DE NOVO CLASSIFICATION REQUEST FOR NIGHTWARE KIT (APPLE IPHONE, APPLE WATCH, APPLE IPHONE CHARGING CABLE, APPLE WATCH CHARGING CABLE)

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Digital therapy device to reduce sleep disturbance for psychiatric conditions. A digital therapy device to reduce sleep disturbance for psychiatric conditions is a prescription device that is intended to provide stimulation using a general purpose computing platform to reduce sleep disturbance in patients who experience this symptom due to psychiatric conditions such as nightmare disorder or post traumatic stress disorder (PTSD).

NEW REGULATION NUMBER: 21 CFR 882.5705

CLASSIFICATION: Class II

PRODUCT CODE: QMZ

BACKGROUND

DEVICE NAME: NightWare Kit (including Apple iPhone, Apple Watch, Apple iPhone Charging Cable, Apple Watch Charging Cable)

SUBMISSION NUMBER: DEN200033

DATE DE NOVO RECEIVED: May 27, 2020

SPONSOR INFORMATION:

NightWare, Inc
153 Ashley Road
Hopkins, Minnesota 55343

INDICATIONS FOR USE

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 posttraumatic stress disorder (PTSD). It is intended for home use.

<u>**LIMITATIONS**</u>

The sale, distribution, and use of the NightWare device are restricted to prescription use in accordance with 21 CFR 801.109.

The NightWare device is intended for use in adults only.

The NightWare device is not intended to be used as a standalone therapy for PTSD and should be used in conjunction with a patient's prescribed medications and other recommended therapy for PTSD-associated nightmares and nightmare disorder, according to relevant consensus guidelines.

The NightWare device is not intended for use in patients who "act out" nightmares (including in patients who sleepwalk or are violent during nightmares)

The long term safety and effectiveness of the NightWare device have not been established.

The long term effects of the NightWare device use on the sleep architecture have not been established.

 Patients who experience drowsiness or daytime sleepiness while using the device should not drive or operate heavy machinery and should contact their healthcare provider.

The "Stress Index" measured by the device is a device-specific measurement that does not represent a clinically validated measure of stress.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

<u>**DEVICE DESCRIPTION**</u>

The NightWare device consists of a software application and the NightWare server. The device uses an Apple Watch and an Apple iPhone for its platform. Patients must use the prescribed iPhone and Apple Watch pre-provisioned by NightWare, Inc.

The watch monitors physiological parameters that indicate that the patient is experiencing a nightmare. Signals from the watch's heart rate sensor, accelerometer, and gyroscope are input to the onboard algorithms on the watch software and sent to the server and processed by NightWare software. The software on the server calculates a device-specific "Stress Index" from watch measurements of heart rate, rotation, and acceleration. When a "Stress Index" threshold is exceeded, the device provides a vibrotactile stimulation on the patient's wrist intended to interrupt the nightmare but not awaken the patient.

Patients need to have at least an intermittent connection to wireless internet through WiFi in order to transmit data to the NightWare server. However, this wireless internet connection is not

needed to receive therapy through the treatment period, as the processing of physiological data and delivery of stimulation occurs on the watch itself.

The "Stress Index" threshold is uniquely calculated for each patient based on an artificial intelligence algorithm. The algorithm differentiates between a patient's normal and abnormal "Stress Index" levels during the night. To create its personalized "Stress Index" threshold, NightWare collects several hours of data during sleep before any intervention is applied. During this initial time, the system monitors the patient's movements and heart rate to delineate the usual low, medium, and high "Stress Index" periods to determine the wearer's usual sleep patterns. The movement and heart rate information is then securely sent to the NightWare server to establish the patient's specific "Stress Index" threshold; when the threshold is reached the vibrotactile stimulation is applied. The "Stress Index" threshold is automatically and periodically updated as needed to accommodate the patient's changing "Stress Index" and thresholds that naturally occur during consistent use.

SUMMARY OF NONCLINICAL/BENCH STUDIES

NightWare is a software as a medical device implemented on a general purpose computing platform, and non-clinical/bench testing was generally not needed to demonstrate the safety and effectiveness of the device.

SOFTWARE
Software Verification & Validation testing and documentation was provided according to a Moderate Level of Concern and FDA's guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" (May 11, 2005) to demonstrate that the device software performs as intended. The software documentation provided a clear description of all features and functions of the software implementing the digital therapy.

SUMMARY OF CLINICAL INFORMATION

Primary validation study design
A 30-day, double-blind sham-controlled randomized clinical trial of the NightWare Digital Therapeutic was performed study the safety and effectiveness of the device to reduce sleep disturbance related to nightmare disorder associated with post-traumatic stress disorder in adults 22 years and older. The NightWare device is referred to as the "Active System." The "Sham System" consisted of the same components as the Active System, but the application only monitored the subjects' sleep and did not provide any intervention or feedback to the subject.

Study Population
Subjects 22 years of age or older with a prior or current diagnosis of PTSD and current nightmares resulting in sleep disturbance.

Relevant Inclusion Criteria
- Documented diagnosis of PTSD via American Psychiatric Association PTSD diagnostic
criteria in the fourth or fifth edition of its Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, DSM-IV_TR, or DSM-5).
- 22 years of age or older
- Pittsburgh Sleep Quality Index (PSQI) score 10 or more at screening.
- Have repetitive nightmares contributing to disrupted sleep as reported by the subject.
- If currently taking Prazosin, must be willing to be tapered off of Prazosin by their prescribing provider. Subject must be off Prazosin for 2 weeks prior to enrollment.

Relevant Exclusion Criteria
- Patient Health Questionnaire-9 (PHQ-9) score greater than or equal to (b) (4), with a score of (b) (4) on question #9 (suicidal ideation) triggering a risk assessment by the study principal investigator or qualified co-investigator
- Responses on the C-SSRS that indicate High Suicide Risk including current suicidal ideation, which will prompt assessment by a licensed psychologist.
- Cardiovascular conditions and medications:
    - Uncontrolled atrial fibrillation
    - Current use of varenicline
    - Current use of beta-blockers (unless ophthalmic solutions)
    - Current use of non-dihydropyridines
    - Circadian rhythm disruption on a regular basis (shiftwork)
- Sleep- and nightmare-related:
    - Known diagnosis of obstructive sleep apnea (OSA)
    - Diagnosis of an active disorder of arousal from non-rapid eye movement sleep
    - Diagnosis of rapid eye movement sleep behavior disorder
    - Diagnosis of narcolepsy
    - Previous or foreseeable legal proceedings involving nightmares or trauma
    - Nocturia that causes awakening from sleep
    - Known sleep walking
    - Acting out of dreams prior to PTSD trauma
- Substance Use:
    - Alcohol Use Disorders Inventory Test (AUDIT) score equal to (b) (or higher
    - Drug Abuse Screening Test-10 (DAST-10) score greater than (b) (4
    - Investigator suspicion of nightmares being secondary to substance abuse or withdrawal
- Diagnosis or investigator suspicion of dementia

Objectives
Primary Effectiveness Objective
Demonstrate that subjects treated with the Active System show improved sleep as assessed by the Pittsburgh Sleep Quality Index (PSQI) as compared to the Sham System.

Primary Safety Objectives

Demonstrate that the NW digital therapeutic does not lead to:
- Worsening of daytime sleepiness as assessed by the Epworth Sleepiness Scale (ESS).
- Increase in suicidality as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS).

Secondary Objectives
Demonstrate each of the following for the Active System as compared to Sham System:
- Evaluate the difference between average PSQI-Addendum for PTSD (PSQI-A) at baseline (Day 0) and average PSQI-A at Day 30.
- Evaluate changes in PTSD severity as assessed by the PTSD Checklist (PCL-5, past month version).
- Assess subjective sleep quality with the Likert Scale for Sleep Quality at Days 0, 7, and 30 to assess improvement in sleep.
- Demonstrate that there is not an increase in symptoms of depression as assessed by Patient Health Questionnaire-9 (PHQ-9, past month version).
- Evaluate changes in quality of life as assessed by the Functional Outcomes of Sleep Questionnaire (FOSQ-10).
- Evaluate changes in nightmare severity as measured by the Trauma Related Nightmare Scale (TRNS).
- Evaluate changes in nightmare frequency as assessed by TRNS.
- Evaluate changes in quality of life as assessed by Veterans Rand 12 Quality of Life instrument (VR-12).

<u>**Outcome measures**</u>
Primary Efficacy Outcome of Active System as compared to Sham System:
- Change in average PSQI score at baseline (Day 0) and average PSQI score at the post- enrollment assessment at Day 30.

Primary Safety Outcome:
- Comparison between average ESS at baseline and Day 30.
- Comparison of suicide risk (Low, Medium, High) between C-SSRS at baseline and Day 30.

Secondary and Observational Outcomes:
- Change in average PSQI-A at baseline and Day 30 as compared to sham.
- Change in average PCL-5 at baseline and Day 30 as compared to sham.
- Change in average PHQ-9 at baseline and Day 30 as compared to sham.
- Change in of average TRNS at baseline and Day 30 as compared to sham.
- Change in average FOSQ-10 Quality of Life Measure at baseline and Day 30 as compared to sham.
- Change in average VR-12 at baseline and average VR-12 at Day 30 as compared to sham.

<u>**Sites**</u>
This study was conducted at the Minneapolis Veterans Affairs Health Care System.

Results
Enrollment: In the study, 130 potential participants were screened, 70 were enrolled, and 63 adults completed the study procedure. Six patients in the Active arm withdrew or were lost to follow-up, and one in the sham arm withdrew. One patient dropped out of the Active arm after reporting that the device disrupted sleep; none of the other dropouts or losses to follow-up were determined to be directly related to device usage. The study results are displayed in Tables 1 and 2, and the most relevant safety and effectiveness outcomes are discussed below.

Safety:
- *Primary safety:* Patients in both the Active and Sham arms of the study reported a 1.2 point decrease (less sleepiness) in the Epworth sleepiness scale (ESS). The difference was not statistically significant at the p (b) (4) level.

- *Primary safety:* Patients in the Active arm reported a 0.2 point decrease in the C-SSRS, and patients in the Sham arm reported no change in the C-SSRS. The difference was not statistically significant at the p (b) (4) level. Due to a protocol violation, the first 20 patients enrolled in the study were mistakenly not administered the C-SSRS, but this occurred in both study arms. A complete tabulation of C-SSRS results are provided in Table 2.

Effectiveness:
- *Primary effectiveness:* Patients in the active arm had a mean PSQI improvement of 3.2 points, and patients in the sham arm had a mean improvement of 2.2 points. The difference was not statistically significant at the p (b) (4) level.

- *Secondary/observational effectiveness:* For the secondary and observational outcome measures listed above trends toward improvement of the symptoms assessed by the respective outcomes were observed. One of the key secondary outcome measures was the PQSI-A, which is a measure of seven sleep disturbance items often reported by adults with PTSD (including sleep disturbance due to anxiety, nervousness, bad dreams, terrors or screaming during sleep). Patients in the active arm had a mean PSQI-A improvement of 3.3 points; patients in the sham arm had a mean improvement of 1.4 points. The difference was not statistically significant at the p (b) (4) level.

Adverse events
Two adverse events were reported during the study. Neither was determined to have a likely relation to device use. One patient was hospitalized for suicidality after study enrollment but prior to use of the investigational device. Another patient who was enrolled and using the device was diagnosed with sleep apnea, but the factors contributing to sleep apnea were determined to be likely present before device use began.

Baseline Outcome Measure	Active (n = 29)	Sham (n = 34)	p-value
CSSRS 1 Month Score	-0.2 (0.8)	0.0 (1.0)	0.2943
PSQI	-3.2 (3.7)	-2.2 (2.9)	0.2606
PHQ-9	-2.0 (3.7)	-1.0 (3.8)	0.2719
PCL	-9.9 (13.4)	-6.5 (9.9)	0.2727
ESS	-1.2 (4.1)	-1.2 (3.1)	0.9739
TRNS	-4.8 (7.3)	-2.7 (4.4)	0.1909
FOSQ	1.4 (2.8)	0.8 (2.3)	0.3683
PSQI-A	-3.3 (4.9)	-1.4 (3.5)	0.0938
VR12	2 (5.8)	1.6 (6.9)	0.8093

Table 1. Change in outcomes at Day 30 (as compared to baseline, Day 0) for Active and Sham arms. Data shown are mean, with standard deviation in parenthesis. P-values represent a two-sample t-test.

Score	Description	Baseline		Completion	
		Active	Sham	Active	Sham
0	No ideation	(b) (4)			
1	Wish to be dead				
2	Non-specific active suicidal thoughts				
3	Active suicidal ideation, no intent to act, no plan				
4	Active suicidal ideation, some intent to act, no plan				
5	Active suicidal ideation with specific plan and intent				
Total >0					

Table 2: Reports of suicidal ideation (according to the C-SSRS) at baseline and completion (Day 30) for Active and Sham arms

Conclusions

No device-related adverse events were observed in the 30 day study.

There was a 0.2 point difference between the Active and Sham arms in the C-SSRS suicidality safety endpoint, and no difference between arms was observed in the ESS daytime sleepiness safety endpoint.

There was a 1 point difference between the Active and Sham arms in the PSQI sleep assessment primary effectiveness endpoint, but the difference was not statistically

significant. There was a (b) (4) point difference between the Active and Sham arms in the PSQI-A endpoint, which incorporates a nightmare component and is considered a more relevant assessment of sleep disturbances in PTSD. Considering the low risk of the device, both the beneficial 3.2 point decrease for the PSQI and beneficial 3.3 point decrease in the PSQI-A in the treatment arm were judged to support that the device would be beneficial to this patient population by providing an acceptable adjunct therapy to their treatment plan, in comparison to other medical treatment approaches which may have potentially more risks to the patient.

No statistically-significant differences were observed in any of these endpoints. The study enrolled fewer patients than prospectively planned, hence, there is a high likelihood that the study is underpowered to detect a statistically significant difference in these endpoints.

Although the study was likely underpowered to detect a statistically significant difference in endpoints between the Active and Sham arms, the results show trends in improvement in outcomes related to sleep disturbance and more specifically sleep disturbance related to nightmares.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population. The device is indicated for use in adults only.

LABELING
The NightWare Instructions for Use are consistent with the clinical data and cover all the hazards and other clinically relevant information that may impact use of the device. The labeling is sufficient and satisfies the requirements of 21 CFR § 801.109 for prescription devices. The sole contraindication listed is for patients who are known to "act out" their nightmares (including sleepwalking or displaying outbursts of violence). Both physician and patient labeling include instructions for use with images and computing requirements. The physician labeling includes a summary of the clinical study discussed in this document.

The following precautionary statements are included within the device labeling:

- Federal law restricts this device to sale by or on the order of a physician.
- 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.
- If daytime sleepiness occurs, the user is instructed to contact their healthcare provider and not to operate heavy machinery or drive.
- If NightWare causes awakenings not associated with nightmares, the user is instructed to contact their healthcare provider.
- NightWare is intended for adults 22 years or older.

- The long term safety and effectiveness of the NightWare device have not been established.
- The long term effects of the NightWare device use on the sleep architecture have not been established.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of a digital therapy device to reduce sleep disturbance for psychiatric conditions and the measures necessary to mitigate these risks.

Identified Risks to Health	Mitigation Measures
Ineffective treatment leading to worsening sleep	Clinical performance testing
Ineffective treatment leading to worsening condition-specific symptoms	Clinical performance testing
Device software failure leading to delayed access and treatment	Software verification, validation, and hazard analysis
Improper device use leading to worsening sleep	Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the digital therapy device to reduce sleep disturbance for psychiatric conditions is subject to the following special controls:

(1) Clinical performance testing under the labeled conditions for use must evaluate the following:
  (i) The ability of the device to provide therapy for patients with sleep disturbance due to psychiatric conditions, using a validated measure;
  (ii) Worsening of any condition-specific symptoms using a validated measure for assessment of the particular condition; and
  (iii) Increase in symptoms of disturbed sleep or sleepiness using a validated measure.

(2) Software must clearly describe all features and functions of the software implementing the digital therapy. Software verification, validation, and hazard analysis must also be provided.

(3) The labeling must include the following:
  (i) Patient and physician labeling must include instructions for use, including images that demonstrate how to interact with the device;
  (ii) Patient and physician labeling must list the minimum operating system (OS) and general purpose computing requirements that support the software of the device;
  (iii) Patient and physician labeling must include a warning that the digital therapy device is not intended for use as a standalone therapeutic device;
  (iv) Patient and physician labeling must include a warning that the digital therapy device does not represent a substitution for the patient's medication; and

(v) Physician labeling must include a summary of the clinical performance testing conducted with the device.

BENEFIT-RISK DETERMINATION

The risks of the device are based on the data collected in the clinical study described above.

Two adverse events were reported. However, none were determined to be device-related.

One patient reported that the device disturbed their sleep and therefore withdrew from the study. It is possible that the device's vibrotactile stimulation may actually result in sleep fragmentation and increase the arousal index, leading to sleep disruption as a result. The supporting clinical trial did not perform the polysomnography measurements needed to assess this, nor was the study duration sufficient to investigate this effect. However, at 30 days, no change in daytime sleepiness was observed according to the Epworth Sleepiness scale. The NightWare device does not appear to worsen daytime sleepiness or drowsiness in the short term. The long term effects of the device on sleepiness and sleep fragmentation are not known; if there is any evidence of increased sleepiness, the device labeling advises that patients should contact their healthcare provider.

In this study, 76% of patients reported a lifetime history of suicidal ideation, and suicidal ideation is prevalent within the intended use population. In the supporting validation study, patients in the Active arm at 30 days showed no worsening suicidal ideation on average according to the C-SSRS. The NightWare device therefore does not appear to worsen suicidal ideation during short duration use. Some uncertainty exists in the assessment of suicidal ideation due to the 20 protocol violations that occurred at the beginning of the study; however, these were balanced across the Active and Sham groups. Longer term influence of device use on suicidality are not known, but therapies that reduce sleep disturbance due to nightmares would be expected to lessen suicidality.

The probable benefits of the device are based on the data collected in the clinical study described above.

The 30 day, randomized, controlled, blinded pivotal validation study of 70 patients demonstrated a 3.2 point change in the PSQI for patients in the Active treatment arm and a 2.2 point change for patients in the Sham treatment arm at day 30 as compared to baseline, for a 1.0 point difference in the PSQI between treatment groups. For the PSQI-A, patients in the Active treatment arm showed a greater benefit relative to sham with a (b) (4) point difference between groups. The PSQI-A is likely a more useful endpoint for the assessment of sleep disturbance in the intended patient population for the NightWare device. The reason for this is that the PSQI-A explicitly assesses aspects of sleep disturbance that are related to dreams and nightmares as well as the anxiety and panic associated with those dreams and nightmares. The NightWare device was judged, in comparison to the potential low risks, to have greater benefit on the PSQI-A than the PSQI, which suggests greater effectiveness for reducing sleep disturbance related to

nightmares in patients with PTSD as opposed to reducing sleep disturbance as measured by the PSQI in a general population.

There is uncertainty in the benefit demonstrated in the clinical study described above. Seven patients did not complete the study, with the majority of them (6) being in the Active treatment group. While one patient explicitly noted that their dropout was due to the device interrupting sleep, the reasons for the other patient dropouts are unclear. The results include numerical differences only between treatment groups and wide confidence intervals, likely due to the study being underpowered as a result of the early termination. The study was not of sufficient duration to assess the longer term effectiveness of the NightWare device. Despite a number of sources of uncertainty, there is evidence of potential benefit due to the improvement in the PSQI-A and PSQI scores as compared to the sham device.

Additional benefit/risk factors include patient tolerance for risk and risk mitigations due to the device's design. Patients are likely to tolerate uncertainty in benefit, because the device is low risk and offers a passive, non-pharmaceutical method to reduce sleep disturbance in a chronic condition. Additionally, patients may easily remove the device if they believe it to be ineffective or that it is interrupting or worsening their sleep and is not mitigating their sleep disturbance due to nightmares.

Finally, as a Breakthrough-designated device, no other cleared or approved devices address the medical need being met by the NightWare device. Although there are other clinical and pharmaceutical options that address this medical need, this device offers a non-pharmaceutical option that can be used in the home setting.

For the reasons described above, the probable benefits of the NightWare device outweigh the probable risks in light of the listed special controls and the general controls.

Patient Perspectives

Patient perspectives considered for the NightWare Kit (Apple iPhone, Apple Watch, Apple iPhone Charging Cable, Apple Watch Charging Cable) during the review include:

Three patients were interviewed on their experiences using the device for 5 weeks. All three patients reported benefit from the device use, noting that the device provided a non-pharmaceutical treatment alternative. The patients noted that the pharmaceutical treatment could leave them feeling "in a fog," while the NightWare device did not.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

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 posttraumatic stress disorder (PTSD). It is intended for home use.

the probable benefits outweigh the probable risks for the NightWare Kit (Apple iPhone, Apple Watch, Apple iPhone Charging Cable, Apple Watch Charging Cable). The device provides benefits to this patient population and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the NightWare Kit (Apple iPhone, Apple Watch, Apple iPhone Charging Cable, Apple Watch Charging Cable) is granted and the device is classified as follows:

Product Code: QMZ
Device Type: Digital therapy device to reduce sleep disturbance for psychiatric
conditions
Regulation Number: 21 CFR 882.5705
Class: II