NightWare Digital Therapeutic

NightWare INC. Protocol: NW101002 Version 1.1

CLINICAL STUDY PROTOCOL TITLE: Traumatic Nightmares Treated by NightWare (To Arouse Not Awaken): A Randomized Controlled Trial

NCT NUMBER: NCT04040387

PRODUCT: NightWare Digital Therapeutic

PROTOCOL NUMBER: NW101002

STUDY SPONSOR: NightWare, INC. 153 Ashley Road Hopkins, MN 55343

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Data Analysis Plan NW101002 Trial

Primary Safety Analyses The hypothesis for the primary safety endpoint is that the Active NW System will not lead to worsening of daytime sleepiness as measured by the Epworth Sleepiness Scale, which provides a score between 0 and 24 with higher values indicating a higher degree of sleepiness. Specifically, the hypothesis is that on average a user of NW will have a mean ESS score measured at 30 days following the start of NW digital therapeutic system use that is not higher than their ESS score measured at baseline. This hypothesis will be tested similarly to the primary efficacy hypothesis using a one sample t-test.

The hypothesis for the secondary safety endpoint is that the Active NW System will not lead to an increase in suicide risk as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) from baseline (Day 0) to Day 30. C-SSRS has ratings of “none”, “low”, “moderate”, and “high”. Those possible participants rated as “high” on the C-SSRS at Visit 1 will NOT qualify for the study and, if deemed necessary by the PI, will be given immediate assessment by a licensed Mental Health Provider, who will determine the next therapeutic steps. This hypothesis will be tested similarly to the primary efficacy hypothesis using a one sample t-test.

All measures used in this study will be evaluated using an intention-to-treat analysis; that is, all study participants completing the study will be included in the data analysis in the group to which they were assigned at enrollment. Additionally, a per-protocol analysis will be completed for all measures used in the study. For this analysis, use of the study device at least 50% of the study nights during the first 30 nights of the study will constitute adequate adherence to the study treatment.

The Trauma-Related Nightmare Scale questionnaire is not designed to produce a score when it is administered. The individual questions on this scale will be evaluated separately from one another.

Missing data is inevitable and can be handled in multiple ways. The data will need to be evaluated to determine the randomness of the missing data. First we will identify the distribution of the missing values and their impact then we will determine a path to deal with missing data. Depending on the impact of the missing values, we will omit participants without full data, omit missing values, impute missing values with the mean, or use multiple imputation.

Secondary and Exploratory analyses will be carried out with appropriate regression modeling techniques and hypothesis tests. In particular, we will use longitudinal data analysis methods, such as generalized estimating equations and generalized linear mixed models, to assess temporal variation in the longitudinal outcome measures, and we will carry out two sample t-tests of the secondary hypotheses. At the conclusion of the trial, the data will be assessed as both intention to treat (ITT) and per protocol. The effect sizes at the conclusion of the analyses will be compared using standard techniques. If the effect size of the per protocol analysis is greater than 10%, data will be reported as intention to treat to decrease probability of type I errors. Both analyses will follow the outline below:

Secondary outcomes, data will be presented as mean(standard deviation) or median (interquartile range), as appropriate for continuous variables. Categorical variables will be presented as frequency (percentage). Continuous data will be assessed for normality, and transformed as appropriate (e.g. log transformation, square root transformation, etc.). Patient demographics and characteristics will listed an compared. Continuous variables will be analyzed by category, intervention vs control, by two-sided ttest or Mann-U Whitney, as appropriate. Categorical variables will be compared by Chi-Square test or Fisher's Exact test as appropriate. Longitudinal data will be analyzed by repeated measures tests as appropriate for the variables.

Repeated measure ANOVA will be used to determine the difference in responses at the time points between groups for all survey types and questions, as appropriate. If determined inappropriate Poisson regression models will be used to determine the univariate, univariable, effect size.

Upon secondary outcomes analysis , multivariable, adjusted, models will be used to determine controlled effect sizes. Each variable with a p-value of 0.25 or less in standard distribution test will be included in the model. Backward stepwise regression modeling may be used to best fit the model.

Time-to-event analyses will be conducted to determine time to survey effects over the longevity of the study (baseline, visit 2, day 30, day 60, day 90) for all survey results within the secondary outcomes. Univariate Cox regression models may be used to determine hazard ratios for the survey scores if appropriate.

Correlation coefficients (i.e. Spearman, Pearson) may be used to determine the inter-survey reliability. If determined to be reliable, multivariate analyses may be conducted for surveys.

All statistical analyses will be carried out by the Principal Investigator and/or a PhD Biostatistician.