Oscar Clinical Guideline: Prescription Digital Therapeutics (PG142, Ver. 2)

Prescription Digital Therapeutics

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Prescription Digital Therapeutics (PDTs) are a novel class of software-driven therapeutic interventions that aim to diagnose, prevent, manage, or treat medical disorders or diseases. They are authorized by the FDA, and their safety and effectiveness are evaluated through clinical trials, with clinical results published in peer-reviewed journals. PDTs can be used independently or in combination with medications, devices, or other treatments to optimize patient care and health outcomes. They are prescribed and initiated by qualified and licensed healthcare practitioners.

Despite the potential benefits and growing interest in PDTs, it is essential to acknowledge the limitations in the current body of evidence supporting their effectiveness. The published peer-reviewed literature on PDTs is limited, with studies often having small sample sizes, short durations, or lacking control groups. Additionally, the rapid pace of technological advancements often outpaces the publication of clinical trial results, creating a gap in the available evidence.

Given the insufficient evidence in the published peer-reviewed literature, the Plan considers Prescription Digital Therapeutics (PDTs) experimental and investigational. Further research, including large-scale, well-designed clinical trials and long-term follow-up studies, is necessary to establish the efficacy of PDTs and provide clear guidance for their integration into clinical practice. Until such evidence becomes available, it is essential for healthcare providers and patients to exercise caution when considering the use of PDTs in treatment plans.

Both PDTs and OTC digital therapeutics harness the power of technology to improve patient care, enhance self-management, and support healthcare providers in delivering personalized treatment plans. However, there is an important distinction between the two, with PDTs having a more rigorous evaluation process and a higher standard of evidence required for their authorization and use.

Table 1a*: Prescription (Rx) Digital Therapeutics (PDTs), i.e., for prescription use only

Prescription DTx Products	**Intended Use/Indications for Use** *(Abbreviated descriptions, please see Table 1b in Appendix for detailed summary)*
AspyreRx by Better Therapeutics Inc.	type 2 diabetes
BlueStar Rx® by Welldoc	type 1 and 2 diabetes
Canvas Dx by Cognoa	Autism Spectrum Disorder (ASD) diagnosis aid for pediatrics
CureSight™ by NovaSight	improve visual acuity of patients with amblyopia
DaylightRx By Big Health	generalized anxiety disorder (GAD)
d-Nav® by Hygieia	type 2 diabetes
Drowzle Pro by Resonea	prescreening tool for obstructive sleep apnea
EndeavorRx® by Akili	attention-deficit/hyperactivity disorder (ADHD)
Halo AF Detection System by LIVMOR	AF detection using photoplethysmography

Home Vision Monitor (HVM), fka myVisionTrack by Vital Art and Science	home vision test for maculopathy
Insulia® by Voluntis	type 2 diabetes
INVU by Nuvo	fetal heart rate and uterine activity monitoring
Leva® by Axena Health	urinary and fecal incontinence
Luminopia One by Luminopia	improve amblyopia vision in children
Mahana IBS by Mahana Therapeutics	Irritable Bowel Syndrome (IBS)
MindMotion GO by MindMaze	physical rehabilitation for adults.
My Dose Coach by Sanofi	type 2 diabetes
Nerivio® by Theranica	migraine
NightWare Kit by NightWare	nightmare relief device for adults
Regulora by metaMe Health	Irritable Bowel Syndrome (IBS)
RelieVRx, fka EaseVRx by AppliedVR	chronic low back pain (CLBP)
Rejoyn by Otsuka Pharmaceutical	Major Depressive Disorder (MDD)
reSET® by Pear Therapeutics	substance use disorder (SUD)
reSET-O® by Pear Therapeutics	opioid use disorder (OUD)
SleepioRx by Big Health	chronic insomnia/insomnia disorder

Somryst® by Pear Therapeutics	insomnia
SparkRx® by Limbix	depression
Tidepool Loop by Tidepool	auto insulin control for diabetes

*Not a complete list.

In contrast, Over-the-Counter (OTC) digital therapeutics are health and wellness apps available to consumers without a prescription. They provide general health information, help track or manage health conditions, and offer support in maintaining a healthy lifestyle. OTC digital therapeutics may not undergo the same level of clinical evaluation or FDA authorization as PDTs, and they often serve as complementary tools rather than primary treatment options. While healthcare professionals may prescribe these technologies, they can often be acquired without a prescription as over-the-counter (OTC) products. As a result, they are generally not covered under a member's insurance plan. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Table 2*: Over-the-Counter (OTC) Digital Therapeutics (DTx), i.e., a prescription is not required

DTx Products	Intended Use
BlueStar®, by Welldoc	type 1 and 2 diabetes
Dario® Blood Glucose Monitoring System, by DarioHealth	type 1 and 2 diabetes
Daylight®, by Big Health	generalized anxiety disorder
Deprexis®, by Orexo	depression
Freespira®#, by Freespira, Inc.	post-traumatic stress disorder (PTSD), panic disorder, and panic attack
HelloBetter® Chronic Pain, by GET.ON Institut für Online Gesundheitstrainings GmbH	chronic pain
HelloBetter® Diabetes and Depression, by	depression in people with diabetes

GET.ON Institut für Online Gesundheitstrainings GmbH	
HelloBetter® Panic, by GET.ON Institut für Online Gesundheitstrainings GmbH	panic disorder with or without agoraphobia
HelloBetter® Stress and Burnout, by GET.ON Institut für Online Gesundheitstrainings GmbH	stress and burnout
HelloBetter® Vaginismus Plus, by GET.ON Institut für Online Gesundheitstrainings GmbH	vaginismus, dyspareunia and genito pelvic pain/penetration disorder (GPPPD)
Kaiku Health, by Kaiku Health	cancer care
Propeller®, by Propeller Health	asthma and chronic obstructive pulmonary disease (COPD)
Sleepio®, by Big Health	insomnia
vorvida®, by Orexo	reduce alcohol use

[#] Permission from a licensed healthcare professional is needed, but a prescription is not required.

[*]Not a complete list.

NOTE: *This Clinical Guideline addresses FDA-cleared or approved clinician-prescribed software apps on mobile devices (e.g. phone, laptop, smartwatch, tablet) for health management with the aim of evaluating, diagnosing, or treating medical conditions or symptoms. It does not cover mobile software not cleared or approved by the FDA, including OTC or consumer-available apps for general wellness or used by healthcare professionals for remote health monitoring.*

Definitions

"**Artificial intelligence (AI)**" involves the integration of computer systems, databases, and advanced algorithms to mimic human capabilities, such as decision-making and problem-solving. Common applications include customer service, facial and voice recognition, and recommendation/search engines. AI is being explored for various clinical purposes, such as detecting medical conditions or diagnosing illnesses based on medical imaging or histopathology (disease-induced changes in cells or tissues). AI is also used to augment the analysis of facial phenotypes related to genetic syndromes.

"**Augmented reality (AR)**" and "**virtual reality (VR)**" employ computer simulation and modeling to enable interaction with an artificial three-dimensional (3D) environment. AR blends digital imagery with

the real world and can be viewed through a camera or display, such as a smartphone or head-mounted or heads-up display (HUD). Users typically wear equipment (gloves, goggles, headset) that provides sensory feedback to the computer based on their movements. AR has been utilized as a surgical training tool for medical students and is being explored to guide surgical techniques by overlaying images onto patients. VR is being investigated as an adjunctive treatment tool for cognitive rehabilitation, enhanced physical therapy, memory improvement, and pain reduction. VR applications for mental health under study include augmenting therapy for anxiety, depression, phobias, and post-traumatic stress disorder.

"**Digital Health Technology (DHT)**" encompasses applications, software, and programs utilized within the healthcare and social care sectors. These technologies can function independently or be integrated with other products such as medical devices or diagnostic tests.

"**Digital Therapeutic (DTx)**" are treatment interventions delivered to patients through high-quality software programs. These interventions aim to treat, manage, or prevent diseases or disorders and can be used independently or alongside medications, devices, or other therapies to enhance patient care and health outcomes.

"**Health Technology Assessment (HTA)**" is a systematic, multidisciplinary evaluation of the properties, effects, and impacts of health technology. The assessment considers social, economic, organizational, and ethical aspects of a health intervention or technology with the primary goal of informing policy decisions.

"**Mobile applications (apps, mobile apps)**" are software programs specifically designed for use on mobile devices like smartphones. Mobile health (mHealth) apps offer a broad range of personal health management options for wellness and chronic conditions (e.g., fitness tracking, meditation guidance, stress reduction, weight management). Mobile medical apps (MMAs) are medical devices that function as mobile apps, meet the definition of a medical device, and either serve as an accessory to a regulated medical device or transform a mobile platform into a regulated medical device. Both MMAs and mHealth apps may incorporate games or use gamification to establish and maintain desired health behaviors.

"**Prescription digital therapeutics (PDTs)**" are a category of digital health products that utilize software applications to treat medical conditions or improve health outcomes. These products require a prescription from a healthcare provider and often engage patients via mobile apps or web platforms. PDTs can be used independently or alongside conventional treatments like medications or therapy.

These digital tools can provide personalized treatment plans, monitor patient progress, and offer real-time feedback.

"**Real-World Data (RWD)**" comprises information about a patient's health status and/or healthcare delivery, routinely gathered from various sources.

"**Real-World Evidence (RWE)**" pertains to the clinical evidence concerning a medical product's usage and potential benefits or risks, derived from the analysis of real-world data. RWE can be produced through various study designs or analyses, including but not limited to, randomized trials, large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective).

"**Software as a Medical Device (SaMD)**" refers to software intended to be used for medical purposes without being part of a hardware medical device. PDTs are a specific category of SaMD that provide therapeutic interventions.

Policy Statement on Prescription Digital Therapeutics (PDTs) Efficacy Information

The Plan recognizes the potential of Prescription Digital Therapeutics (PDTs) in healthcare. PDTs are software-based interventions designed to prevent, manage, or treat medical disorders or diseases. While the FDA has authorized several PDTs, and numerous clinical trials have been conducted, the current body of peer-reviewed literature does not provide sufficient evidence to conclusively support their effectiveness across all applications.

Many studies on PDTs have limitations such as small sample sizes, short durations, lack of control groups, or inconsistent results across different clinical settings. The rapid pace of technological advancements often outpaces the publication of clinical trial results, creating a gap in available evidence. Additionally, the diversity of PDTs in terms of target conditions, platforms, and therapeutic approaches makes it challenging to draw firm conclusions on their overall effectiveness.

Some PDTs have shown promise for specific conditions, but the current evidence base lacks robust long-term outcomes data and comparative effectiveness studies against standard treatments. The Plan will continue to monitor emerging evidence and update this policy as new research becomes available.

Medical Necessity Criteria for Prescription Digital Therapeutics (PDTs)

The Plan acknowledges that some PDTs have demonstrated potential benefits in clinical trials and received FDA authorization. However, current published peer-reviewed literature does not provide sufficient evidence to establish long-term safety, efficacy, and effect on net health outcomes across all PDT applications. Therefore, the Plan does not currently have medical necessity criteria for PDTs.

The Plan will continue to monitor emerging evidence and may update this policy as new research becomes available that demonstrates:

- Long-term safety and efficacy in well-designed clinical trials.
- Comparative effectiveness against standard treatments.
- Sustained benefits in real-world settings.
- Cost-effectiveness.

Individual case reviews may be considered for specific clinical scenarios where standard treatments have been exhausted or are contraindicated.

Experimental or Investigational / Not Medically Necessary

Prescription Digital Therapeutics (PDTs) for any indication or use are considered experimental, investigational, and unproven due to insufficient clinical evidence and peer-reviewed medical literature establishing long-term safety, efficacy, and effect on net health outcomes. This includes but is not limited to all current FDA-authorized PDTs for[1†]:

- ADHD (including EndeavorRx)
- Amblyopia (including CureSight, Luminopia One)
- Anxiety disorders
- Chronic pain management (including RelieVRx)
- Depression (including SparkRx)
- Hypertension management
- Insomnia (including Somryst)
- Irritable Bowel Syndrome (including Mahana IBS)
- Migraine (including Nerivio)
- Obesity and weight management
- Pregnancy monitoring (including INVU)
- PTSD and nightmare disorder (including NightWare)
- Substance use disorders (including reSET and reSET-O)

- Type 1 and 2 diabetes (including BlueStar Rx, AspyreRx, d-Nav, Insulia)
- Urinary/fecal incontinence (including Leva)

⇵*This list is not exhaustive, and the Plan maintains its position that PDTs for any indication or use are considered experimental, investigational, or unproven until:*

1. *Robust clinical evidence demonstrates long-term efficacy.*
2. *Well-designed comparative effectiveness studies show clear benefit over standard treatments.*
3. *Real-world evidence confirms sustainable positive health outcomes.*
4. *Professional society guidelines provide strong recommendations based on high-quality evidence.*

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name	
CPT/HCPCS Codes considered medically necessary if criteria are met: *Please note that the provided list may not cover every digital health product, as some may not have a specific code assigned to them.*	
Code	*Description*
0687T	Treatment of amblyopia using an online digital program; device supply, educational set-up, and initial session
0688T	Treatment of amblyopia using an online digital program; assessment of patient performance and program data by physician or other qualified healthcare professional, with report, per calendar month
0704T	Remote treatment of amblyopia using an eye tracking device; device supply with initial set-up and patient education on use of equipment
0705T	Remote treatment of amblyopia using an eye tracking device; surveillance center technical support including data transmission with analysis, with a minimum of 18 training hours, each 30 days
0706T	Remote treatment of amblyopia using an eye tracking device; interpretation and report by physician or other qualified healthcare professional, per calendar month
0731T	Augmentative AI-based facial phenotype analysis with report

0740T	Remote autonomous algorithm-based recommendation system for insulin dose calculation and titration; initial set-up and patient education
0741T	Remote autonomous algorithm-based recommendation system for insulin dose calculation and titration; provision of software, data collection, transmission, and storage, each 30 days
0770T	Virtual reality technology to assist therapy (List separately in addition to code for primary procedure)
0771T	Virtual reality (VR) procedural dissociation services provided by the same physician or other qualified health care professional performing the diagnostic or therapeutic service that the VR procedural dissociation supports, requiring the presence of an independent, trained observer to assist in the monitoring of the patient's level of dissociation or consciousness and physiological status; initial 15 minutes of intraservice time, patient age 5 years or older
0772T	Virtual reality (VR) procedural dissociation services provided by the same physician or other qualified health care professional performing the diagnostic or therapeutic service that the VR procedural dissociation supports, requiring the presence of an independent, trained observer to assist in the monitoring of the patient's level of dissociation or consciousness and physiological status;each additional 15 minutes intraservice time (List separately in addition to code for primary service)
0773T	Virtual reality (VR) procedural dissociation services provided by a physician or other qualified healthcare professional other than the physician or other qualified healthcare professional performing the diagnostic or therapeutic service that the VR procedural dissociation supports; initial 15 minutes of intraservice time, patient age 5 years or older
0774T	Virtual reality (VR) procedural dissociation services provided by a physician or other qualified healthcare professional other than the physician or other qualified healthcare professional performing the diagnostic or therapeutic service that the VR procedural dissociation supports; each additional 15 minutes intraservice time (List separately in addition to code for primary service)
99091	Collection and interpretation of physiologic data (e.g. ECG, blood pressure, glucose monitoring) digitally stored and/or transmitted by the patient and/or caregiver to the physician or other qualified healthcare professional, qualified by education, training, licensure/ regulation (when applicable) requiring a minimum of 30 minutes of time, each 30 days
99453	Remote monitoring of physiologic parameter(s) (eg, weight, blood pressure, pulse oximetry, respiratory flow Billed once per rate), initial; set-up and patient education on use of episode of care. equipment.

99454	Device(s) supply with daily recording(s) or programmed alert(s) transmission, each 30 days.
99457	Remote physiologic monitoring treatment management services, 20 minutes or more of clinical staff/physician/other qualified health care professional time in a calendar month requiring interactive communication with the patient/caregiver during the month
99458	Remote physiologic monitoring treatment management services, clinical staff/physician/other qualified health care professional time in a calendar month requiring interactive communication with the patient/caregiver during the month; additional 20 minutes.
99199	Unlisted special service, procedure or report [when specified as a mobile-based health management software application]
A9291	Prescription digital behavioral therapy, fda cleared, per course of treatment
A9292	Prescription digital visual therapy, software-only, FDA cleared, per course of treatment
A9999	Miscellaneous DME supply or accessory, not otherwise specified
E1399	Durable medical equipment, miscellaneous [when specified as a mobile-based health management software application]
E1905	Virtual reality cognitive behavioral therapy device (cbt), including pre-programmed therapy software
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 codes considered medically necessary if criteria are met:	
Code	*Description*
	All diagnoses

Appendix

A. Table 1b*: Prescription (Rx) Digital Therapeutics (PDTs), i.e., for prescription use only

Prescription DTx Products	Intended Use/Indications for Use
AspyreRx by Better Therapeutics Inc.	type 2 diabetes AspyreRx is a PDT developed by Better Therapeutics Inc. to address cardiometabolic diseases, with a current focus on adults with type 2 diabetes mellitus (T2DM). This mobile application leverages cognitive behavioral therapy (CBT) principles to foster positive behavioral changes in patients, ultimately aiming to improve glycemic control. AspyreRx operates on the premise that behavior is a learned phenomenon, susceptible to transformation through targeted therapeutic interventions. The app delivers a personalized 90-day treatment program, tailoring its approach to each patient's unique needs and circumstances.
BlueStar Rx® by Welldoc	type 1 and 2 diabetes BlueStar Rx is a tool for healthcare providers and patients aged 18 and older with type 1 or type 2 diabetes. It securely captures, stores, and transmits blood glucose data to help with diabetes self-management. The software analyzes blood glucose test results, supports medication adherence, and provides coaching messages based on real-time data. It is designed for use on mobile phones or personal computers in home or professional healthcare settings. For bolus insulin users with type 1 or 2 diabetes, BlueStar Rx includes a dose calculator. For basal insulin users with type 2 diabetes, it offers an Insulin Adjustment Program (IAP) to calculate appropriate long-acting basal insulin doses. The IAP also calculates dose adjustments for bolus and premixed insulin users with type 2 diabetes, targeting those not achieving glycemic targets. The IAP algorithms are not designed for titrating NPH, regular human insulin, or human premixed insulins. Healthcare providers must activate and configure the IAP with patient-specific parameters. BlueStar Rx is not intended to replace the care provided by a licensed healthcare professional, such as prescriptions, diagnosis, or treatment, and is for Rx use.

Canvas Dx by Cognoa	Autism Spectrum Disorder (ASD) diagnosis aid for pediatrics Canvas Dx is a diagnostic tool that uses an algorithm to analyze data submitted by parents and healthcare providers as an aid in the diagnosis of ASD in pediatric patients. It is not intended to be used as a standalone diagnostic device but as an adjunct to the diagnostic process. The software generates a positive or negative diagnosis based on the data provided. Canvas Dx is designed to be completed in minutes and is readily accessible.
CureSight™ by NovaSight	improve visual acuity of patients with amblyopia The CureSight™ system is an eye-tracking-based technology designed to improve visual and stereo acuity in children aged 4 to under 9 years with amblyopia under dichoptic conditions. The system comprises the CureSight-CS100 device (console and anaglyph glasses) and the CureSight Web-App/Portal. It separates visual stimuli on a monitor into two digital channels, one for each eye, allowing tailored video content to be presented simultaneously to both eyes. During treatment, patients wear dichoptic anaglyph glasses for 90 minutes per day, 5 days a week, for 16 weeks, totaling around 120 hours. The eye tracker monitors each eye's gaze position, and a real-time software algorithm dynamically blurs the central image area for the non-amblyopic eye, forcing the visual system to use the central vision area of the amblyopic eye. The size and intensity of the blur depend on the visual acuity of both eyes. CureSight™ is indicated for improving visual and stereo acuity in amblyopia patients aged 4 to under 9 years, associated with anisometropia and/or mild strabismus, under the guidance of a trained eye care professional. The system is intended for both previously treated and untreated patients as an adjunct to full-time refractive correction like glasses, which should also be worn under the anaglyph glasses during treatment. CureSight™ is intended for prescription use only in an at-home environment.
DaylightRx by Big Health	generalized anxiety disorder (GAD) Daylight is a prescription digital therapeutic designed to treat generalized anxiety disorder (GAD) in adults aged 22 years and older. It delivers cognitive behavioral therapy (CBT) techniques through a mobile application and is intended to be used as an adjunct to usual care under the guidance of a licensed healthcare provider.
d-Nav® by Hygieia	type 2 diabetes The d-Nav® System is designed to help optimize insulin management for adults with Type 2 diabetes. It includes two user-interactive software elements: a patient user interface for entering glucose data and receiving recommended insulin doses, and a Health Care Provider (HCP) interface for setting up the patient software with physician-prescribed insulin instructions.

	The system also contains the d-Nav Get-Dose Library, which calculates the next insulin dose. There are four models of the d-Nav System, varying based on whether glucose measurements are entered manually or automatically, and if the Get-Dose Library Update Insulin Instruction function resides on the device or in the cloud. Use of the d-Nav System is limited to HCPs who have been trained by Hygieia or a Hygieia trained person on its proper use and patient app setup.
Drowzle Pro by Resonea	prescreening tool for obstructive sleep apnea Drowzle Pro, an FDA-cleared standalone software medical device, is designed to record a patient's respiratory patterns during sleep, serving as a prescreening tool for Obstructive Sleep Apnea (OSA). It is compatible with Apple iPhone 7, iPhone 8, or iPhone X running iOS v10.0 or later and is available by prescription only for adults aged 21 and above. The device is intended for home-based screening of adults suspected of having sleep breathing disorders. By recording sleep breathing patterns, Drowzle sends the data to secure cloud servers for analysis and interpretation, along with the user's profile data, to monitor sleep-related health risks over time. The results aid healthcare professionals in determining the need for further diagnosis and evaluation. However, Drowzle is not meant to replace full polysomnography (PSG) when additional parameters like sleep stages, limb movements, or EEG activity are required (FDA, 2022a; Resonea, 2022).
EndeavorRx® by Akili	attention-deficit/hyperactivity disorder (ADHD) EndeavorRx is a digital therapeutic designed to improve attention function in children ages 8-12 years old with primarily inattentive or combined-type ADHD who have a demonstrated attention issue. It uses adaptive algorithms to deliver stimuli that engage the patient and improve their attention function through a video game experience that leverages art, music, storytelling, and reward cycles. The program is delivered through a software-as-medical device (SaMD) that resides on the user's mobile device and can be executed at home. It should be considered as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs. The program inputs are steering and tapping, and the outputs are a visual display of game progression and audio. The program includes features to ensure it is used per the prescribed regimen, including lock-out after the allocated gameplay and reminders to maximize compliance.
Halo AF Detection System by LIVMOR	AF detection using photoplethysmography The LIVMOR Halo AF Detection SystemTM is a medical device software that detects irregular pulse rhythms suggestive of atrial fibrillation (AF) using

	photoplethysmograph (PPG) data. It consists of an algorithm, a patient user interface, and a physician user interface. The system works in conjunction with the LIVMOR Halo+ Home Monitoring SystemTM and a compatible smartwatch to capture PPG data. Designed for intermittent monitoring while the user is at rest at night, the Halo AF Detection System analyzes PPG signals recorded by the Halo Watch. Once the signal quality is assessed, the data is analyzed, and any rhythm suggestive of AF is flagged for physician review through the LIVMOR HeartView physician portal. The system is intended for patients diagnosed with or susceptible to AF, allowing them to monitor and record their pulse rhythms for their physicians to be alerted of any detected irregular heart rhythms. The LIVMOR Halo AF Detection System should be used exclusively with the LIVMOR Halo+ Home Monitoring SystemTM, as it has not been validated for use with other pulse monitoring systems.
Home Vision Monitor (HVM), fka myVisionTrack by Vital Art and Science	<u>home vision test for maculopathy</u> The myVisionTrackTM is a vision function test that can be performed on a commercially available cell phone. It uses a shape discrimination hyperacuity (SDH) vision test to allow patients to monitor their own vision at home and detect significant changes in vision function. It is intended for use in patients with maculopathy, including age-related macular degeneration and diabetic retinopathy, to detect and characterize central 3 degrees metamorphopsia (visual distortion) and aid in monitoring disease progression. The myVisionTrackTM is not intended for diagnosis and diagnosis is the responsibility of the prescribing eye-care professional.
Insulia® by Voluntis	<u>type 2 diabetes</u> Insulia Diabetes Management Companion is a mobile and web-based diabetes management system designed for adult type 2 diabetes patients and their healthcare team. It includes a mobile medical application for patients, a web-based application, and a secure database to store patient data. Insulia provides secure capture, storage, and transmission of blood glucose data and other diabetes-related healthcare information to support effective diabetes management. It includes a basal calculator intended to provide guidance to patients in response to blood glucose measurements and other diabetes-related events. The system is only indicated for use with specific types of insulin and should not be used for intermediate-acting insulin or premixed insulin. Insulia is not intended for use by pregnant women, non-adult patients, or those on a basal-plus or a basal-bolus regimen. The system is intended to be used by healthcare professionals and

	their adult type 2 diabetes patients treated with long-acting insulin analog, but it does not replace the care provided by licensed healthcare professionals.
INVU by Nuvo	fetal heart rate and uterine activity monitoring INVU, developed by Nuvo, is a wearable device designed for continuous monitoring of fetal heart rate, maternal heart rate, and uterine activity during pregnancy. The system consists of a sensor band that transmits data wirelessly to a mobile application. The device utilizes abdominal surface electrodes to capture fetal and maternal electrocardiogram signals, while acoustic sensors record fetal and maternal phonocardiogram signals.
Leva® by Axena Health	urinary and fecal incontinence The Leva Pelvic Health System is a prescription intra-vaginal device that helps women rehabilitate and strengthen their pelvic floor muscles and monitor their progress during pelvic floor muscle training. The device wirelessly facilitates pelvic floor muscle training and transmits real-time performance data through a dedicated mobile application on the patient's mobile device. It is intended for strengthening and rehabilitating weak pelvic floor muscles for the treatment of stress, mixed, and mild to moderate urgency urinary incontinence, as well as chronic fecal incontinence in women. The device interacts with the user via smartphone technology.
Luminopia One by Luminopia	improve amblyopia vision in children Luminopia One is a software-only digital therapeutic that improves visual acuity in amblyopia patients aged 4-7 with anisometropia and/or mild strabismus. It is intended for use with commercially available Head-Mounted Displays (HMDs) and as an adjunct to full-time refractive correction, such as glasses. The device consists of four software-only components: the Mobile Application, the Prescription Manager Portal, the Patient Portal, and the Backend Service Layer. The Mobile Application has two software units, the Video Content Platform and the Therapeutic Algorithms. The Video Content Platform allows patients to select videos to watch, while the Therapeutic Algorithms modify the videos shown to improve vision. The Mobile App is designed to be used with HMDs that serve as a computing platform and a viewing device for dichoptic presentation of the content in the app. Luminopia One is intended for prescription use only, in an at-home environment, and is an adjunct to treatment instructions prescribed by a trained eye-care professional.
Mahana IBS by Mahana Therapeutics	Irritable Bowel Syndrome (IBS) Mahana, fka Parallel is a Prescription Digital Therapeutic (PDT) mobile application that delivers Cognitive Behavioral Therapy (CBT) to patients aged 22 years and older with Irritable Bowel Syndrome (IBS). It is available

	by prescription only and is intended to provide 3 months of CBT as an adjunct to any other IBS treatments. The therapy period is composed of ten sessions, personalized to treat IBS by asking patients questions and getting them to complete interactive tasks. The app is designed to reduce the severity of IBS symptoms and is intended to be used together with other IBS treatments.
MindMotion GO by MindMaze	physical rehabilitation for adults. MindMotion GO is a medical device software designed for physical rehabilitation of adults in the clinic and at home. It is used in combination with the Microsoft Kinect v2 and Leap Motion controller to provide rehabilitation exercises for the upper extremity, trunk, and lower extremity. The software offers audio-visual feedback and graphic movement representations for patients, and provides patient performance metrics for the medical professional. Patient assessment, exercise guidance, and approval by the medical professional are required prior to use.
My Dose Coach by Sanofi	type 2 diabetes My Dose Coach is a mobile application intended for single patient use outside the clinic by a previously diagnosed Type 2 Diabetic who has been prescribed a once-daily long-acting basal insulin. It provides dose suggestions based on the healthcare professional's instructions and the patient's fasting blood glucose levels and hypoglycemia occurrence. The HCP configures the dose instructions for the specific patient and activates the application using the specific patient instructions. The app is not intended to replace the care or advice of a physician or HCP.
Nerivio® by Theranica	migraine The Nerivio is a wearable, battery-powered device that delivers low energy electrical pulses to the upper arm for 45 minutes per treatment, and is controlled by a mobile application via Bluetooth protocol. It is indicated for acute and/or preventive treatment of migraine with or without aura in patients 12 years of age or older and is self-administered by the user immediately after the onset of migraine headache or aura. It is a prescription use, self-administered device for use in the home environment.
NightWare Kit by NightWare	nightmare relief device for adults The NightWare device is a software application used with an Apple Watch and iPhone for patients experiencing nightmares. The watch monitors physiological parameters, and the device provides a vibrotactile stimulation on the patient's wrist to interrupt the nightmare without awakening the patient. The device has a personalized "Stress Index" threshold, calculated for each patient based on an artificial intelligence algorithm. The NightWare digital therapeutic is indicated for the temporary reduction of sleep disturbance related to nightmares in adults 22 years or older who suffer from nightmare disorder or have nightmares from posttraumatic stress disorder (PTSD) and is intended for home use.

Regulora by metaMe Health	Irritable Bowel Syndrome (IBS) Regulora™ is a prescription-only digital therapeutic software designed to treat abdominal pain caused by Irritable Bowel Syndrome (IBS) in adults aged 22 and older. As a Software as a Medical Device (SaMD), Regulora can be accessed and used on a user's mobile device from home. The program offers seven unique gut-directed hypnotherapy treatment sessions over 12 weeks, each lasting around 30 minutes. These sessions aim to induce relaxation and influence somatic control mechanisms through metaphorical storytelling and suggestions. Regulora also includes IBS symptom tracking for patients to share with their doctor. The software is intended for use in conjunction with other IBS treatments over a 3-month period.
Rejoyn by Otsuka Pharmaceutical	Rejoyn is a prescription digital therapeutic (PDT) designed to treat Major Depressive Disorder (MDD) symptoms in adults aged 22 years and older who are on antidepressant medication. It delivers cognitive-emotional and behavioral therapy through a mobile application available on iOS and Android devices. Rejoyn is intended to be used as an adjunct to clinician-managed outpatient care under the guidance of a licensed healthcare provider.
RelieVRx, fka EaseVRx by AppliedVR	chronic low back pain (CLBP) EaseVRx is a prescription-use immersive virtual reality (VR) system designed to provide adjunctive treatment for patients aged 18 and older diagnosed with chronic lower back pain (moderate to severe pain lasting longer than three months). It aims to reduce pain and pain interference associated with chronic lower back pain through in-home use. The system incorporates principles of cognitive behavioral therapy (CBT), other behavioral methods, and mindfulness strategies to treat chronic pain. The device consists of an off-the-shelf VR head-mounted display, a Breathing Amplifier, and AppliedVR-developed software. The Breathing Amplifier is a mechanical attachment that enhances user engagement by amplifying exhalations into the on-board microphone. An optional hand-held controller can be used for navigating the user interface. EaseVRx follows an 8-week treatment program with daily sessions lasting 2-16 minutes (average of 6 minutes). Each week focuses on a specific theme, and daily treatment sessions align with that theme in terms of clinical messaging and content purpose. The program covers themes such as understanding the body, attention and distraction, relaxation strategies, sleep and pain management, and transferring learning outside of VR using acceptance and mindfulness. The system offers various types of VR experiences, utilizing principles of VR design like immersion, gamification, and interactivity for increased session engagement and improved learning. These experiences reinforce different

	pain relief skills and cater to different user preferences.
reSET® by Pear Therapeutics	<u>substance use disorder (SUD)</u> reSET is a 12-week treatment for patients 18 years of age and older with Substance Use Disorder (SUD) who are currently enrolled in outpatient treatment under the supervision of a clinician. It provides cognitive behavioral therapy using the community reinforcement approach (CRA) as well as contingency management and fluency training to enhance learning. The therapy is delivered through 62 interactive modules, taking about 10 to 20 minutes to complete each module. The reSET app requires a mobile operating system and is intended as an adjunct to outpatient treatment of buprenorphine drug therapy, not as a stand-alone therapy for SUD.
reSET-O® by Pear Therapeutics	<u>opioid use disorder (OUD)</u> The reSET-O app is designed to help patients with OUD stay in outpatient treatment by providing a 12-week cognitive behavioral therapy program as an adjunct to other treatments. The app combines contingency management with OUD-specific CBT known as the community reinforcement approach. The app contains 67 interactive modules that are sequentially unlocked as patients progress through the therapeutic. The modules consist of on-demand audio, text, and video and are designed to deliver approximately 30 minutes of treatment. It is recommended that patients complete 4 modules per week.
SleepioRx by Big Health	Sleepio is a prescription digital therapeutic designed to treat chronic insomnia or insomnia disorder in adults aged 18 years and older. It delivers Cognitive Behavioral Therapy for Insomnia (CBT-I) through a mobile application accessible via iOS and Android devices, as well as through a web platform. Sleepio is intended to be used as an adjunct to usual care under the guidance of a licensed healthcare provider. Healthcare providers have access to a dashboard to monitor patient engagement and progress.
Somryst® by Pear Therapeutics	<u>insomnia</u> Somryst is a 9-week digital cognitive behavioral therapy (CBT-I) program for chronic insomnia in patients 22 years or older. It includes six therapeutic cores, with one completed per week, and patient- and clinician-facing dashboards. Somryst is contraindicated in patients with conditions worsened by sleep restriction, untreated obstructive sleep apnea,

	parasomnias, epilepsy, high risk of falls, pregnancy, and unstable or degenerative illness.
SparkRx® by Limbix	<u>depression</u> SparkRx is a digital therapeutic that provides cognitive behavioral therapy as adjunct treatment for symptoms of depression in patients aged 13 to 22 years. The program has 5 levels, completed in 7 weeks, and includes interactive exercises to help patients understand and cope with their depression, as well as earning rewards. At the end of the program, patients make a plan for managing their symptoms after SparkRx. *NOTE: It has not been cleared by the FDA but is available without prescription during the COVID-19 public health emergency.*
Tidepool Loop by Tidepool	<u>auto insulin control for diabetes</u> Tidepool Loop is a mobile application that uses algorithm technology to automatically adjust the delivery of basal insulin based on readings from a compatible integrated continuous glucose monitor (iCGM) and an alternate controller enabled insulin infusion pump. It can also recommend and control the delivery of correction boluses. Tidepool Loop is intended for the management of type 1 diabetes mellitus in patients 6 years of age and older and is for single patient use. The software algorithm is downloaded to a qualified mobile device and requires input of specific therapy settings established with the help of a healthcare provider. Tidepool Loop predicts glucose levels up to 6 hours in the future and adjusts insulin delivery accordingly. The Tidepool Loop Bolus Recommendation Tool (TLBRT) can be used to recommend and deliver correction boluses. The TLBRT is disabled when closed-loop mode is off, and iCGM values are not automatically populated into the glucose field.

*Not a complete list.

B. Overview of the review of clinical evidence.

<u>AspyreRx, by Better Therapeutics Inc.</u>

A randomized controlled trial (RCT) conducted by Hsia et al. in 2022 evaluated AspyreRx's safety and efficacy:

- Study Population: 669 adults with T2DM and HbA1c levels between 7% and <11%.

- Intervention: Participants were randomly assigned to either the AspyreRx group or a control app group, with both receiving standard of care management.
- Primary Outcome: Change in HbA1c after 90 days
- Results:
    - AspyreRx group: -0.28% change in HbA1c.
    - Control group: +0.11% change in HbA1c.
    - Treatment group difference: 0.39% ($P < 0.0001$).

While the initial results are promising, longer-term studies are necessary to establish the sustained benefits of AspyreRx in T2DM management.

BlueStar Rx®, by Welldoc

BlueStar is a digital health platform for type 2 diabetes that offers AI-driven guidance on six crucial dimensions of chronic disease care, including blood pressure, pre-diabetes, and heart failure. In a randomized controlled trial with 163 participants, BlueStar helped improve HbA1c levels by an average of 1.9% compared to a 0.7% improvement in the control group. However, another study involving 223 participants found no significant difference in HbA1c levels between the immediate treatment group and the wait-list control group. BlueStar usage varied significantly across clinical sites, and the app's clinical efficacy remains to be established. Further research is needed to understand patient adherence and site-specific factors impacting app usage.

Canvas Dx, by Cognoa

Canvas Dx is a promising diagnostic aid for ASD but requires further validation through well-designed randomized studies with larger sample sizes from the general population. Abbas et al. (2017) applied machine learning to develop a low-cost, quick, and easy-to-use autism screening tool, which showed improved accuracy compared to standard screening tools. However, the study faced limitations, including confounding factors and limited statistics, necessitating further research. In a 2020 study, Abbas and colleagues evaluated a multi-modular, machine learning-based assessment of autism via a mobile app, which outperformed baseline autism screening assessments. The study had limitations as well, such as its retrospective design, potential for bias, and the need for validation in primary care settings.

CureSight™, by NovaSight

A prospective, multicenter randomized controlled trial (Wygnanski-Jaffe et al., 2022) compared CureSight, a digital binocular, eye-tracking-based home treatment, to traditional eye patching for treating amblyopia in 103 children aged 4 to 9 years. Over 16 weeks, the CureSight group received 90 minutes of treatment five days a week, while the patching group wore an adhesive patch for 2 hours a day, seven days a week. The primary efficacy endpoint was the mean improvement in amblyopic eye visual acuity from baseline to week 16.

Results showed that the mean improvement from baseline in the CureSight group was 0.28±0.13 logMAR and 0.23±0.14 logMAR in the patching group, meeting the primary efficacy endpoint of non-inferiority. Adherence to the regimen was higher in the CureSight group (91% vs 83%). Secondary outcomes, such as stereoacuity and binocular visual acuity improvement, were similar in both groups and not significantly different.

However, there were limitations to the study, including limited generalizability due to 90% of subjects being anisometropic amblyopes, potential bias due to authors' affiliations with NovaSight, Ltd., and the need for a larger sample size and longer-term follow-up to determine sustained improvement in amblyopic eye visual acuity. There were no position statements or guidelines addressing the use of CureSight or digital therapies for amblyopia. The American Academy of Ophthalmology's 2018 Amblyopia Preferred Practice Pattern states that there is inadequate evidence to support binocular therapy for amblyopia treatment.

DaylightRx, by Big Health

The primary evidence supporting DaylightRx comes from the Generalized Anxiety Therapy Effectiveness (GATE) trial, which was a randomized controlled trial (RCT) involving 351 adults diagnosed with GAD. While the GATE trial demonstrated that participants using DaylightRx showed significant improvements in anxiety symptoms and higher remission rates compared to the control group, there are limitations that impact the generalizability and conclusiveness of the findings:

1. The study sample, although moderately sized, may not be sufficient to represent the diverse population of individuals with GAD. Participants were recruited via social media, which may introduce selection bias.
2. The control group received online anxiety psychoeducation, which may not be equivalent to standard care or other active treatments, potentially overestimating the effect size of DaylightRx.
3. The primary endpoint was at 10 weeks post-randomization with a follow-up at 24 weeks. Longer-term efficacy and safety beyond this period remain unestablished.

4. The full peer-reviewed publication of the GATE trial results is not available, limiting the ability to critically appraise the study methodology and results comprehensively.

While DaylightRx has received FDA clearance as a Class II medical device, the current published peer-reviewed literature provides insufficient evidence to conclusively support its effectiveness. Further research is needed, including large-scale, well-designed clinical trials with long-term follow-up, to establish the efficacy and safety of DaylightRx conclusively. This research should address the current limitations by including diverse populations, appropriate control conditions, and transparent reporting of methods and results in peer-reviewed publications.

d-Nav®, by Hygieia

Current evidence regarding the d-Nav Insulin Guidance System is limited to a single study with a small sample size, and long-term data on net health outcomes are lacking. Bergenstal et al. (2019) conducted a multicenter RCT with 181 patients 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 was the average change in HbA1c from baseline to 6 months, and 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 frequency of hypoglycemic events was similar between the groups. The study concluded that automated insulin titration guidance with healthcare provider support provides superior glycemic control compared to healthcare provider support alone. However, these findings need validation with larger sample sizes and longer-term follow-up.

Drowzle Pro, by Resonea

Drowzle Pro, a mobile software system for in-home screening of obstructive sleep apnea (OSA), was evaluated in a longitudinal cohort study involving 59 individuals who received a clinically indicated polysomnography (PSG) in a sleep lab. Researchers compared the Drowzle algorithm to PSG results and found that the algorithm had a sensitivity of 93.7%, specificity of 63.0%, negative predictive value of 89.5%, and positive predictive value of 75.0% in detecting moderate and severe OSA. However, there is a lack of data addressing the impact of screening results on OSA diagnosis and management compared to generally accepted medical practice standards, and studies evaluating real-world application are lacking.

EndeavorRx®, by Akili

EndeavorRx, a game-based therapeutic intervention, aims to improve attention and cognitive function in children aged 8-12 with ADHD. In a randomized controlled trial involving 348 children, participants received either EndeavorRx or a digital control intervention. The study found a significant improvement in attention performance in the EndeavorRx group compared to the control group, with no serious adverse events. However, the study had limitations, such as enrolling only children with an objective baseline deficit in attention and not receiving medical treatment for ADHD. The study also had a short follow-up period of 28 days. It is unclear whether the treatment results in clinically significant outcomes or benefits according to generally accepted standards of medical practice.

Halo AF Detection System, by LIVMOR

The Halo AF Detection System is a wearable smartwatch device developed by LIVMOR for monitoring pulse rhythms to detect atrial fibrillation (AF). In a multi-center clinical trial with 269 patients, the Halo System demonstrated 100% sensitivity in identifying patients with AF and 93% specificity in identifying patients without AF when compared to electrocardiogram (ECG) recordings, the gold standard for measuring heart rhythms.

However, there is currently a lack of published peer-reviewed evidence on the Halo device. A retrospective propensity-matched cohort study published in 2021 found that wearables users had similar pulse rates to non-users, but utilized significantly more healthcare. The study authors emphasized the need for prospective, randomized, long-term evaluations of wearable technology's associations with health outcomes and healthcare use.

Home Vision Monitor (HVM), fka myVisionTrack, by Vital Art and Science

Korot et al. (2021) conducted a cohort survey study of 417 participants to analyze the uptake and engagement of the Home Vision Monitor (HVM) application. The study involved adult patients receiving intravitreal injections for retinal disease at Moorfields Eye Hospital between May 2020 and February 2021. Engagement was positively correlated with comfort with technology, White British ethnicity, visual acuity, a diagnosis of neovascular AMD, and the number of intravitreal injections. It was negatively associated with advancing age.

Several limitations were present in the study, including difficulties in defining relevant metrics such as uptake and engagement, as well as the study cohort being well-educated and technologically familiar.

Additionally, the survey did not include a diverse range of participants with different educational backgrounds.

No published studies have assessed clinically meaningful outcomes, and it remains uncertain whether the treatment improves net health outcomes compared to generally accepted medical practices.

Insulia®, by Voluntis

The Insulia Diabetes Management Companion, developed by Voluntis, has no published studies, but its predecessor, the Diabeo system, was evaluated in the TeleDiab-2 study by Franc et al. (2019). This 13-month randomized controlled trial involved 191 participants with inadequately controlled type 2 diabetes, who were divided into three groups: standard care (n=63), interactive voice response system (n=64), and Diabeo-BI app software (n=64).

At the 4-month follow-up, the telemonitoring groups showed a significantly higher reduction in HbA1c compared to the standard care group ($p<0.002$). Twice as many patients in the telemonitoring groups achieved target fasting blood glucose levels, and insulin doses were titrated to higher levels. No severe hypoglycemia was observed in the telemonitoring groups, and mild hypoglycemia frequency was similar across all groups.

However, the current data is limited to a short evaluation period, and sample sizes for the comparative arms were modest. No clinical outcomes have been reviewed by the FDA, so the cited clinical study does not establish any efficacy claim for Insulia in the United States.

INVU, by Nuvo

A prospective, open-label study conducted by Schwartz et al. in 2022 aimed to validate INVU's uterine contraction detection algorithm:

- Study Design: Two-center investigation.
- Participants: Women with singleton pregnancies at ≥32 weeks' gestation in the first stage of labor.
- Comparison: INVU was evaluated against an intrauterine pressure catheter in a subgroup of participants.
- Results: The positive agreement for contraction detection was 89.0% (1191/1338 contractions).

While these initial results are promising, further validation studies are necessary to fully establish the system's efficacy and reliability in various clinical scenarios.

Leva®, by Axena Health

Leva Pelvic Health System is an FDA-cleared medical device consisting of an intravaginal wand with motion sensors and app-based software for treating urinary incontinence in women. The system aims to strengthen and rehabilitate weak pelvic floor muscles. Patients perform exercises using the leva wand and app for 2.5 minutes twice a day for 8-12 weeks. Exercise data is transmitted to the patient's smartphone and healthcare providers receive summaries and reports for follow-up care.

Rosenblatt et al. (2019) conducted a study with 23 premenopausal women using the leva system for 6 weeks. They found significant improvements in Urogenital Distress Inventory (UDI) scores, Patient's Global Impression of Severity scores, pelvic floor muscle contraction duration, repeated contractions in 15 seconds, and maximum pelvic floor angle. No device-related adverse events were reported.

Weinstein et al. (2022) conducted a randomized-controlled trial comparing the leva system with pelvic floor muscle training (PFMT) alone in 61 women with stress-predominant urinary incontinence. No significant differences were found in UDI scores or Patient Global Impression of Improvement between the intervention and control groups. However, the intervention group experienced significant improvements in Pelvic Organ Prolapse and Colorectal-anal Distress Inventories and Pelvic-Floor-Impact Questionnaire scores, as well as a decrease in daily SUI episodes. This study was stopped prematurely due to device technical considerations.

An Evolving Evidence Review (2023) found little support for the leva Pelvic Health System in treating urinary incontinence in female patients, and no clinical studies compared PFMT with leva to PFMT with other biofeedback devices. No professional society position statements or clinical practice guidelines specifically mentioned the leva Pelvic Digital Health System.

Luminopia One, by Luminopia

Two studies, a pivotal RCT (Xiao et al., 2022) and a pilot study (Xiao et al., 2021), evaluated the efficacy of Luminopia One for treating amblyopia in children. In the phase 3 RCT conducted by Xiao et al. (2022), 105 amblyopic children aged 4 to 7 years were randomized to receive either Luminopia One with glasses (treatment group) or glasses alone (control group). The primary outcome measure was the change in amblyopic eye visual acuity from baseline to 12 weeks.

At 12 weeks, the Luminopia treatment group improved amblyopic eye visual acuity by 1.8 lines compared to the control group, which improved by 0.8 lines. A statistically significant difference in visual acuity improvement was reported as early as 4 weeks. Furthermore, 62% of patients in the treatment group improved by two lines or more in the weak eye, compared to 33% in the control group. No major adverse events were reported, but mild adverse events such as headache, new heterotropias, and worsened VA were noted in 19.6% of children using Luminopia One and 13% of those wearing glasses. Due to the positive results, the trial was terminated early.

No position statements or guidelines specifically addressed the use of Luminopia One or digital therapeutics for amblyopia. The American Academy of Ophthalmology (AAO) Amblyopia Preferred Practice Pattern (2018) stated that there was insufficient evidence to recommend vision therapy techniques or binocular therapy for the treatment of amblyopia.

Mahana IBS, by Mahana Therapeutics

A pilot RCT analyzed Regul8, an early web-based version of Mahana™ for IBS, which underwent technological modifications and content upgrades to become the FDA-cleared digital therapeutic mobile application called Parallel. It is designed to deliver cognitive behavioral therapy (CBT) for patients aged 22 and older diagnosed with IBS, and is available by prescription only for a 3-month treatment, intended to reduce symptom severity when used alongside other IBS treatments.

The premise behind Parallel was evaluated in the Assessing Cognitive Behavioural Therapy for IBS (ACTIB) trial, a three-arm RCT involving 558 participants. The trial compared telephone-delivered CBT (TCBT), web-based CBT (WCBT) with minimal therapist support, and treatment as usual (TAU). At 12 months, both TCBT and WCBT groups showed significantly lower IBS Symptom Severity Score (IBS-SSS) and Work and Social Adjustment Scale (WSAS) scores compared to TAU, but the study was limited by substantial loss to follow-up and dissimilarities between the interventions and the Parallel application.

A 24-month follow-up to the ACTIB trial found that the improvements in IBS-SSS and WSAS scores for the TCBT group were maintained, but the differences in the WCBT group were not sustained. Given the continued substantial loss to follow-up and the loss of 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.

A Hayes Evolving Evidence Review concluded that while a large body of evidence exists evaluating CBT for IBS generally, and several large RCTs evaluate an earlier website-delivered version of Mahana IBS (called Regul8), these resources are of unknown relevance to the current mobile application version. Clinical studies specifically examining Mahana IBS for use on mobile phones or tablets are necessary before conclusions can be drawn about its effectiveness.

MindMotion GO, by MindMaze

There is no published peer-reviewed evidence for MindMotion™GO, a telerehabilitation program for stroke survivors. As a result, it is unclear how it compares to other telerehabilitation programs, in-clinic programs, or traditional physical therapy in terms of effectiveness or safety. The information available on the manufacturer's website and in regulatory documentation is limited, and no guidelines related to MindMotion GO were identified. Developed by MindMaze, MindMotion GO is an FDA-cleared medical device software used with Microsoft Kinect v2 and Leap Motion controller to support the physical rehabilitation of adults in various settings. The software employs game-based digital therapies, audio-visual feedback, and performance metrics, with individual assessment and guidance from healthcare professionals required prior to use.

My Dose Coach, by Sanofi

Tamez-Perez et al. (2021) conducted a noncomparative, prospective, single-arm study to evaluate the safety and effectiveness of a Prescription Digital Therapeutic (PDT) app for managing Type 2 Diabetes Mellitus (T2DM) in 158 patients. At the 4-month follow-up, 141 patients completed the study, with a mean reduction in HbA1c of 1.97% from baseline, which was considered statistically significant. Over half (58.9%) of the patients achieved the predefined glycemic target within 66 days. The results suggest improvements in HbA1c and patient well-being. However, the study has limitations, including being single-center, lacking a control or comparator group, and having insufficient follow-up to establish long-term outcomes.

Nerivio®, by Theranica

Grosberg et al. (2021) conducted a single-arm study assessing the efficacy and safety of Remote Electrical Neuromodulation (REN) in 91 patients with chronic migraine. Primary outcomes showed 59.3% experienced pain alleviation and 20.9% experienced pain removal. However, the study was limited due to the lack of a control or comparator group.

Hershey et al. (2021) compared REN's efficacy to standard-care medications in treating migraines in 35 adolescents. The study found that REN achieved pain freedom and pain relief in more participants than medications. However, larger-scale, blinded comparative-effectiveness and tolerability studies are needed.

Moisset et al. (2020) conducted a systematic review and meta-analysis of RCTs on neurostimulation methods for treating migraines, including two Nerivio Migra-based REN studies. The meta-analysis found Nerivio was associated with a higher likelihood of pain-free status at 2 hours post-treatment than sham, but no other outcomes were analyzed, and no comparisons with other active treatments were made. Larger, well-conducted trials with longer follow-ups are needed.

A Hayes Evolving Evidence Review study (2021) found minimal support for using Nerivio Migra to treat acute migraine attacks. However, the American Headache Society's consensus statement provided weak support for using Nerivio for managing acute migraine episodes, suggesting that patients with migraine may be treated with neuromodulatory devices.

NightWare Kit, by NightWare

Davenport and Werner (2023) conducted a randomized sham-controlled clinical trial with 65 veterans with trauma-related nightmares. In the "high usage" subsample, the Active condition showed significantly greater improvement compared to Sham on the PSQI (4.1 vs 1.9; P = .016, d = 0.72) and NWL (6.1 vs 2.7; P = .002, d = 0.94).

Currently, there is a lack of published peer-reviewed evidence available. The FDA approval was based on a 30-day randomized sham-controlled trial with 70 patients. The study showed improvements in sleep quality for those using NightWare compared to the sham group, with no changes in suicidality or sleepiness. However, more extensive research and peer-reviewed evidence are needed to support the device's efficacy.

Regulora, by metaMe Health

Regulora, developed by metaMe Health Inc., is an FDA-cleared prescription-only digital therapeutic software designed to treat abdominal pain due to irritable bowel syndrome (IBS). Accessible through the user's mobile device, it provides behavioral therapy through gut-directed hypnotherapy for patients aged 22 and older diagnosed with IBS. Regulora is indicated as a 3-month treatment and is intended to be used in combination with other IBS treatments. Currently, there is no published peer-reviewed evidence evaluating the efficacy of Regulora.

Rejoyn, by Otsuka Pharmaceutical

The Mirai trial, a multicenter, randomized, double-blind, controlled study, evaluated the efficacy of Rejoyn, a prescription digital therapeutic for major depressive disorder (MDD). The study involved 386 adults with MDD who were on antidepressant therapy, randomly assigned to either Rejoyn (n=194) or a sham control application (n=192) for 6 weeks.

The primary outcome, measured by the Montgomery-Åsberg Depression Rating Scale (MADRS), showed a statistically significant improvement in the Rejoyn group compared to the sham group in the Intent-to-Treat (ITT) population at Week 6 (mean change difference: -2.12 points, p=0.0211). Secondary outcomes, including the Patient Health Questionnaire-9 (PHQ-9) and Clinical Global Impression-Severity Scale (CGI-S), also demonstrated significant improvements in the Rejoyn group. Notably, no side effects were assessed as related to Rejoyn during the trial.

- While statistically significant, the average between-group difference in MADRS scores was 2.12 points, which is less than the 8 points defined as clinically meaningful.

While Rejoyn has received clearance from the U.S. Food and Drug Administration (FDA) as a Class II medical device, the current published peer-reviewed literature provides insufficient evidence to conclusively support its effectiveness.

RelieVRx, fka EaseVRx, by AppliedVR

The study evaluating EaseVRx (now known as RelieVRx) for the treatment of chronic low back pain (cLBP) was a single-cohort, double-blinded, cross-sectional, placebo-controlled, randomized clinical trial. The study enrolled 188 subjects with cLBP, who were randomly assigned to either the EaseVRx treatment group or a sham group. The treatment group received EaseVRx devices and 3-D YR cognitive behavioral-based treatment, while the sham group received YR devices displaying 2-D non-immersive nature footage with neutral music.

The primary effectiveness endpoints were average pain intensity and pain interference with activity, mood, sleep, and stress at eight weekly time points during the eight-week treatment phase. Results from the study showed that 66% of EaseVRx participants and 41% of sham participants achieved a reduction of >30% in pain intensity. For pain interference with activity, mood, sleep, and stress, 71%, 74%, 70%, and 76% of EaseVRx participants, respectively, achieved a reduction of >30%, while 56%, 60%, 60%, and 63% achieved a reduction of >50%.

No participants reported adverse events of any type during the trial. Seven (9.7%) participants from the EaseVRx group and 5 (6.7%) participants from the sham group reported experiencing nausea and motion sickness during the treatment phase, while 15 (20.8%) participants from the EaseVRx group and 4 (5.3%) participants from the sham group reported discomfort with the headset. These adverse events were common and temporary and resolved by discontinuing use or adjusting the device.

EaseVRx is indicated for patients aged 18 and older. However, complete data from patients aged 18-22 was not available, so it is unclear whether there is enough data to support effectiveness in this population.

Based on the results of the study, it can be concluded that EaseVRx showed a clinically meaningful improvement in the treatment of cLBP compared to the sham group. However, given that the study was a single-cohort, cross-sectional study with a relatively small sample size, additional well-designed and large-scale clinical trials are needed to further evaluate the safety and effectiveness of EaseVRx for the treatment of cLBP. As a result, the Plan considers EaseVRx (now known as RelieVRx) experimental and investigational.

reSET®, by Pear Therapeutics

The study by Campbell et al. (2014) evaluated the effectiveness of the Therapeutic Education System (TES), an internet-delivered behavioral intervention with motivational incentives, in the treatment of substance abuse disorder. The study was conducted with 507 adult men and women who were randomly assigned to receive 12 weeks of either treatment as usual (TAU) or TAU plus TES, which replaced 2 hours of standard therapy per week. TES consisted of 62 interactive computer modules with strategies for obtaining and maintaining abstinence and prize-based incentives tied to abstinence and treatment adherence. The primary outcomes were abstinence from drugs and excessive drinking and time to dropout. The results showed that the TES group had a lower dropout rate and a higher abstinence rate, especially among participants who had a positive drug or alcohol screening at the start of the study. The authors recommend further research to assess the effectiveness of TES in non-specialty settings and to differentiate the impacts of the community reinforcement approach and contingency management aspects of TES.

reSET-O®, by Pear Therapeutics

ReSET-O is an FDA-cleared software application that provides cognitive behavioral therapy for opioid use disorder as an adjunct to outpatient treatment that includes buprenorphine and contingency

management. The therapy is based on the Community Reinforcement Approach (CRA) and requires a prescription from a licensed healthcare provider for patient use. In a 12-week clinical trial of 170 opioid-dependent adults, reSET-O was found to increase retention in treatment (82.4% retention rate) compared to buprenorphine treatment and contingency management alone (68.4%). Maracich et al. (2021) conducted a secondary analysis of 170 adult participants and found that adding a digital therapeutic to treatment-as-usual (buprenorphine maintenance therapy, clinician interaction, and contingency management) resulted in significantly greater odds of opioid abstinence (77.3%) and lower risk of leaving treatment compared to treatment-as-usual alone (62.1%). In a real-world analysis of 3144 individuals, the abstinent rate was observed to be 66% when including patients with missing data as positive and 91% when excluding patients with missing data. The study found that high engagement with therapy was positively associated with abstinence and retention in treatment.

The 2020 ICER evidence report states that there is no direct, peer-reviewed evidence of the effectiveness of digital health technologies like reSET-O in relevant populations, and outcomes of medication-assisted therapy combined with DHTs are comparable to MAT alone. Though two recent uncontrolled studies suggested potential benefits with reSET-O, they carry a high risk of bias.

The evidence findings suggest that reSET-O, when added to buprenorphine treatment and contingency management, showed no significant decrease in illicit drug use but demonstrated a statistically significant increase in patient retention rates. While some studies indicate potential benefits with reSET-O, there are limitations such as a single study site, small population, and high risk of bias. More research is needed to evaluate the generalizability and effectiveness of reSET-O in real-world settings.

SleepioRx, by Big Health

The primary evidence supporting SleepioRx comes from the CrEDIT trial, a randomized controlled trial involving 336 adults with insomnia disorder. While the trial demonstrated statistically significant improvements in insomnia symptoms for the SleepioRx group compared to the control group, several limitations impact the generalizability and conclusiveness of the findings:

1. Although the sample size was moderate, participants were recruited via social media, which may introduce selection bias. The study population may not adequately represent the diverse population of individuals with insomnia disorder.
2. The control group received online sleep hygiene education, which may not be equivalent to standard care or other evidence-based treatments, potentially overestimating the effect size of SleepioRx.

3. The primary endpoint was at 10 weeks post-randomization with follow-up at 24 weeks. Long-term efficacy and safety beyond this period remain unestablished.
4. As of the current date, the full peer-reviewed publication of the CrEDIT trial results is not available, limiting the ability to critically appraise the study methodology and results comprehensively.

While SleepioRx has received clearance from the U.S. Food and Drug Administration (FDA) as a Class II medical device, the current published peer-reviewed literature provides insufficient evidence to conclusively support its effectiveness. Further research is needed, including large-scale, well-designed clinical trials with long-term follow-up, to establish the efficacy and safety of SleepioRx conclusively. Future studies should address current limitations by including diverse populations, appropriate control conditions, and transparent reporting of methods and results in peer-reviewed publications.

Somryst®, by Pear Therapeutics

Two studies have been conducted to evaluate the effectiveness of an online self-help insomnia program, Somryst, in reducing depression symptoms and improving sleep in individuals with chronic insomnia. In the first study by Christensen et al. (2016), 1149 participants with insomnia and depression symptoms were randomly assigned to either receive SHUTi (a 6-week online insomnia program based on cognitive behavioral therapy for insomnia) or HealthWatch (an interactive, attention-matching, internet-based placebo-controlled program). The results showed that SHUTi recipients had significantly lower depression symptoms compared to HealthWatch recipients at both 6 weeks and 6 months. No adverse events were noted. The authors concluded that online CBT-I is a practical and effective approach to reducing depression symptoms.

In the second study by Ritterband et al. (2017), 303 adults with chronic insomnia were randomly assigned to either receive SHUTi or an online patient education program. The results showed that the overall group x time interaction was significant for all primary sleep outcomes, favoring the SHUTi group. Treatment effects were sustained at the 1-year follow-up with 56.6% of participants reaching remission status and 69.7% deemed treatment responders. The authors concluded that internet-delivered CBT-I may play a crucial role in providing effective behavioral treatments for insomnia. However, it is important to note that the studies have limitations such as small sample sizes and high attrition rates, and the results may not be generalizable to a wider population.

A Hayes Evolving Evidence Review concluded there is moderate evidence supporting Somryst in the treatment of insomnia, noting "Clinical studies showed greater reduction in symptoms of chronic insomnia with Somryst than sham (1 RCT) and online patient education (3 RCTs)."

Additionally, the DREAM study provides promising real-world evidence supporting the effectiveness of Somryst in delivering cognitive-behavioral therapy for insomnia (CBT-I). The study demonstrated significant and sustained reductions in insomnia severity, depression, and anxiety symptoms, with large effect sizes comparable to those observed in randomized controlled trials (RCTs). However, while the results align with existing evidence supporting CBT-I as the first-line treatment for chronic insomnia, limitations such as the lack of a comparator group, moderate adherence rates, and fewer patients achieving full remission compared to RCTs highlight the need for further research. These findings suggest that Somryst is a valuable tool for addressing insomnia, particularly in populations with limited access to in-person therapy, but it may not yet meet the threshold to be considered a proven standard of care.

SparkRx®, by Limbix

Limbix SparkRx is a 5-week, self-guided digital therapeutic application designed to treat depressive symptoms in adolescents. A virtual randomized controlled trial (RCT) was conducted to evaluate its clinical effectiveness compared to a control app. 121 adolescents aged 13-21 with moderate to severe depression were randomly assigned to use either SparkRx or the control app for five weeks. The participants and their guardians completed pre and post-intervention questionnaires to evaluate depression and anxiety symptoms and global health, and participants completed weekly in-app PHQ-8 assessments. Results showed that participants who received SparkRx showed a clinically meaningful reduction in depression symptoms, with 24% showing a treatment response and 17% in remission. For participants who consistently engaged with the program, SparkRx led to a statistically significant reduction in depression symptoms compared to the control group ($p=0.023$) and a higher remission rate of 21% compared to 4% for the control group. Adherence to SparkRx was high, with a mean participant adherence of 63.5% of 5 expected program modules. No participants experienced serious adverse events or unanticipated adverse effects. SparkRx is not cleared or approved by the US FDA and is not intended to be used without supervision of a healthcare provider or as a substitute for any treatment or medication. It is intended to provide a neurobehavioral intervention in patients 13-22 years of age as an adjunct treatment for depression symptoms.

The Plan considers Limbix SparkRx as experimental and investigational because the product has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The claims made regarding

the safety and efficacy of SparkRx have not been validated by the FDA. The recent virtual randomized controlled trial (RCT) conducted to evaluate the clinical effectiveness of SparkRx as a treatment for depressive symptoms during the COVID-19 pandemic showed a reduction in depression symptoms in participants who received SparkRx, but the results of the intention-to-treat analysis comparing SparkRx to the control group were not significant. Additionally, the high engagement with SparkRx was noted, but the safety of the product has not been fully established. Therefore, the Plan considers SparkRx to be experimental and investigational until further research and FDA clearance or approval can validate its safety and efficacy as a treatment option for depression.

Tidepool Loop, by Tidepool

Tidepool Loop is a medical device that is designed to help manage insulin delivery for people with type 1 diabetes. An observational study was conducted by the Jaeb Center for Health Research in collaboration with clinical research centers and Tidepool to collect data on the do-it-yourself (DIY) Loop system. The study enrolled 1,127 participants diagnosed with type 1 diabetes and collected data on the efficacy, safety, usability, and quality of life/psychosocial effects of the DIY Loop System. The data was collected continuously and uploaded automatically from a user's own iPhone and analyzed by the Jaeb Center for Health Research.

The results of the study showed that the use of DIY Loop improved the mean time-in-range (70-180 mg/dL) and decreased the mean HbA1c levels in the participants. The incidence of severe hypoglycemia and diabetic ketoacidosis was also found to be lower in participants using the DIY Loop compared to before using the device. Participants reported highly positive psychosocial and quality of life outcomes associated with the use of DIY Loop.

However, it is important to note that the study included participants who may not be part of the intended user population and used DIY Loop settings that are not possible in Tidepool Loop. Additionally, the results do not necessarily apply to the commercially available Tidepool Loop device, which has specific design changes to enhance safety.

Based on the limited evidence available, the Plan considers Tidepool Loop to be experimental and investigational. Further research and data are needed to determine the long-term efficacy, safety, and overall impact of the device on health outcomes in the intended user population.

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