device Name	**Software Developer**	**May Be Considered Medically Necessary**
See above "Discussion" section for more information		
AspyreRx™	Better Therapeutics, Inc	No
BlueStar®Rx	WellDoc®	No
Canvas Dx™	Cognoa, Inc	No
DaylightRx	Big Health, Inc	No
d-Nav Insulin Guidance System®	Hygieia	No
Drowzle™	Resonea	No
EndeavorRx™	Akili Interactive	No
FibriCheck®	Qompium, NV	No
Freespira®	PaloAlto Health Sciences, Inc	No
Halo™ AF Detection System	LIVMOR, Inc	No
Home Vision Monitor® (HVM),	Vital Art and Science, LLC	No
Insulia®	Voluntis, Inc	No
iSageRx	Amalgam Rx, Inc.	No
MamaLift Plus™	Curio Digital Therapeutics Inc,	No

Mobile Insulin Dosing System	Glooko, Inc.	No
My Dose Coach	Sanofi, Inc	No
NightWare™	Apple Watch®	No
Oleena®	Voluntis, Inc	No
Parallel™	Mahana Therapeutics, Inc	No
Regulora®	metaMe Health Inc	No
Rejoyn	Otsuka America Pharmaceutical, Inc.	No
reSET® and reSET-O®	PursueCare, LLC	No
SleepCheckRx	ResApp Health, Inc	No
Sleepio® Rx	Big Health, Inc	No

Definitions

Cognitive behavioral therapy (CBT): A form of talk therapy that has proven effective for a variety of behavioral health issues. CBT focuses on helping individuals identify and modify unhelpful thinking and behavior patterns, fostering resilience and promoting healthier mental processes.

Mobile application (mobile app): Software application that can be executed (run) on a mobile platform (i.e., a handheld commercial off the-shelf computing platform, with or without wireless connectivity), or a web-based software application that is tailored to a mobile platform but is executed on a server.

Mobile platform: Commercial off-the-shelf (COTS) computing platforms, with or without wireless connectivity, that are handheld in nature (e.g., mobile computers such as smart phones, tablet computers, or other portable computers).

Off-the-self: As purchased or as commonly available, without modification or customization.

Over-the-counter: Non-prescription therapeutic intervention.

Software: A set of instructions, data or programs used to operate a computing device and execute specific tasks; a generic term used to refer to applications, scripts and programs.

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Websites for Additional Information

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History

Status	Date	Action
Reviewed	02/20/2025	Medical Policy & Technology Assessment Committee (MPTAC) review. Added DaylightRx, Reset, ResetO, and Sleepio, applications. Revised Description, Discussion/General Information, References, and Website sections.
	01/30/2025	Updated Coding section with 01/01/2025 HCPCS changes, added G0552, G0553, G0554.
Reviewed	08/08/2024	MPTAC review. Revised Discussion/General Information and Reference sections; added MamaLift Plus and Rejoyn applications.
Reviewed	02/15/2024	MPTAC review. Updated Description, Discussion/General Information and Reference sections; added AspyreRx and FibriCheck applications.
Reviewed	02/16/2023	MPTAC review. Updated the Discussion/General Information and Reference sections; added iSageRx, MIDS, My Dose Coach, Oleena and SleepCheckRx applications.
	09/28/2022	Updated Coding section with 10/01/2022 HCPCS changes; revised descriptor for A9291.

Reviewed	02/17/2022	MPTAC review. Updated the Discussion/General Information and Reference sections; added CanvasDx, Home Vision Monitor, Parallel, Regulora, and Somryst applications. Updated Coding section with 04/01/2022 HCPCS changes; added A9291.
Revised	02/11/2021	MPTAC review. Updated the Discussion/General Information and Reference sections. Changed ‘health care’ to ‘healthcare’ in the MN criteria. Added the Halo AF Detection System and Apple’s NightWare to Table 1. (considered NMN). Reformatted Coding section.
	09/11/2020	Updated the Discussion/General Information section, added the EndeavorRx for the treatment of ADHD in children to Table 1. (considered NMN).
New	02/20/2020	MPTAC review. Initial document development.
