Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Digital Health Technologies: Therapeutic Applications

Description/Background

Digital health technologies are broad terms that encompass categories such as mobile health, health information technology, wearable devices, telehealth and telemedicine, and personalized medicine. These technologies span a wide range of uses, from applications in general wellness to applications as a medical device, and include technologies intended for use as a medical product, in a medical product, as companion diagnostics, or as an adjunct to other medical products (devices, drugs, and biologics). The scope of this review includes only those digital technologies that are intended to be used for therapeutic application and meet the following 3 criteria: 1) Must meet the definition of "Software as a medical device" which states that software is intended to be used for a medical purpose, without being part of a hardware medical device or software that stores or transmits medical information. 2) Must have received marketing clearance or approval by the U.S. Food and Drug Administration (FDA) either through the *de novo* premarket process or 510(k) process or pre-market approval and 3) Must be prescribed by a healthcare provider.

The FDA article summarizes that device software functions includes mobile medical applications (FDA,2022)[1]. The widespread adoption and use of software technologies is opening new and innovative ways to improve health and health care delivery. Software functions that meet the definition of a device may be deployed on mobile platforms, other general-purpose computing platforms, or in the function or control of a hardware device. The FDA's policies are independent of the platform on which they might run, are function-specific, and apply across platforms. The term "software functions" includes mobile applications (apps).Mobile apps can help people manage their own health and wellness, promote healthy living, and gain access to useful information when and where they need it. These tools are being adopted almost as quickly as they can be developed. Users include health care professionals, consumers, and individuals. The FDA encourages the development of mobile

medical apps (MMAs) that improve health care and provide consumers and health care professionals with valuable health information. The FDA also has a public health responsibility to oversee the safety and effectiveness of medical devices, including mobile medical apps.

Scope of Review

Software has become an important part of product development and is integrated widely into digital platforms that serve both medical and non-medical purposes. The 3 broad categories of software use in medical devices are:

1. Software used in the manufacture or maintenance of a medical device (eg, software that monitors x-ray tube performance to anticipate the need for replacement),
2. Software that is integral to a medical device or software in a medical device (eg, software used to "drive or control" the motors and the pumping of medication in an infusion pump),
3. Software, which on its own is a medical device referred to as "Software as a Medical Device" (SaMD) (eg, software that can track the size of a mole over time and determine the risk of melanoma).

The International Medical Device Regulators Forum, a consortium of medical device regulators from around the world led by the U.S. Food and Drug Administration (FDA) defines SaMD as "software that is intended to be used for one or more medical purposes that perform those purposes without being part of a hardware medical device".[2] Such software was previously referred to by industry, international regulators, and health care providers as "standalone software," "medical device software," and/or "health software," and can sometimes be confused with other types of software.

The scope of this review includes only those digital technologies that are intended to be used for therapeutic application and meet the following 3 criteria:

1. Must meet the definition of "Software as a medical device" (SaMD) which states that software is intended to be used for a medical purpose, without being part of a hardware medical device or software that stores or transmits medical information.
2. Must have received marketing clearance or approval by the U.S. FDA either through the *de novo* premarket process or 510(k) process or pre-market approval and,
3. Must be prescribed by a healthcare provider.

BCBSA Evaluation Framework for Digital Health Technologies

SaMDs, as defined by the FDA, are subject to the same evaluation standards as other devices; the Blue Cross and Blue Shield Association Technology Evaluation Criterion are as follows:

1. The technology must have final approval from the appropriate governmental regulatory bodies.
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
3. The technology must improve the net health outcome.[a]
4. The technology must be as beneficial as any established alternatives.
5. The improvement must be attainable outside the investigational settings.[b]

[a] The technology must assure protection of sensitive patient health information as per the requirements of The Health Insurance Portability and Accountability Act of 1996 (HIPAA).
[b] The technology must demonstrate usability in a real-world setting.

Other regulatory authorities such as the United Kingdom's National Institute for Health and Care Excellence (NICE) have proposed standards to evaluate SaMD. [3]

RelieVRx
The RelieVRx program is a prescription-use immersive virtual reality system intended to provide adjunctive treatment based on cognitive behavioral therapy skills and other evidence-based behavioral methods for patients (age 18 and older) with a diagnosis of chronic lower back-pain (defined as moderate to severe pain lasting longer than three months). The device is intended for in-home use for the reduction of pain and pain interference associated with chronic lower back pain.

Freespira®
Freespira is intended for use as a relaxation treatment for the reduction of stress by leading the user through guided and monitored breathing exercises. The device is indicated as an adjunctive treatment of symptoms associated with panic disorder and/or PTSD, to be used under the direction of a healthcare professional, together with other pharmacological and/or non-pharmacological interventions.

NightWare(TM)
The NightWare is a therapeutic platform using a proprietary AppleWatch® application. The app learns the wearer's sleep patterns and customizes treatment to the individual. The app monitors the wearer's heart rate and movement while sleeping and arouses the wearer with a vibration alert when a stress threshold is reached so as not to awaken the individual. Users wear the watch only while sleeping and not during the day. NightWare is an FDA-cleared medical device with a Breakthrough Device designation and is indicated for the reduction of sleep disturbance associated with nightmares in adult patients 22 years of age or older who suffer from nightmare disorder or have nightmares from post-traumatic stress disorder (PTSD). Nightware is not a standalone therapy for PTSD. The device should be used in conjunction with prescribed medications for PTSD and other recommended therapies for PTSD-associated nightmares and nightmare disorder, according to relevant consensus guidelines. Nightware is intended to be used under the supervision of a healthcare provider.

Regulatory Status

Digital Health Therapeutics that meet the current scope of review are shown in Table 1.

Table 1. Digital Health Therapeutics

Application	Manufacturer	FDA Cleared Indication	Description	FDA Product Code	FDA Marketing Clearance	Year
Freespira® (Canary Breathing System)	Freespira (previously PaloAlto Health Sciences)	Freespira is intended for use as a relaxation treatment for the reduction of stress by leading the user	It is a small breathing sensor with a tablet that is used twice a day for 17 minutes. Individuals are trained to use the Sensor with the Mobile App to measure and	HCC, CCK	K131586, K180173	2013, 2018

		through guided and monitored breathing exercises. The device is indicated as an adjunctive treatment of symptoms associated with panic disorder and/or PTSD, to be used under the direction of a healthcare professional, together with other pharmacological and/or non-pharmacological interventions.	display their EtCO2 level and RR and how different breathing habits affect EtCO2 levels.[11]			
NightWare(TM)	NightWare, Inc	The NightWare digital therapeutic is indicated to provide vibrotactile feedback on an Apple Watch based on an analysis of heart rate and motion during sleep 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 PTSD. It is intended for home use.	The NightWare is a therapeutic platform using a proprietary AppleWatch® application. The app learns the wearer's sleep patterns and customizes treatment to the individual. The app monitors the wearer's heart rate and movement while sleeping and arouses the wearer with a vibration alert when a stress threshold is reached so as not to awaken the individual. Users wear the watch only while sleeping and not during the day. NightWare is an FDA-cleared medical device with a Breakthrough Device designation and is indicated for the reduction of sleep disturbance associated with nightmares in adult patients 22 years of age or older who suffer from nightmare disorder or have nightmares from post-traumatic stress disorder (PTSD). Nightware is not a standalone therapy for PTSD. The device should be used in conjunction with prescribed medications for PTSD and other recommended therapies for PTSD-associated nightmares and nightmare disorder, according to relevant consensus guidelines. Nightware is intended to be used under the supervision of a healthcare provider.		Break through device designation	2020
AppliedVR, Inc. Developed by RelieVRx formally known as EaseVRx	RelieVRx.	AppliedVR, Inc[15,24] Developed by RelieVRx by Inc. Per the manufacturer, RelieVRx was granted FDA breakthrough status on 3/3/21 for the first de novo FDA authorized immersive virtual reality medical device for home use indicated for the treatment of chronic low back pain.	RelieVRx is a Class II medical device, available only by prescription, that consists of a modified proprietary Pico G2 4G VR headset and a patented Breathing Amplifier™ to allow integration of bio-enabled immersive experiences, and preloaded software. The device is locked so it can only be used for treatment of the specified clinical indication. The device delivers a clinically based	QRA	De Novo Classification	2021

			multimodal pain self-management program incorporating evidence-based principles of Cognitive Behavioral Therapy and other neuroscience based behavioral health methods to reduce pain intensity and pain interference with daily activities, sleep, mood, and stress for patients diagnosed with moderate to severe chronic low back pain. The device engages all four major regions of the brain to address maladaptive neuroplastic changes associated with chronic pain. RelieVRx therapy is administered daily as a 3–16-minute module (averaging 7 minutes per day) over the course of 56 days. The headset delivers the 3-dimensional 360° multimodal pain self-management curriculum and is tested to meet American National Standards Institute (ANSI) medical device standards.			

EtCO2: exhaled carbon dioxide; FDA: U.S. Food and Drug Administration; PTSD: post-traumatic stress disorder; RR: respiration rate; SaMD: software as a medical device.

Medical Policy Statement

The use of Freespira is considered **experimental and investigational** for all indications including treatment of panic disorder and/or post traumatic stress disorder.

The use of NightWare is considered **experimental and investigational** for all indications including treatment of nightmare disorder or nightmares from PTSD.

The use of RelieVRx is considered **experimental and investigational** for all indications including treatment of chronic lower back pain.

Inclusionary and Exclusionary Guidelines

NA

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

NA

Other codes (investigational, not medically necessary, etc.):

E1905* A9291 A9292

*E1905 Ex: RelieVRx

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Panic Disorder and Post-Traumatic Stress Disorder

Clinical Context and Therapy Purpose

Panic disorder is an anxiety disorder associated with marked impairment in social and occupational functioning, significant impact on quality of life, and high utilization of health care services.[4] Fearful interpretation of bodily symptoms such as tachycardia, shortness of breath, chest tightness, and dizziness with catastrophic beliefs is the core of the diagnosis and differentiates it from other anxiety disorders. Many individuals with panic disorder

hyperventilate and it has been suggested that respiratory abnormality associated with panic disorder may be due to a hypersensitivity to carbon dioxide (CO_2). Based on the recognition of subtle respiratory irregularities associated with hyperventilation in individuals with panic disorder, and CO_2 sensitivity, Meuret et al. (2008) developed a breathing intervention focused on normalizing both exhaled carbon dioxide levels (ETCO2) and respiratory rate. [5] The protocol provided breath-to-breath feedback of ETCO2, while modeling paced breathing at 4 different respiratory rates. Administered as twice daily, 17-min sessions over a 4-week period, the authors reported that by study end, 86% of subjects reported zero weekly panic attacks; an improvement that was durable over time, as 73% reported zero weekly attacks 1-year post-treatment. Freespira incorporates this protocol in their approach to managing panic disorder.

Post-traumatic stress disorder (PTSD) is marked by symptoms of hyperarousal, difficulties with emotional regulation, negative affect, and autonomic dysfunction.[6] Carbon dioxide hypersensitivity may be responsible for mediating some PTSD symptoms as CO_2 challenge tests in individuals with established PTSD have been shown to provoke a panic attack.[7,8] Since the characteristic of CO_2 hypersensitivity is shared by both PTSD and panic disorder, extending the use of Freespira to a population with PTSD is a logical and potentially valuable clinical tool given the lack of medication-free treatment options for PTSD.

The purpose of prescribed therapeutic digital applications is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with panic disorder and PTSD. Panic symptoms may be associated with more shallow and rapid breathing. Freespira addresses rapid and shallow breathing that may contribute to panic symptoms through training of respiratory control.

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest are individuals with panic disorder and PTSD.

Interventions

The digital therapy being considered is Freespira.

Freespira consists of biofeedback software that monitors respiratory rate and CO_2 and provides feedback to the user via a tablet on expiration and respiratory rate in order to control breathing. The treatment includes a proprietary handheld CO_2 sensor, nasal cannula, and tablet with pre-loaded software. The user is instructed to complete two 17-minute sessions per day for 4 weeks, with weekly check-in with a therapist. Target respiratory rate is 13 during week 1, 11 during week 2, 9 during week 3, and 6 during week 4.

Comparators

The following practice is currently being used to treat mental health disorders: medications and in-person psychological and behavioral therapy.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Follow-up after treatment and at 6 to 12 months following the end of treatment is of interest to monitor outcomes.

Outcome measures for panic disorder and PTSD are described in Table 2.

Table 2. Outcome Measures

Outcome	Measure (Units)	Description and Administration	Thresholds for Improvement/Decline or Clinically Meaningful Difference
CAPS-5	Clinician Administered PTSD Scale	30-item clinician-administered scale that rates the severity of PTSD symptoms drawn from DSM-5 criteria (see Appendix).	Response is a 13 point change. Remission is a CAPS-5 score < 25.
CGI-S	Clinical Global Impression Severity	A single-item clinician-rated measure of severity of psychopathology, using a 7-point Likert scale ranging from 'normal' to 'among the most extremely ill individuals'.	
CHRT-SR	Concise Health Risk Tracking Self-Report	12-item self-report inventory that assesses suicidal and related thoughts.	
C-SSRS	Columbia Suicide Severity Rating Scale	Measures suicidal ideation.	
$EtCO_2$	End-tidal carbon dioxide, mm Hg	CO_2 monitor	Normal is > 35 mm Hg.
PHQ-9	The Patient Health Questionnaire 9-item depression scale	Self-report scale that asks individuals to rate the presence of DSM-4 symptom criteria ranging from '0' (not at all) to '3' (nearly every day).	
PDSS	Panic Disorder Severity Scale	7-item clinician-rated scale that indicates the severity and frequency of panic symptoms, fear of subsequent attacks, and avoidance behaviors.	Response is a 40% or greater reduction in scores. A score of 5 or less is considered remission.
SF-36	36-Item Short Form Health Survey	Self-rated survey of health impact on daily function.	

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

- Consistent with a 'best available evidence approach', within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Two pivotal single-arm studies have been reported on the Freespira app for panic disorder[9] and PTSD.[10] Study characteristics and results of these studies are summarized in Tables 3 and 4, respectively. No limitations in study relevance were noted. Multiple limitations in design and conduct summarized in Table 6 preclude the meaningful interpretation of their findings. Both studies have significant dropout rate and consequently data is missing for more than 30% of study participants in both studies. For example, study dropout rate was 33%, 39%, and 52% at 2, 6, and 12 months of follow-up in Tolin et al (2017) and 24% and 31% at 2 and 6 months of follow-up in Ostacher et al (2021). No clear description of reasons for missingness, characteristics of missing observations, or sensitivity analyses of missing data assumptions were provided. In addition to the 2 pivotal studies, one single-arm study published by Kaplan et al (2020) funded by a payer (Highmark Health) reported findings in 52 individuals with a diagnosis of panic disorder.[11] The primary goal of this study was to determine if treatment with Freespira in individuals with panic disorder would significantly reduce the cost of care in the 12 months following treatment. This single-arm study suffers from similar drawbacks as the first 2 pivotal studies.

Table 3. Summary of Key Study Characteristics for Freespira

Study	Study Design	Setting	Participants	Interventions
Tolin et al (2017)[9]	Single arm trial	Multi-site (4 sites, 2016 to 2016)	• Inclusion Adults age 18 to 65 years with a primary diagnosis of panic disorder using Mini International Diagnostic Interview • Rated as “moderately ill” or greater on the CGI-S • Either off medications or stable on medications for at least 3 months • ExclusionReceiving other psychological treatment • Unresponsive to cognitive-behavioral therapy • Evidence of organic mental disorder, severe suicidality, psychotic disorder, substance dependence, uncontrolled cardiovascular or pulmonary disease, or seizures	Twice a day 17-minute home sessions with Freespira for 4 weeks (N=69)
Ostacher et al (2021)[10]	Single arm trial	Single center (2017 to 2019)	• Inclusion Adults 18 years and older with a primary DSM-5 diagnosis of PTSD (see Appendix) • CAPS-5 score of ≥ 30, CGI-S score of ≥ 4 • Stable psychotropic medication • Exclusion Any concurrent evidenced-based therapy for PTSD • Concurrent psychotic disorder, alcohol or drug use disorder requiring acute medical treatment, epilepsy or recent seizures; and cardiovascular or pulmonary disease.	Twice a day 17-minute home sessions with Freespira for 4 weeks (N=55).

Kaplan et al (2020)[11]	Single arm trial	Single health system (multiple sites)	• Inclusion Adults 18 years and older with primary diagnosis of panic disorder • CGI-S ≥4 (moderately ill) • Either off medications or stable on medications prior to, during, or immediately after the 4 week Freespira treatment • ExclusionReceiving other psychological treatment • Evidence of organic mental disorder, severe suicidality, psychotic disorder, substance dependence, uncontrolled cardiovascular or pulmonary disease, or seizures	Twice a day 17-minute home sessions with Freespira for 4 weeks, with weekly check-in visits to their therapist (N=52)

CAPS-5: Clinician Administered PTSD Scale; CGI-S: Clinical Global Impression Severity; DSM: Diagnostic and Statistical Manual of Mental Disorders; PTSD: post-traumatic stress disorder.

Table 4. Summary of Key Study Results for Freespira

Study	**PDSS (±SD)**	**Responder/Remission at 12 months**	**Participant Flow**
Tolin et al (2017)[9])	Baseline: 14.8 (±3.6) Post-treatment: 5.4 (±4.4) Change versus baseline: 9.4 At 2-month follow-up: 6.0 (±5.2) Change versus baseline: 8.8 At 12-month follow-up: 5.0 (±6.2) Change versus baseline: 9.4	Response[a]: 81.8% Remission[b]: 69.7%	Enrolled: 69 Received treatment: 66 (96%) Completed treatment: 53 (77%) Completed Post treatment assessment: 48 (70%) Completed 2 month follow-up: 46 (67%) Completed 6 months follow-up: 42 (61%) Completed 12 months follow-up: 33 (48%)
	CAPS-5 Score (±SD)	**Responder/Remission at 2 months**	
Ostacher et al (2021)[10]	Baseline: 49.5 (±9.2) Post-treatment: 31.8 (±14.1) Change versus baseline: 17.7 At 2-month follow-up: 27.1 (±17.8) Change versus baseline: 22.4 At 6-month follow-up: 26.2 (±18.4) Change versus baseline: 23.4	Response[c]: 88% (95% CI 74% to 96%) Remission[d]: 48%	Enrolled: 55 Received treatment: 55 (100%) Completed treatment: 48 (87%) Completed Post treatment assessment: 48 (87%) Completed 2 month follow-up: 42 (76%) Completed 6 months follow-up: 38 (69%)
	PDSS (±SD)	**Responder/Remission at 12 months**	
Kaplan et al (2020)[11,]	Baseline: 14.4 (±3.8) Post-treatment: 4.9 (±3.4) Change versus baseline: 9.5 At 6-month follow-up: 4.1 (±4.3)	Response[a]: 91% Remission[b]: 68%	Enrolled: 52 Received treatment: 50 (96%) Completed Post treatment assessment: 44 (85%) Completed 2 month follow-

	Change versus baseline: 10.3 At 12-month follow-up: 4.4 (±4.5) Change versus baseline: 10		up: 27 (52%) Completed 6 months follow-up: 22 (42%)

CAPS-5: Clinician Administered PTSD Scale; PDSS: panic disorder severity scale; PTSD: post-traumatic stress disorder; SD: standard deviation.
[a] 40% or greater reduction in scores on the PDSS.
[b] Score of 5 or less on the PDSS.
[c] Percent of individuals having ≥ 6-point decrease in CAPS-5 at 2 months.
[d] Percent of individuals who meet the criteria for response plus no longer meeting DSM-5 criteria for PTSD and having a CAPS-5 score < 25.

Table 5. Study Relevance Limitations for Freespira

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Tolin et al (2017)[9])					
Ostacher et al (2021)[10]					
Kaplan et al (2020)[11]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 6. Study Design and Conduct Limitations for Freespira

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Tolin et al (2017)[9])	1. Participants not randomly allocated; 4. Inadequate control for selection bias;	1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician;		1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 6. Not intent to treat analysis (ITT analysis reported but definition of ITT is unclear);	1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference;	3. Confidence intervals and/or p values not reported; 5. Other (missing/unclear information on following: definition of intention to treat, primary hypothesis, primary outcome and its timing, reason for missing data, lack of

						control for type I error for multiple statistical comparisons and whether definitions of response and remission were pre-specified).
Ostacher et al (2021)[10]	1. Participants not randomly allocated; 4. Inadequate control for selection bias;	1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician;		1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 6. Not intent to treat analysis (ITT analysis reported but definition of ITT is unclear);	1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference;	3. Confidence intervals and/or p values not reported; 5. Other (missing/unclear information on following: definition of intention to treat, primary hypothesis, primary outcome and its timing, reason for missing data, lack of control for type I error for multiple statistical comparisons and whether definitions of response and remission were pre-specified)
Kaplan et al (2020)[11]	1. Participants not randomly allocated; 4. Inadequate control for selection bias;	1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician;	1. Not registered	1. High loss to follow-up or missing data; 2. Inadequate handling of missing data;		3. Confidence intervals and/or p values not reported;

ITT: intention to treat.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Panic Disorder and Post-Traumatic Stress Disorder

Panic symptoms in panic disorder and PTSD have been associated with more shallow and rapid breathing. The prescription digital therapy Freespira provides feedback to the user to learn to slow the breathing rate over a training period of 4 weeks. The evidence on Freespira for individuals with panic disorder includes 2 single-arm studies and 1 single-arm study in individuals with PTSD. All of the studies report an improvement in symptoms, but are limited by loss to follow-up ranging from 24% to 58% and multiple limitations in the design and conduct. A well-designed blinded RCT with a clear design for testing a pre-specified hypothesis is needed. Given the high loss to follow-up and lack of a control group in these studies, the benefit of a 4-week program of respiratory biofeedback in individuals with panic disorder and PTSD is uncertain.

Nightmare Disorder and Post-Traumatic Stress Disorder-Associated Nightmares

Clinical Context and Therapy Purpose

The purpose of prescribed therapeutic digital applications is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with nightmare disorder and PTSD-associated nightmares.

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest are individuals with nightmare disorder and PTSD-associated nightmares.

Interventions

The digital therapy being considered is NightWare. NightWare is intended to reduce nightmares in individuals with nightmare disorder and PTSD-associated nightmares in conjunction with standard therapy.

NightWare uses an artificial intelligence algorithm to learn an individual's normal and abnormal sleeping heart rate and motion in conjunction with an Apple Watch, Apple iPhone, and NightWare server. Upon detection of abnormal activity, the watch provides short vibrations to disrupt the nightmare without waking the patient. The watch is intended to be worn only during sleep and is used in addition to usual treatment for PTSD-associated nightmares and nightmare disorder.

Comparators

The following practices are currently being used to treat PTSD-associated nightmares: medications; image rehearsal therapy; cognitive behavioral therapy (CBT); cognitive behavioral therapy for insomnia (CBT-I); eye movement desensitization and reprocessing; exposure, relaxation, and rescripting therapy.[12]

The following practices are currently being used to treat nightmare disorder: medications; image rehearsal therapy; CBT; exposure, relaxation, and rescripting therapy; hypnosis; lucid dreaming therapy; progressive deep muscle relaxation; sleep dynamic therapy; self-exposure therapy; systematic desensitization; testimony method.[13]

Outcomes

The general outcomes of interest are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Follow-up after treatment and at 6 to 12 months following the end of treatment is of interest to monitor outcomes.

Outcome measures for nightmare disorder and PTSD-associated nightmares are described in Table 7.

Table 7. Outcome Measures

Outcome	Measure (Units)	Description and Administration	Thresholds for Improvement/Decline or Clinically Meaningful Difference (if known)
ESS	Epworth Sleepiness Scale	The ESS is a short self-administered questionnaire that asks individuals how likely they are to fall asleep in 8 different situations (eg, watching TV, sitting quietly in a car, or sitting and talking to someone).	The scale ranges from 0 to 24. An ESS of ≥10 is considered excessively sleepy. A decrease of 2 points is considered the clinically meaningful difference.
PHQ-9	The Patient Health Questionnaire 9-item depression scale	Self-report scale that asks individuals to rate the presence of DSM-4 symptom criteria ranging from ‘0’ (not at all) to ‘3’ (nearly every day).	
PSQI	Pittsburgh Sleep Quality Index	17-item self-rated questionnaire on initiating and maintaining sleep, and on sleep-related daytime function.	Clinically meaningful difference is 3 points.
PSQI-A	Pittsburgh Sleep Quality Index - Addendum	Assesses PTSD-related sleep quality.	
SF-36	36-Item Short Form Health Survey	Self-rated survey of health impact on daily function.	

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

One pivotal double-blind sham-controlled RCT conducted in a Veterans Administration Center has been reported in the manufacturers "Instructions for Use".[13,14]

Study characteristics and results of this trial are summarized in Tables 8 and 9 respectively. The trial was designed to enroll 240 participants with PTSD and nightmares, however, only 70 were enrolled. Data from 63 trial participants were included on the primary and secondary outcome measures. The primary outcome was the difference in the Pittsburg Sleep Quality Index (PSQI). The change from baseline was numerically higher for the NightWare group compared to sham, but the difference did not achieve statistical significance. There was no statistical difference observed in multiple other secondary endpoints such as change from baseline to day 30 in the active treated arm versus sham in the following outcome measures: PTSD Checklist for DSM-5 (PCL-5), Patient Health Questionnaire 9-item depression scale (PHQ-9), Trauma-Related *Nightmare* Survey (TRNS), Functional Outcomes of Sleep Questionnaire (FOSQ-10), and Veterans RAND 12 Item Health Survey (VR-12). The 2 primary safety measures of Nightmare device were to assess worsening of daytime sleepiness as assessed by the Epworth Sleepiness Scale (ESS) and increase in suicidality as assessed by the Columbia Suicide Severity Rating Scale (CSSRS).

Multiple limitations in design and conduct are summarized in Table 10 and 11 and preclude meaningful interpretation of study findings. This trial failed to achieve recruitment goals and was likely underpowered.

Table 8. Summary of Key RCT Characteristics for NightWare

Study	Study Design	Setting	Participants	Interventions	
				Active	Control
FDA De Novo Summary for NightWare[13,]	Double-blind RCT	Single center (2019 to 2020)	• Inclusion Documented diagnosis of PTSD (DSM 4 or 5 diagnostic criteria) (see Appendix) • 22 years of age or older • PSQI score 10 or more at screening • Have repetitive nightmares contributing to disrupted sleep as reported by the participant • Exclusion High suicide risk including current suicidal ideation	Individuals wore an Apple Watch with artificial intelligence software that produced short vibrations when sleep disturbance was detected.	Sham system consisting of an Apple watch with software but the watch did not vibrate during the night.

			• Cardiovascular comorbidities (uncontrolled atrial fibrillation) • Use of varenicline, beta-blockers, non-dihydropyridines • Circadian rhythm disruption on a regular basis (shiftwork) • Other sleep- and nightmare-related comorbidities • Active substance use • Primary Outcome Change in average PSQI score from day 0 to day 30 between active versus sham arm		

DSM: Diagnostic and Statistical Manual of Mental Disorders; PSQI: Pittsburgh Sleep Quality Index; PTSD: post-traumatic stress disorder; RCT: randomized controlled trial.

Table 9. Summary of Key RCT Results for NightWare

Study	Efficacy (Mean Change in PSQI-A ± SD)	Safety
FDA De Novo Summary for NightWare[13.]		
NightWare (change from baseline to day 30) (n=29)	-3.2 (± 3.7)	CCRS: -0.2 (±0.8) ESS: -1.2 (± 4.1)
Sham (change from baseline to day 30) (n=34)	-2.2 (± 2.9)	CCRS: 0 (± 1.0) ESS: 1.2 (± 3.1)
p-Value	.26	CCRS:.29 ESS:.97

CSSRS: Columbia Suicide Severity Rating Scale; ESS: Epworth Sleepiness Scale; FDA: Food and Drug Administration; PSQI: Pittsburgh Sleep Quality Index; PSQI-A; Pittsburgh Sleep Quality Index for PTSD-associated sleep quality; PTSD: post-traumatic stress disorder; RCT: randomized controlled trial; SD: standard deviation.

Table 10. Study Relevance Limitations for NightWare

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
FDA De Novo Summary for NightWare[13]					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 11. Study Design and Conduct Limitations for NightWare

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
FDA De Novo Summary for NightWare[13,]	3. Allocation concealment unclear; 4. Inadequate control for selection bias;	1. Participants or study staff not blinded (unclear) 2. Outcome assessors not blinded (unclear) 3. Outcome assessed by treating physician (unclear)		6. Not intent to treat analysis	1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference;	3. Confidence intervals not reported; 5. Other (unclear reporting on lack of achieving recruitment goal for trial: primary hypothesis, lack of control for type I error for multiple statistical comparisons).

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Nightmare Disorder and Post-Traumatic Stress Disorder-Associated Nightmares

The evidence on NightWare includes a single trial that did not meet the primary efficacy endpoint. This trial failed to achieve recruitment goals and was likely underpowered. A well-designed blinded RCT with a clear design for testing a pre-specified hypothesis is needed. Given these limitations, the benefit of NightWare in individuals with nightmare disorder and PTSD-associated nightmares is uncertain.

Low Back Pain

Garcia (2021)[16] The study presents a 3-month follow-up results for 8-week self-administered therapeutic virtual reality (VR) compared to Sham VR in adults with chronic low back pain. Across multiple pain indices, therapeutic VR had clinically meaningful benefits, and superiority over Sham VR. Home-based, behavioral skills VR yielded enduring analgesic benefits; longer

follow-up is needed. The post-treatment efficacy for an 8-week home-based therapeutic virtual reality (VR) program was studied in a double-blind, parallel arm, randomized placebo-controlled study. Participants were randomized 1:1 to 1 of 2 56-day VR programs: 1) a therapeutic immersive pain relief skills VR program; or 2) a Sham VR program within an identical commercial VR headset. Immediate post-treatment results demonstrated clinically meaningful and superior reduction for therapeutic VR compared to Sham VR for average pain intensity, indices of pain-related interference (activity, mood, stress but not sleep), physical function, and sleep disturbance. The objective of the current report was to quantify treatment effects to post-treatment month 3 and describe durability of effects. Intention to treat analysis revealed sustained benefits for both groups and superiority for therapeutic VR for pain intensity and multiple indices of pain related interference ex: activity, stress, sleep and physical activity from pretreatment to post treatment month 3. The between-group difference for sleep disturbance was non-significant and pain-interference with mood did not survive multiplicity correction at 3 months. For most primary and secondary outcomes, treatment effects for therapeutic VR showed durability, and maintained superiority to Sham VR in the 3-month post-treatment period. The 3-month follow-up results for 8-week self-administered therapeutic virtual reality (VR) compared to Sham VR in adults with chronic low back pain was reported. Across multiple pain indices, therapeutic VR had clinically meaningful benefits, and superiority over Sham VR. Home-based, behavioral skills VR yielded enduring analgesic benefits, but longer follow-up is needed.

Garcia (2021)[17] In a randomized controlled trial, the test was a self-administered behavioral skills-based VR program as a nonpharmacological home-based pain management treatment for people with chronic low back pain (cLBP). The method randomized 180 individuals with cLBP to 1 of 2 VR programs: (1) EaseVRx (8-week skills-based VR program); or (2) Sham VR (control condition). All participants will receive a VR headset to minimize any biases related to the technology's novelty. The Sham VR group had 2D neutral content in a 3D theater-like environment. The primary outcome is average pain intensity and pain-related interference with activity, stress, mood, and sleep. The secondary outcomes include patient-reported physical function, sleep disturbance, pain self-efficacy, pain catastrophizing, pain acceptance, health utilization, medication use, and user satisfaction. They hypothesize superiority for the skills-based VR program in all of these measures compared to the control condition. Team statisticians blinded to treatment assignment will assess outcomes up to 6 months posttreatment using an approach suitable for the longitudinal nature of the data. The results of the study was approved by the Western Institutional Review Board on July 2, 2020. The protocol (NCT04415177) was registered on May 27, 2020. In total, 186 participants were recruited. Multiple manuscripts was generated from this study. In Conclusion: Effectively delivering behavioral treatments in VR could overcome barriers to care and provide scalable solutions to chronic pain's societal burden. Their study could help shape future research and development of these innovative approaches. This study was not compared against another technology. More studies are needed to show efficacy of the technology.

Garcia (2023)[18] Prior work established post-treatment efficacy for an 8-week home-based therapeutic virtual reality (VR) program in a double-blind, parallel arm, randomized placebo-controlled study. Participants were randomized 1:1 to 1 of 2 56-day VR programs: 1) a therapeutic immersive pain relief skills VR program; or 2) a Sham VR program within an identical commercial VR headset. Immediate post-treatment results demonstrated clinically meaningful and superior reduction for therapeutic VR compared to Sham VR for average pain intensity, indices of pain-related interference (activity, mood, stress but not sleep), physical

function, and sleep disturbance. The objective of the current report was to quantify treatment effects to post-treatment month 3 and describe durability of effects. Intention-to-treat analyses revealed sustained benefits for both groups and superiority for therapeutic VR for pain intensity and multiple indices of pain-related interference (activity, stress, and newly for sleep; effect sizes ranged from d_{rm} = .56-.88) and physical function from pre-treatment to post-treatment month 3. The between-group difference for sleep disturbance was non-significant and pain-interference with mood did not survive multiplicity correction at 3 months. For most primary and secondary outcomes, treatment effects for therapeutic VR showed durability, and maintained superiority to Sham VR in the 3-month post-treatment period.

Maddox et al. (2023)[19] summarized the randomized sham controlled study whether an 8-week supported study by RelieVRx, self-administered in-home, behavioral skills virtual reality program for chronic low back pain (RelieVRx) that trains diaphragmatic breathing, biofeedback, cognition and emotion regulation, mindfulness, and pain education skills, is superior to a strong active Sham at day 56 for improving pain intensity and pain interference, in a large real-world sample. Participants included a national sample of demographically diverse individuals with self-reported nonmalignant chronic low back pain ≥3 months duration with an average pain intensity and pain interference of ≥4/10. Participants were randomized 1:1 to RelieVRx or active Sham, and data was collected from January 31, 2022, to October 31, 2022. Maddox et all evaluated group differences in brief pain inventor, pain intensity, and pain interference to day 56 (end of treatment). Results of the 1067 participants (772 women, 293 men, and 2 others; mean ± SD age, 50.8±13.2 years) randomized (1:1) into 2 groups: RelieVRx (n=536) and Sham (n=531) comprised the modified intention-to-treat analytic dataset. RelieVRx was superior to Sham for pain intensity and pain interference reductions from pretreatment to day 56 (difference from Sham, pain intensity: 0.406 [0.170-0.642] and pain interference: 0.523 [0.285-0.760]). Pain intensity and interference reductions for RelieVRx at day 56 were clinically meaningful (pain intensity: 2.0 [out of 10] points [1.73-2.06], pain interference: 2.3 points [1.99-2.33]). In conclusion, An 8-week self-administered behavioral skills virtual reality program was found to impart clinically meaningful improvements above a strong active control comparison on pain intensity and pain interference in clinically severe and diverse adults with chronic low back pain.

Gomez et al. (2021)[20] This systematic review and meta-analysis investigated the effectiveness of virtual reality (VR) interventions in treating chronic low back pain (CLBP), Fourteen studies were included and significant differences were found in favor of VR compared to no VR in reducing pain intensity and kinesiophobia both post-intervention and at follow-up. However, no significant differences were found in disability. VR interventions showed promise in reducing pain intensity and kinesiophobia in CLBP patients, but high heterogeneity exists and may affect result consistency. The review suggests the need for further research to explore different VR interventions, durations, and follow-up effects.

Knoop et al. (2023)[21] The study presents findings from a randomized sham-controlled study assessing the effectiveness of an in-home virtual reality program for chronic lower back pain in a diverse sample of patients. The study suggests that the virtual reality program could be beneficial in managing chronic lower back pain, but further research is needed to confirm its effectiveness across different populations and settings. The study concluded the editorial by stating that therapeutic VR interventions, such as RelieVRx have potential in complex patient groups such as cLBP but does not seem to be as effective as the authors present. The small effects of RelieVRx could possibly be enhanced and become clinically relevant when provided

to a more targeted patient group (such as patients having inadequate pain coping or distress), eventually supplemented by physical VR exercises and offered and monitored by a clinician.

Rohaj et al.(2023)[22] The perspective article summarizes Virtual Reality Trial Using EaseVRx For Chronic Low Back Pain (2021) and EaseVRx for Reduction of Chronic Pain and Opioid Use (2022) and how digital therapeutics (DTx) are broadening treatment options for chronic low back pain by integrating precision medicine, patient education, and public health strategies. It emphasized the importance of personalized approaches in managing chronic pain and highlights the potential of DTx in providing multiple treatments tailed to individual needs. The author, Aarushi Rohaj, likely explores how these advancements can improve patient outcomes and contribute to public health efforts in addressing chronic pain. RelievVRx is an example of prescription virtual reality app used in the article that reduces pain severity as an adjunct treatment for moderate to severe low back pain. In summary, It is important to advance the development of personalized digital intervention and health education for policy makers and health care systems. EaseVRx, a software-based virtual reality (VR) medical device, is intended to offer users a prescription pain management tool that manages the symptoms associated with chronic pain and reduces or eliminates the risk of opioid dependence. EaseVRx is based on principles of cognitive behavioral therapy, pain psychology, mindfulness-based stress reduction, biofeedback, and distraction therapy commonly used in interdisciplinary pain rehabilitation programs. The investigators will conduct a proof-of-concept randomized study to assess the feasibility and efficacy of using EaseVRx as a 56-day, VR-based, at-home program among 100 chronic low back pain patients by gathering pilot data on the efficacy of the intervention in decreasing pain, reducing opioid/non-opioid pharmacotherapy, and improving pain-related quality of life. While VR has been tested in academic medical centers and shown to be efficacious in the management of acute pain, this study will investigate the feasibility of VR use at home to manage chronic pain in preparation for a larger efficacy trial.

Applied VRx (2024)[23] New feasibility study indicates that VR has the potential to drive physiological changes in the body and brain associated with pain relief. The study, which included a single-blind, sham-controlled design, compared brain activation patterns and physiological metrics before, during, and after VR experiences in people experiencing chronic low back pain (CLBP). The research used AppliedVR's, RelieVRx® medical device, an eight-week, skills-based program that helps chronic low back pain (CLBP) patients learn self-management skills, combined with Kernel Flow and FlowVR compact, affordable, TD-fNIRS brain measurement headset customized for use in VR to measure brain hemodynamic changes associated with pain relief. While participants in the RelieVRx and sham groups both experienced varying levels of pain relief after completing the eight-week treatment, researchers determined that participants in the RelieVRx group experienced enhanced brain activation coherence change that previously has been related to reduced pain from pre-to-post treatment. Those patients receiving the VR sham control demonstrated a decline in brain coherence. Additionally, those receiving treatment from the RelieVRx device achieved a slower breathing rate as compared to the sham VR group. These results suggest that active RelieVRx treatment can create physiological changes in the body and have an impact on coherent global brain activity. This study is part of an ongoing collaboration between AppliedVR and Kernel. Both organizations will continue to deepen and expand their research to larger and more diverse populations.

Section Summary: Low Back Pain

The evidence reviewed individuals with chronic low back pain who received virtual reality as a treatment modality included systematic reviews, a randomized 2 arm parallel-group study, one proof of concept randomized study, a randomized sham-controlled study, several double-blinded randomized and placebo-controlled studies. Relevant outcomes are pain scores, quality of life, and medication utilization. Several questions still remain concerning of the efficacy of this treatment based on the limitations of the included trials which demonstrates a need for high-quality randomized trials with long-term follow-up to establish the effectiveness and durability of the treatment of chronic low back. RelieVRx (AppliedVR Inc) formally known as EaseVRx is not recommended as an alternative or adjunct to established treatments. The evidence is insufficient to determine that the technology results in an improvement in health outcomes. Larger and longer studies are needed to determine the efficacy of virtual reality for chronic low back pain.

Summary of Evidence PTSD

For individuals with panic symptoms who receive Freespira, the evidence includes several single-arm studies. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Panic symptoms in individuals with panic disorder and post-traumatic stress disorder (PTSD) have been associated with more shallow and rapid breathing, and Freespira is intended to lead to more regular breathing through biofeedback over a 4 week training period. There are 2 single-arm studies in individuals with panic disorder and 1 single-arm pilot study on the use of Freespira in individuals with PTSD. All of the studies report an improvement in symptoms but are limited by loss to follow-up that ranges from 24% to 58% and multiple limitations in the design and conduct. A well-designed blinded randomized controlled study with a clear design for testing a pre-specified hypothesis is needed. Given the high loss to follow-up and lack of a control group in these studies, the benefit of a 4-week program of respiratory biofeedback in individuals with panic disorder and PTSD is uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with nightmare disorder or PTSD-associated nightmares who receive NightWare, the evidence includes a single trial. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The single pivotal trial did not meet the primary efficacy endpoint. This trial failed to achieve recruitment goals and was likely underpowered. A well-designed blinded randomized controlled study with a clear design for testing a pre-specified hypothesis is needed. Given these limitations, the benefit of NightWare in individuals with nightmare disorder and post-traumatic stress disorder-associated nightmares is uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Summary of Evidence: Low Back Pain

The evidence reviewed individuals with chronic low back pain who received virtual reality by RelieVRx (AppliedVR Inc) formally known as EaseVRx as a treatment modality included systematic reviews, a randomized 2 arm parallel-group study, one proof of concept

randomized study, a randomized sham-controlled study, several double-blinded randomized and placebo-controlled studies. Relevant outcomes are pain scores, quality of life, and medication utilization. Several questions still remain concerning of the efficacy of this treatment based on the limitations of the included trials which demonstrates a need for high-quality randomized trials with long-term follow-up to establish the effectiveness and durability of the treatment. RelieVRx (AppliedVR Inc) formally known as EaseVRx is not recommended as an alternative or adjunct to established treatments. The evidence is insufficient to determine that the technology results in an improvement in health.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.[2]

No relevant guidelines that include NightWare or Freespira were identified.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 12.

Table 12. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04040387[a]	TNT/NW: Traumatic Nightmares Treated by NightWare (To Arouse Not Awaken)	270	Aug 2023
NCT05365607[a]	NightWare and Cardiovascular Health in Adults With PTSD	50	Apr 2024
Unpublished			

NCT03934658[a]	A Remote Randomized Double-Blind Sham-Controlled Clinical Trial of NightWare in Adults With Post-Traumatic Stress Disorder and Co-Morbid Nightmare Disorder	400 (actual enrolled 81)	Dec 2021
NCT03039231	Investigation of the Freespira Breathing System in the Treatment of Post Traumatic Stress Disorder (PTSD)	55	August 2019
NCT04415177	Virtual Reality Trial Using EaseVRx For Chronic Low Back Pain (Aarushi Rohaj et al.) *No Study Results Posted on ClinicalTrials.gov for this Study*	188	Completed 2021
NCT04139564	EaseVRx for the Reduction of Chronic Pain and Opioid Use (Aarushi Rohaj et al.) *Results Submitted - Not Posted on ClinicalTrials.gov*	108	Completed August 2022

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

Government Regulations

National:

No NCD

Local:

No LCD

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Digital Health Technologies For Attention Deficit and Hyperactivity Disorder

Digital Health Technologies: Diagnostic Applications

Digital Health Therapies for Substance Use Disorders

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 3/22/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/24	4/16/24		JUMP policy newly created, adopt BCBSA policy 3.03.02 as written with the addition of HCPCS code update E1905 added RelieVRx by AppliedVR, Inc. as E/I. FDA information added. (jf) Vendor Managed: NA Post JUMP: • add ex: in the code section • added “encompass” in the first paragraph of the description section.

Next Review Date: 2 Qtr, 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: DIGITAL HEALTH TECHNOLOGIES: THERAPEUTIC APPLICATIONS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not Covered
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.