3.03.02	Digital Health Technologies: Therapeutic Applications		
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Section:	3.0 Mental Health	**Page:**	Page 1 of 20

Policy Statement

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

II. The use of NightWare is considered **investigational** for all indications including treatment of nightmare disorder or nightmares from post-traumatic stress disorder (PTSD).

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

- N/A

Description

Digital health technologies is a broad term that includes 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.

Related Policies

- Digital Health Therapies for Attention Deficit/Hyperactivity Disorder
- Digital Health Therapies for Substance Use Disorders

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Digital health technologies that meet the current scope of the review are shown in Table 1.

Table 1. Examples of Prescription Digital Health Applications

Application	Manufacturer	FDA Cleared Indication	Description	FDA Product Codes	Clearance	Date
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 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.	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 display their EtCO2 level and RR and how different breathing habits affect EtCO2 levels.	HCC, CCK	K131586, K180173	2013, 2018
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.		Breakthrough device designation	2020

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.

Rationale

Background

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 (e.g., 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 (e.g., 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) (e.g., 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".[1,] 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.[2,]

Literature Review

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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.[3,] 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. [4,] 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.[5,] 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.[6,7,] 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.

Outcome	Measure (Units)	Description and Administration	Thresholds for Improvement/Decline or Clinically Meaningful Difference
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[8,] and PTSD.[9,] 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.[10,] 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)[8,]	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 Exclusion • Receiving 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)[9,]	Single arm trial	Single center (2017 to 2019)	Inclusion • Adults 18 years and older with a primary DSM-5 diagnosis of PTSD (see Appendix)	Twice a day 17-minute home

Study	Study Design	Setting	Participants	Interventions
			• 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.	sessions with Freespira for 4 weeks (N=55).
Kaplan et al (2020)[10],	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 Exclusion • Receiving 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)[8],)	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)[9],	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%)

Study	PDSS (±SD)	Responder/Remission at 12 months	Participant Flow
	PDSS (±SD)	Responder/Remission at 12 months	
Kaplan et al (2020)[10,]	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) Change versus baseline: 10.3 At 12-month follow-up: 4.4 (±4.5) Change versus baseline: 10	Response[a]: 91% Remission[b]: 68%	Enrolled: 52 Received treatment: 50 (96%) Completed Post treatment assessment: 44 (85%) Completed 2 month follow-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)[8,])					
Ostacher et al (2021)[9,]					
Kaplan et al (2020)[10,]					

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)[8,])	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		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	1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically	3. Confidence intervals and/or p values not reported; 5. Other (missing/unclear information on following: definition of intention to

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
		treating physician;		definition of ITT is unclear);	important difference;	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)[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)
Kaplan et al (2020)[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. 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.[11,]

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.[11,]

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 (e.g., 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".[12,13,]

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[12,]	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 • 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	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.

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[12,]		
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[12,]					

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[12,]	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.

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.

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

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

Appendix 1

DSM-5 Diagnostic Criteria for Panic Disorder

1. Recurrent and unexpected panic attacks
2. ≥1 attack has been followed by 1 month or more of one or both of the following
   - Persistent concern about additional attacks or their consequences
   - A significant maladaptive change in behavior related to the attacks
3. The panic attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse or a medication) or a general medical condition
4. The panic attacks are not better accounted for by another mental disorder.

DSM-5 Diagnostic criteria for Nightmares

1. Recurrent episodes of extended, extremely dysphoric, and well-remembered dreams that usually involve efforts to avoid threats to survival or security or physical integrity. The nightmares generally occur in the second half of a major sleep episode.
2. On waking from the nightmare, the individual rapidly becomes oriented and alert.
3. The episodes cause significant distress or impairment in social, occupational or other areas of functioning.
4. The symptoms cannot be explained by the effects of a drug of abuse or medication.
5. The nightmares cannot be attributed to another mental disorder (i.e., posttraumatic stress disorder, delirium) or medical condition.

DSM-5 Diagnostic Criteria for PTSD

The following criteria apply to adults, adolescents, and children older than 6 years.

A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
   1. Directly experiencing the traumatic event(s).
   2. Witnessing, in person, the event(s) as it occurred to others.
   3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
   4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse). **Note:** Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.

B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
   1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). **Note:** In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.
   2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s). **Note:** In children, there may be frightening dreams without recognizable content.
   3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) **Note:** In children, trauma-specific reenactment may occur in play.
   4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
   1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
   2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
   1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia, and not to other factors such as head injury, alcohol, or drugs).
   2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
   3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
   4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
   5. Markedly diminished interest or participation in significant activities.
   6. Feelings of detachment or estrangement from others.
   7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
   1. Irritable behavior and angry outbursts (with little or no provocation), typically expressed as verbal or physical aggression toward people or objects.
   2. Reckless or self-destructive behavior.
   3. Hypervigilance.
   4. Exaggerated startle response.
   5. Problems with concentration.
   6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

F. Duration of the disturbance (Criteria B, C, D and E) is more than 1 month.

G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

H. The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.

Specify whether:
With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

1. **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).

2. **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted). **Note**: To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify whether:
With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate).

References

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12. De novo classification request for Nightware kit (Apple iphone, Apple watch, Apple iphone charging cable, Apple watch charging cable). Available at https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN200033.pdf. Accessed on Accessed on August 9, 2022.
13. Davenport ND, Werner JK. A randomized sham-controlled clinical trial of a novel wearable intervention for trauma-related nightmares in military veterans. J Clin Sleep Med. Feb 01 2023; 19(2): 361-369. PMID 36305584

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	None	
HCPCS	A9291	Prescription digital cognitive and/or behavioral therapy, FDA-cleared, per course of treatment

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/01/2023	New policy.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** Blue font: Verbiage Changes/Additions
New Policy **Policy Statement:** N/A	**Digital Health Technologies: Therapeutic Applications 3.03.02** **Policy Statement:** I. The use of Freespira is considered **investigational** for all indications including treatment of panic disorder and/or post traumatic stress disorder. II. The use of NightWare is considered **investigational** for all indications including treatment of nightmare disorder or nightmares from post-traumatic stress disorder (PTSD).