Two-month transcutaneous auricular Vagus Nerve Stimulation (taVNS) take-home device feasibility study in PTSD

Marcus Elliott, BS[a] Annalese Pfahler[b] Christine Aytug, MBA[c] Blythe Karow, MBA[d] Karen Copeland, Ph.D.[e] Richard Marshall, Ed.D.[f] Neil R. Euliano, Ph.D.[g]

(a) Vice President of R&D, Evren Technologies, Inc. - Marcus.Elliott@evrenvns.com; 404 SW 140th Terrace, Suite 50 Newberry, FL 32669

(b) Neuroscientist, Evren Technologies, Inc. annalese.pfahler@gmail.com; 3320 NW 37th St. Gainesville, FL 32605.

(c) Director of Business Development, Evren Technologies, Inc. - Chris.Aytug@evrenvns.com; 404 SW 140th Terrace, Suite 50 Newberry, FL 32669

(d) President & CEO, Evren Technologies, Inc. - blythe.karow@gmail.com; 4814 NW 44th Ave, #107, Gainesville, FL 32606

(e) Principal, Boulder Statistics - Karen@boulderstats.com 760 Twilight Ln. Steamboat Springs, CO 80487

(f) *Clinical Psychologist, Psychological Associates of Central Florida - Drmarshall@pacflorida.com; 5424 Strickland Ave, Lakeland, FL 33812

(g) CTO, Evren Technologies, Inc. - Neil@conveng.com; 100 SW 75th St UNIT 106, Gainesville, FL 32607

**=Corresponding author*

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Abstract:

Post-Traumatic Stress Disorder (PTSD) is a reaction to trauma that results in a chronic perception of threat, eliciting a sustained pathologically aroused state. Transcutaneous auricular vagus nerve stimulation (taVNS) is a novel, noninvasive method of VNS, which has shown significant promise in treating other psychiatric disorders. In this single-arm, unblinded feasibility study, 12 participants were asked to use the Phoenix® taVNS prototype at home twice a day for two months. The Clinician-Administered PTSD Scale (CAPS-5) and PROMIS-29[1] quality-of-life scales were administered at baseline, one month, and two months. No significant adverse events were reported during the treatment and 11 out of 12 participants were able to comply with the intervention protocol. The change in CAPS-5 score from baseline to two months was 18.8 (paired t-test P=0.0013 95% CI 9.2 – 28.5). This demonstrates that taVNS is both well-accepted and feasible as a potential at-home treatment for PTSD and warrants further investigation.

Background:

Post-Traumatic Stress Disorder (PTSD) is a reaction to trauma that results in a chronic perception of threat, eliciting a sustained pathologically aroused state.[2] A person with PTSD has difficulty shifting to a physiological state appropriate to a non-threating situation. This mobilized neurophysiological state is maladaptive in everyday life and creates substantial health and psychosocial risk. It afflicts people who have been exposed to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence. People with PTSD have difficulty sleeping, nightmares,

persistent flashbacks, sudden outburst of anger or anxiety, numb or detached feelings and they avoid people or places that remind them of the trauma. It is associated with severe impairment in quality-of-life, including poor objective life circumstances, role functioning, and subjective life satisfaction, as well as increased drug abuse rates and greatly increased suicide risk. The lifetime prevalence of PTSD in the United States is estimated at 7.8%.[3]

PTSD sufferers have high levels of co-morbidities. In one study, 60% of men and 44% of women with PTSD were found to meet the diagnostic criteria for three or more other psychological disorders.[3] The risk of suicide can be up to 13 times the risk borne by people without PTSD[4] and studies have shown rates of PTSD and substance use disorders as high as 25-59%.[5] Studies on pandemics (including COVID-19) have indicated that during a pandemic, PTSD rates can significantly increase in both medical personnel and in the general public.[6] Overall PTSD has been associated with a 3.8-fold increased risk of death.[7]

Unfortunately, existing treatments for PTSD are often ineffective, have side effects[8,9], and often have high rates of dropout. Pharmacotherapies generally result in reduction of symptom severity rather than remission.[10] The "gold standard" psychotherapy - exposure therapies for PTSD - are "strongly recommended" by the American Psychological Association,[11] but not all patients respond to exposure therapies. Many will continue to experience symptoms even after therapy, and a majority will experience symptomatic relapse months or years after therapy.[8] The dropout rate from exposure therapy averages 36% and rates ranging from 28% to 68%[12] are reported in the literature, which is not surprising since avoidance is one of the symptom clusters of PTSD. Behavioral health clinicians and their patients have a grave need for a new solution, especially one that does not include the side effects associated with current pharmacological solutions.

Vagus Nerve Stimulation (VNS) via an implanted stimulation device is FDA approved for the treatment of epilepsy and treatment-resistant depression.[13,14] Current systems for implanted VNS require invasive surgery and come with adverse side effects.[15] Transcutaneous auricular vagus nerve stimulation (taVNS) is a novel, noninvasive method of VNS, which has shown significant promise in other psychiatric disorders such as depression, anxiety, and insomnia.[16–20]

The vagus nerve projects through the nucleus tractus solitarius and the locus coeruleus (LC) extending to the hypothalamus, amygdala, hippocampus, and prefrontal cortex, it is directly involved in the sympathetic hyperarousal in PTSD.[21] Through stimulation of the vagus, these brain areas and subsequent neurochemical systems are activated and reregulated. The vagus works to decrease the sympathetic response and boost the parasympathetic response to restore the balance of the autonomic nervous system.

Below we propose a series of potential mechanisms by which VNS, including taVNS, could potentially positively impact the symptoms and underlaying mechanisms involved PTSD.

Fear Extinction

Pathologically intense intrusive and spontaneous memories of traumatic events and the avoidance of these memories are common symptoms of PTSD. The emotional state behind these memories makes them deeply connected in the brain. Extinction of the fear and emotional ties to these memories requires the creation of new memories that override the traumatic ones within the brain. VNS has been found to accelerate the fear extinction process through increased release of norepinephrine in the amygdala and prefrontal cortex.[22] Due to the boost in parasympathetic response caused by VNS and the functionality of the amygdala and the prefrontal cortex, new memories are created.

Amygdala/Hippocampus

Due to the overall general decrease in activity in the amygdala and hippocampus, declarative memory dysfunction is a common problem in PTSD patients.[23] The mediation of neurohormones like

cortisol and epinephrine by the vagus in the hippocampus and amygdala, allows for increased memory formation and retention.[23,24] This increase in memory function aids in the creation of new memories and fear extinction learning.

Serotonin (5HT)

As VNS increases norepinephrine in the amygdala and the prefrontal cortex, serotonin (5HT) cell bodies in the dorsal raphe are also activated.[25] This results in secondary effects on the same brain regions as norepinephrine. Therefore, the increase in serotonin due to VNS could have a similar effect to SSRIs without the negative effects of desensitization to serotonin receptors.[26]

Hypothalamus/HPA Axis

Vagal afferents project to the hypothalamus and activate the HPA axis.[21] VNS treatment increases HPA axis activation helping to rebalance the sympathetic/parasympathetic tone after a stress response. Therefore VNS in PTSD patients restores homeostasis to the dysregulated HPA axis.[27]

Prefrontal Cortex

The prefrontal cortex is known to be involved in social and cognitive functions. Brain pathways for executive functions such as decision making, planning, thinking, and emotional control are located within the prefrontal cortex. The regulation of negative emotion relies on the interaction of the prefrontal cortex with the amygdala and hippocampus. The communication between these brain areas is stunted in PTSD patients. VNS treatment is known to increases norepinephrine in neurons projecting from the LC to the amygdala and into the prefrontal cortex. This increase repairs the stunted connection and revives the regulation of negative emotion through the prefrontal cortex.

Inflammation

The vagus also plays a key role in the regulation of cytokines response to stress. Cytokines such as, IL-6, IFN, and TNF alpha, help signal the immune system to increase or decrease inflammation. An influx of cytokines leads to excessive inflammation which is often found in PTSD patients. Stimulation of the vagus regulates these cytokines to a more normal level. Inflammation markers previously demonstrated to increase in patients diagnosed with PTSD are found to have decreased with after VNS treatment.[28] Depression and anxiety have been associated with increased inflammation and it has been hypothesized that this effect may be bidirectional.[29–31]

The aim of this pilot study was to evaluate comfort level with the taVNS device, compliance with study protocol, and effect of taVNS on symptom severity scores in a PTSD population. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and the PROMIS-29 quality-of-life assessment were used to compare PTSD severity and quality-of-life changes from baseline (BL). taVNS stimulation was delivered using the Evren Technologies Phoenix prototype device, a novel take-home taVNS system.

Materials and Methods

Study Overview

We conducted a single arm, unblinded, longitudinal pilot trial to determine the usability, feasibility, and safety of taVNS in a PTSD population. The pilot trial included participants with a confirmed PTSD diagnosis by the PTSD Checklist for the DSM-5 (PCL-5) and a clinical interview. The study was approved by the Western IRB on 11/20/2019; IRB Tracking Number: 20192797. Data were collected from September 2020 to July, 2021.

Participants

14 participants diagnosed with PTSD were enrolled in the study. 12 participants completed the study with two voluntarily withdrawing at the end of the first (non-treatment) month due to difficulty in completing the CAPS-5 assessment. Thus, there were 12 participants in the treatment portion of the trial. Demographics are shown in Table 1.

Demographic and treatment data

	taVNS stimulation, n=12
Gender Male Female	 n=7 n=5
Age Average (years) Range (years)	 44 21-61
Years with PTSD Average (years) Range (years)	 18.8 1.5-53
Military Veterans (#)	8
Veterans reporting trauma resulted from active duty (#)	8
Veterans reporting trauma resulted from combat (#)	4
Participants reporting significant TBI prior to or during traumatic event (#)	4
Reported taking medication(s)* while enrolled in study	9

Table 1 **medications included: Lexapro, Celexa, Prozac, Wellbutrin, Cymbalta, Zoloft, Seroquel, Topamax, Adderall, Methocarbamol and CBD*

Although the study did not formally screen for Traumatic Brain Injury (TBI), a general health interview was conducted during enrollment. During this interview, four study participants were identified as having significant TBI events during or before the trauma that produced PTSD.

Exclusion Criteria

The primary exclusion criteria included participants with a history of drug or alcohol abuse within the last 6 months, a history of bradycardia or tachycardia, seizures or epilepsy, high risk of suicidality, and participants with psychotic disorders but not mood disorders.

Design

Participants were not required to stop or change any current PTSD treatments or therapies while participating in this trial. They were asked to maintain, to the best of their ability, all medications and treatments, for the duration of the study and to refrain from starting any new medications or treatments until after the final two month assessments.

After enrollment, study participants were monitored via weekly phone check-in meetings for

one month before using the taVNS device. During these meetings a PCL-5 was administered to track self-reported symptoms. After the one-month study initiation, participants were administered a Clinician Administered PTSD Scale (CAPS-5) (one month version) and a PROMIS-29 quality-of-life assessment to establish baseline scores (BL). They were then given the Phoenix prototype taVNS device, a novel take home taVNS device and instructed on how to use it.

The weekly symptom check-in calls continued during the device use period. After both the first and second months of device use, participants repeated the CAPS-5 and PROMIS-29 assessments.

Assessments

The Clinician-Administered PTSD Scale (CAPS-5) assessment and the PROMIS-29 survey were conducted at the end of the first and second month of device use. The CAPS-5 was used to measure improvement in PTSD and is widely considered the gold standard scale for symptom severity measurement. This 30 question assessment measures symptoms over 1 month and is scored between 0 and 80 points. The PROMIS-29 is a validated, self-report questionnaire that assesses Quality-of-life (QOL) over 7 domains.

Qualitative feedback was gathered by study coordinator regarding device usability and compliance during weekly check-in calls.

Device, earpiece, calibration, and stimulation

The stimulation was provided by the Phoenix device, a novel taVNS prototype. The custom-made earclip contacted the concha and cymba conchae of the left ear (Figure 1). The participants were directed to apply a small ball of conductive electrode gel to the inner rim of the ear where the electrodes would be placed. They were asked to use the device twice daily, once in the morning and once in the evening, for 30 minutes each session. Biphasic stimulation pulses were delivered at a rate of 25 Hz, width of 300 ms.

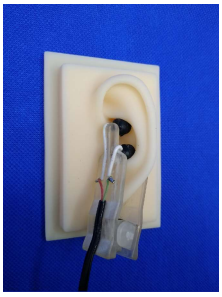

Figure 1: Placement of earclip with 2 electrodes

Calibration process: The initial calibration session was performed under the guidance of a study coordinator. The stimulation current was slowly increased to the perception threshold based on subjective patient feedback and then the stimulation was then further increased up to the lowest level that causes mild discomfort. All testing was performed below the discomfort threshold level and was based on the comfort level of participant. After the initial guided calibration session, participants calibrated the stimulation level before each use to a similar intensity unsupervised.

Results

Overall, study compliance was high. 11 out of 12 participants were compliant with the study protocol. Compliance was defined as a participant using the device >50% of the total recommended number of times, determined via discussion during weekly calls. In a questionnaire after the completion of the study, all participants stated they enjoyed using the device, felt that it positively impacted their symptoms, and would continue using the device if able after the end of the study including the one non-responder.

The device was well tolerated. A few subjects reported minor discomfort due to the hard earpiece but this did not prevent device use or study compliance. All participants were able to use the device after a single short demonstration with minimal difficulty. No adverse events were reported.

Participants demonstrated an average 10.9-point reduction in CAPS-5 scores at month 1 (paired t-test P=0.0206 95%CI 2.0 – 19.8) and an 18.8-point reduction at month 2 (paired t-test P=0.0013 95% CI 9.2 – 28.5). 11 out of the 12 study participants experienced a greater than 6-point reduction in CAPS-5 score (Figure 2). Four study participants achieved full remission levels (CAPS-5 Score <12). One participant was a non-responder with a CAPS-5 reduction of less than 6 points.

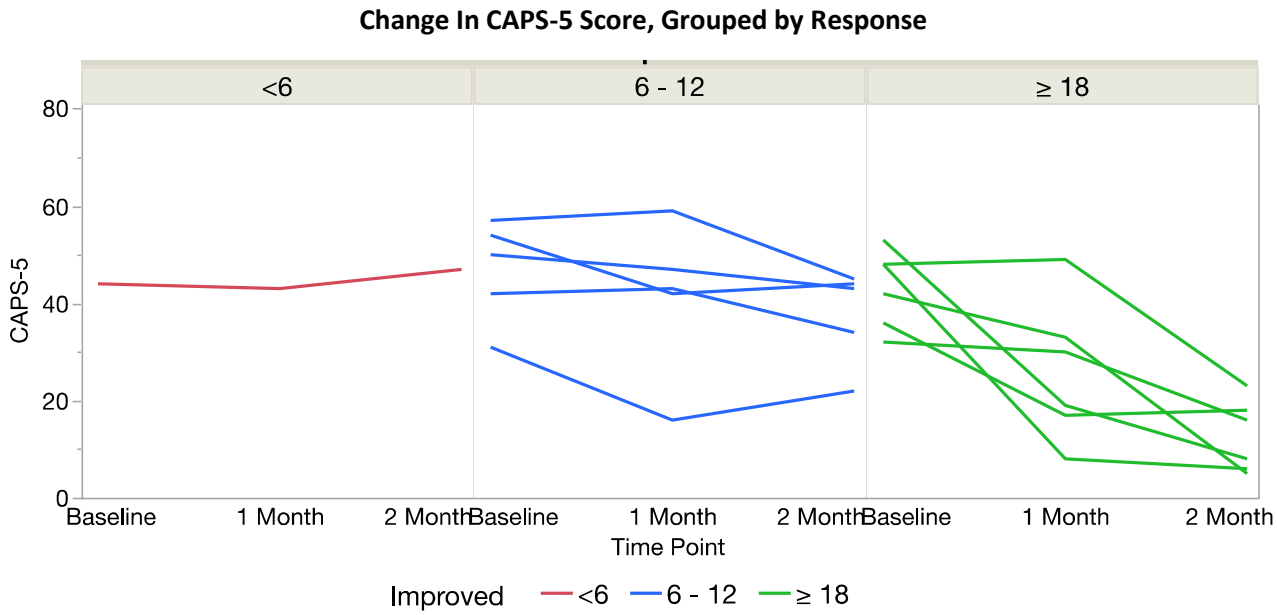

Figure 2 – The average CAPS-5 scores at baseline, 1 month, and 2 months for the 12 study participants charted by level of response (change in CAPS-5 points). Red indicates a treatment non-responder, blue represents a 6-12 point reduction, and green represents a large response to treatment (>18 point reduction).

The analysis of the PROMIS-29 results uses the PROMIS T-score metric.[1] In our study, the change from baseline to two months showed statistically significant improvement in 5 of the 7 domains (paired t-tests), as shown in Figure 3. Anxiety/Fear had an average improvement of 9.1 (p = 0.0021); Depression/Sadness an improvement of 5.9 (p = 0.0294); Fatigue an improvement of 7.6 (p = 0.0036) Sleep Disturbance an improvement of 9.23 (p = 0.0038); and the Ability to Participate in Social

Roles/Activities an improvement of 5.6 (p = 0.0257). Small improvements were seen in both Pain Interference and Physical Function, but they did not reach statistical significance in this study.

Clinically Significant Improvements in 5 of 7 Domains on PROMIS-29

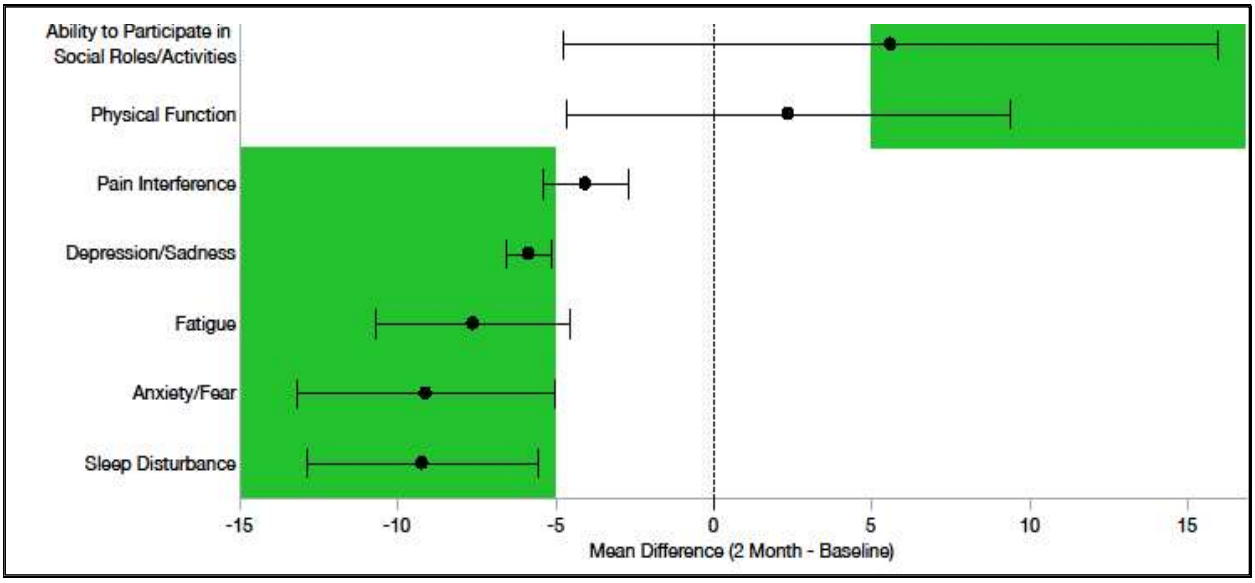

Figure 3 – The figure above displays the average change (2 months-baseline) and 95% confidence intervals for the change in PROMIS-29 T-scores for each domain, when looking at all participants. The green box represents a greater than 5-point change that is generally considered clinically meaningful. Ability to Participate in Social Roles and Physical Function are positively scored, with the other 5 domains being scored on the negative side of the scale. For the latter, a reduction in score is considered an improvement. Only Pain Interference and Physical Function results did not reach clinical significance.

Although the study group only contained four participants with a significant TBI, three of them achieved complete remission (CAPS-5 score <12). The mean CAPS-5 improvement from baseline for the non-TBI vs TBI groups were 10.7 vs 32 (p=0.07) at two months. These results are worth further investigation, especially given that PTSD risk is elevated in people with history of TBI and they often have reduced treatment efficacy with current therapies .[32]

Discussion

The purposes of the present study were to evaluate the feasibility of the study design, the usability of the Phoenix prototype take-home device, and to assess safety of taVNS in participants suffering from PTSD. We found that taVNS twice daily for 30 mins is a feasible study design with 11 out of 12 participants in compliance. All subjects were able to use the device at home and 92% of the subjects were compliant with the protocol for the full 2 months. This is very promising given the low adherence rates typically found in PTSD populations.[33] We also found that the Phoenix prototype was easy-to-use and the stimulation was safe as no adverse side effects were reported.

Although the pilot trial was only a single arm and not powered to determine the efficacy of taVNS in reducing PTSD symptoms, the trends in the data suggest that taVNS may have an effect in producing a meaningful reduction in CAPS-5 scores of people diagnosed with PTSD. These findings are in

alignment with other research which showed that twice daily vagus nerve self-stimulation with transcutaneous cervical VNS for three months similarly reduced PTSD symptoms compared to sham stimulation.[34] In addition, other similar taVNS protocols have demonstrated effectiveness in major depressvie disorder.[17,18]

The data trends also suggest taVNS may increase quality-of-life demonstrated by the PROMIS-29 questionnaire. Five of the seven domains assessed in the PROMIS-29 questionnaire showed statistically significant and clinically meaningful improvement in this small study. The quality-of-life results may indicate broader functional improvements due to this treatment method.

The improvements in quality-of-life are complex and may not be solely explained by a reduction in CAPS-5 symptoms. The participants in this trial had a high level of physical function at baseline which may shed light on the reason these results were not clinically meaningful for this domain.

There is reason to believe that VNS could have an independent positive effect on the individual sub-scores of the quality-of-life assessment, such as Social Activities,[35–42] Depression,[16,17,43] Fatigue,[44,45] Anxiety,[16,17,46–49] and Sleep Disturbance.[16,50,51] This is an area that should be investigated in future studies.

Based on other research, we expected VNS to have a positive effect on pain interference[14] and the lack of statistical significance in this domain of the PROMIS-29 may be due to the relatively low baseline level of pain in this study's participants.

This study was not designed to assess co-morbid TBI and lacked appropriate screening and measures of TBI severity. Given this, though under powered, exploratory analysis of the subgroup of participants with a history of TBI demonstrated appears to indicated a greater response as compared to those without a history of TBI. This may warrant further investigation.

PTSD studies often have low compliance and high dropout rates[12] to treatment. The protocol adherence and satisfaction with the device in this pilot study indicate that taVNS could be feasible for extended home use and ultimately wide adoption by the PTSD population. To the best of our knowledge, we believe this is the first study to demonstrate a positive effect on PTSD and quality-of-life (as measured by CAPS-5 and PROMIS-29) of an at-home taVNS treatment.

Conclusion

This study demonstrated that taVNS is feasible and safe in participants suffering from PTSD. taVNS may be a promising treatment for PTSD due to initial testing showing impressive CAPS-5 score reduction in this small group. Additional randomized, placebo-controlled trials are needed to determine whether taVNS improves PTSD symptoms and quality-of-life in people suffering from PTSD.

Study Limitations

The most significant limitations of this pilot study are the small number of participants, and lack of a sham comparator arm. These will hopefully be addressed in future studies in this population.

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Eric Porges, PhD - eporges@phhp.ufl.edu ; Assistant Professor in the Center for Cognitive Aging & Memory, Department of Clinical and Health Psychology, at the University of Florida.

Damon Lamb, PhD – dlamb@ufl.edu; Assistant Professor, Dept of Neuroscience at the University of Florida

John Williamson, PhD – john.williamson@neurology.ufl.edu; Associate Professor, Dept of Neurology, Director, Research Center for Neuropsychological Studies at the University of Florida

Weaver Gaines – weaver.gaines@evrenvns.com; current CEO Evren Technologies

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DECLARATIONS

Statements relating to ethics and integrity policies:

- The study was approved by the Western IRB on 11/20/2019; IRB Tracking Number: 20192797. Data were collected from September 2020 to July, 2021.
- Data availability statement: The data that support the findings of this study are available from the corresponding author, RM upon reasonable request.
- Conflict of interest: All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; or (c) approval of the final version. Elliott, Aytug, Karow, and Euliano are all equity holders in Evren Technologies, Inc., hence, they might benefit financially from publication of this paper. The remaining authors certify that they have no known conflicts of interest.
- Ethical standards statement: Research was conducted in accordance with the principles embodied in the Declaration of Helsinki and under the aegis of the wcg IRB (#2019001). All subjects gave their informed consent for inclusion before they participated in the study. No identifiable information is included in the publication. All study data is treated as confidential, and any data revealing personal information is kept in a locked cabinet.
- Patient consent statement: Each participant signed an informed consent to participate in the study. As no identifiable information is included in the publication, no consent to publish was obtained.
- Permission to include material from other sources: There is no material from other sources.
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Marcus Elliott, BS – Project manager: wrote draft protocol, screened patients, managed study documents, drafted manuscript
Annalese Pfahler – reviewed, confirmed and organized references
Christine Aytug, MBA – edited and submitted manuscript
Blythe Karow, MBA – developed protocol strategy, managed trial issues
Karen Copeland, Ph.D. – analyzed data and provided statistical support
Richard Marshall, Ed.D. - obtained patient consents and histories, executed trial protocol
Neil R. Euliano, Ph.D. – Designed device, supported protocol design and data analysis