Randomized Study Of Novel Enuresis Alarm (GoGoband®)Vs Standard Bedwetting Alarm

Protocol Number
2000031281

NCT05214131

Protocol Version
February 20, 2024
Version #6

IDE Number:
IDE Holder:

PRINCIPAL INVESTIGATOR:

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Confidentiality Statement:

2000031281

February 20, 2024

REVISION HISTORY:

Include the IRB approved protocol version number and date for each revision of the protocol. All version history should remain in the table and never be deleted. The oldest IRB approved version of the protocol should be listed on the top row. The most recent IRB approved version should be listed on the bottom row.

Revision #	Version Date
1	Sept 1 2021
2	Sept 9 2021
3	November 18, 2021
4	December 28, 2021
5	Jan 15 2022
6	February 20, 2024

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Synopsis

Primary Objective

Identify the dry night rate in patients using the GoGoband® nocturnal enuresis device vs a standard Pflaunger bedwetting alarm.

Secondary Objective (if applicable)

to ascertain if familial incidence of nocturnal enuresis has an effect on outcomes

Study Duration: total 3 years, 2 years active with 1 year for analysis

Study Design

Include a high-level description of the study design.

This is a prospective randomized comparison of GoGoband® vs standard nocturnal enuresis alarm

Number of Study Sites

Study sites will include all clinic sites where patients are seen in the Yale New Haven Health System

Yale New Haven Children's Hospital clinic WP2
Yale New Haven Children's Hospital Longwharf Clinic
Yale New Haven Children's Hospital Trumbull clinic
Yale New Haven Children's Hospital Norwalk clinic
Yale New Haven Children's Hospital Greenwich Clinic

Study Population

Define the study population, source of the participants, and selection rationale. Study subjects should be representative of the population of interest.
Provide a brief description of the study population (e.g., healthy/sick, children/adult, inpatient/outpatient, demographic groups), the characteristics of different study groups, if applicable, and the source of participants. Do not list inclusion/exclusion criteria here, as these will be listed in the upcoming sections.

Study population will consist of children seen in our Bladder and continence program who present with nocturnal enuresis. Patients will be evaluated with validated questionnaire to confirm that they are monosymptomatic nocturnal enuretics and will be asked if they wish to participate in the study if they are between 6 yrs and 21 years of age.

Number of Participants: 150 children and adolescents

Primary Outcome Variables

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Variables: Wetting event: Dry or Wet Did patient wear the device: yes or no used to measure compliance Is the patient considered cured (dry 29/30 nights) : yes or no Is the patient partially better (improvement of 50% or more compared to pre treatment) Did the patient show no improvement (<50% improvement compared to Pre treatment)
Secondary and Exploratory Outcome Variables (if applicable) Did parents wake to assist child when alarm goes off: yes or no (2 nd measure of compliance) What is the role of parental assistance in Dry night rates Is there a correlation with parental NE and response to alarm

Abbreviations

Abbreviation	Explanation
MNE	Mono symptomatic nocturnal enuresis
NMNE	Non Mono symptomatic nocturnal enuresis
SNEA	Standard Nocturnal enuresis Alarm
DV	Dysfunctional Voiding
DVQ	Dysfunctional Voiding questionnaire
PPG	Photoplethysmography

Glossary of Terms

Glossary	Explanation

Table of Contents

1 Introduction

1.1 Introductory Statement

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to ICH GCP guidelines, and according to CFR 21 Part 812, other applicable government regulations, and Institutional research policies and procedures.

2 Background

2.1.1 Device Preclinical Experience

GoGoband® is a new biometric, artificial intelligence and machine learning powered wearable bedwetting alarm that uses Pavlovian or classical conditional training to increase the effectiveness of enuresis alarm treatment. This is accomplished with the use of heart rate data, heart rate variability (HRV) analysis and real time monitoring that combines the use of algorithms developed with machine learning to learn the individual profile of each patient. Each device consists of a photoplethysmography (PPG) heart rate sensor worn on the calf, a beside tablet, a Bluetooth moisture sensor and a parent app. The first 7-10 wetting episodes are utilized to develop the individualized program based on HRV data to predict when an impeding urination event is going to happen. Artificial intelligence in our web-based database develops hundreds of thousands of models and selects the best one to predict a urination event. As time moves along the machine learning continues to modify the signaling parameters as the child's bedwetting improves. In the weaning phase the system gradually eliminates alarming episodes in a controlled fashion and as the children continues to progress it will eliminate all alarming. Once this stage is completed and the child remains dry for a week consecutively, they are deemed cured. This process can last a few days to several months with some children using the alarm remaining dry on day one and never having another accident without the alarm going off and others remain in need of the system to continue to wake them and keep them dry.

Our most recent data indicates that we can achieve a dry night rate as high as 94% in compliant patients that use the device at least 80% of the time. these results are in stark contrast to the best reported outcomes of 70% in European SNEA studies.

In summary the GoGoband® is a new biometric, artificial intelligence and machine learning powered wearable bedwetting alarm that uses Pavlovian or classical conditional training to increase the effectiveness of enuresis alarm treatment. The non-intelligent alarms on the market today rely on a form of operant conditioning which in many cases relies on negative reinforcement i.e. waking the child up to change the bed or do their laundry.

2.1.2 Device Clinical Experience

Data to be presented at the American urological association meeting scheduled for Sept 10, 2021 based on quality Improvement study

Abstract ID: 21-3995
Abstract Title: A Novel Bedwetting Alarm Utilizing Real Time Heart Rate Analysis and Artificial Intelligence to Wake Patients Prior to Wetting: Preliminary Outcomes
Presenting Author: Israel Franco
Session Details
Type: Podium - PD15
Title: Pediatric Urology I
Date: Friday, September 10, 2021
Time: 3:30 PM - 5:30 PM
Building: Venetian-Sands Expo Center
Room: Marco Polo 804

A copy of the abstract is attached below

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21-3995

A NOVEL BEDWETTING ALARM UTILIZING REAL TIME HEART RATE ANALYSIS AND ARTIFICIAL INTELLIGENCE TO WAKE PATIENTS PRIOR TO WETTING: PRELIMINARY OUTCOMES

Israel Franco, New Haven, CT, Jon Coble, Michael Kohonoski, Steve Zyglowicz, Ashland, VA*

INTRODUCTION AND OBJECTIVE: Bedwetting alarms (BWA) have been around for more than half a century with little innovation in the field. GOGOBand® utilizes real time heart rate variability (HRV) analysis and applied artificial intelligence (AI) to create an alarm that is capable of waking the patient up prior to wetting . Our Aim was to evaluate the efficacy the new Smart GoGoBand®.

METHODS: Data was retrieved and analyzed from our servers, of patients who purchased the GOGOBand® which includes a heart rate monitor, moisture sensor, bedside tablet and app for the parents phone in this study. There are 3 modes, training; where the individualized HRV parameters are used to build the alerting model. Once patients are done with training, they enter the Predictive mode where they receive an alarm if an impending urination event is noted. In Weaning mode the alerting is gradually suppressed. Only patients that used the alarm for more than 30 days were included. Data analysis was done with SPSS and xlstat.

RESULTS: A total of 40 subjects that have used the system for more than 30 nights were included in this analysis. Gender mix was 33 males (82.5%) and 7 females (17.5%). The mean age of the subjects is 10.6 yrs. Subjects wet the bed an average of 6.2 nights per week prior to treatment. Severity and number of accidents per night had no impact on the ability to achieve dryness with the GOGO Band® device in logistical regression analysis. The data was also segregated based on compliance since it became clear during the analysis that compliant patients achieved better results than non-compliant patients.

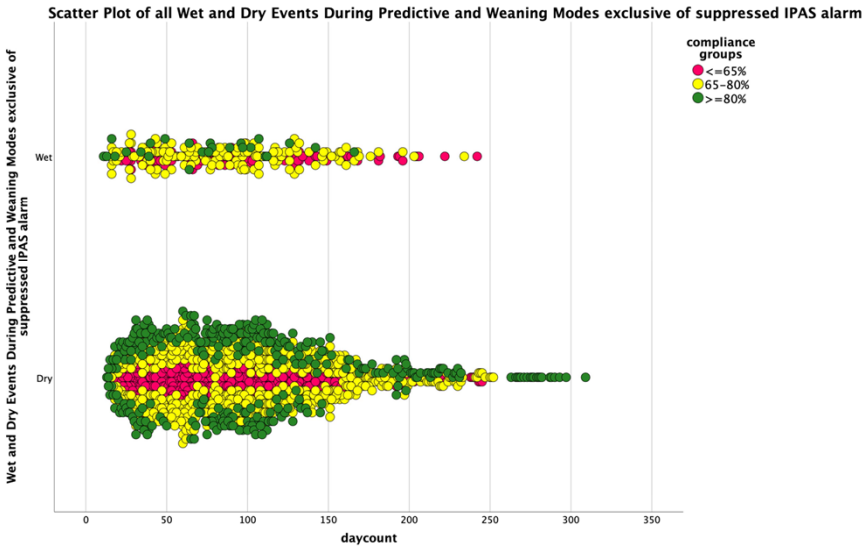
Mode	% dry with <65% compliance	% dry with 65-80% compliance	% dry with >80% compliance	Total nights
Training	17.6[a]	[a]71.6	10.8[a]	251
Predictive	80.2[a]	78.6[a]	93.8[b]	760
Weaning	80.6[a]	86.8[b]	92.9[c]	1460
Total	80.4[a]	81.9[a]	92.1[b]	2451

Each different letter superscript in each row denotes a statistically different outcome (p<0.05).

The figure depicts the degree of predictive alarming and the patient's ability to stay dry. It is clear that the high compliance patients (green dots) have less alarming events indicating that the system is just not functioning randomly but the machine learning algorithm has learned to sense when an accident is impending.

CONCLUSIONS: Our findings indicate that the GOGOBand® in high compliance patients has a 93% dry night rate that surpasses standard alarms. The data indicates that there are physiological changes which lead to a change in bladder-brain processing that allows for the patient to sleep through the night and not wet themselves.

Source of Funding: NONE



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More recent data which includes 60 patients yet to be presented indicates that success rates are higher during the weaning phase

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Control/ Tracking Number: 2021- A- 519- SPU
Activity: Abstract
Current Date/ Time: 7/ 26/ 2021 9:51:45 PM

Analysis of 60 patients treated with the GoGoBand AI Powered Bedwetting Alarm

Author Block: Israel Franco, MD[1], Jon Coble, MBA,[2], Michael Kohonowski, MBA,BSE[3], Michael Kohonowski, MBA,BSE[3], Steve Zyglowicz, BSE[3].
[1]Yale University, New Haven, CT, USA, [2]GoGoBand, Ashland, VA, USA, [3]Gogoband, Ashland, VA, USA.

Abstract:
BACKGROUND: Bedwetting alarms (BWA) have been around for more than half a century with little innovation in the field. GOGOBand® utilizes real time heart rate variability (HRV) analysis and applied artificial intelligence (AI) to create an alarm that is capable of waking the patient prior to wetting . Our Aim was to evaluate the if the e! cacy continues to remain high with the addition of 20 new patients to our servers. **METHODS:** Data was retrieved and analyzed from our servers, of patients who purchased the GOGOBand® which includes a heart rate monitor, moisture sensor, bedside tablet and app for the parents phone in this study. There are 3 modes, training, where the individualized HRV parameters are used to build the alerting model. Once patients are done with training, they enter the Predictive mode where they receive an alarm if an impending urination event is noted. In Weaning mode the alerting is gradually suppressed. Only patients that used the alarm for more than 30 days were included. Data analysis was done with SPSS and xlstat. **RESULTS:** : A total of 60 subjects that have used the system for more than 30 nights were included in this analysis. Gender mix was 46 males (76.6%) and 14 females (23.3%). The mean age of the subjects is 10.2 yrs. Subjects wet the bed an average of 6.2 nights per week prior to treatment. Severity and number of accidents per night had no impact on the ability to achieve dryness with the GOGO Band® device in logistical regression analysis. The data was also segregated based on compliance since it became clear during the analysis that compliant patients achieved better results than non- compliant patients. A crosstab analysis was performed and is reported in table 1. The data clearly indicates that compliant patients > 80% are able to remain dry 96% of the time once they enter the weaning phase. **CONCLUSIONS:** Our findings indicate a 96% success rate in patients that are weaning, this translates to 1.2 wet nights per 30 days. This compares to the same group when starting the use of the alarm had only 14.4 dry nights per 30 days. The addition of the 20 patients indicates that that our results are enduring and seem to be improving as we continue to increase the number of patients that are on the system.

compliance groups			training	predictive	Wean	Total
<=65%	dry	Count	311_a	881_b	1584_c	2776
		% within group	59.70%	77.30%	87.50%	80.00%
	wet	Count	210_a	258_b	226_c	694
		% within group	40.30%	22.70%	12.50%	20.00%
>=65 and <=80%	dry	Count	92_a	240_a	228_b	560
		% within group	70.80%	71.90%	86.00%	76.80%
	wet	Count	38_a	94_a	37_b	169
		% within group	29.20%	28.10%	14.00%	23.20%
>=80%	dry	Count	26_a	490_b	145_b	661
		% within group	48.10%	91.10%	96.00%	89.00%
	wet	Count	28_a	48_b	6_b	82
		% within group	51.90%	8.90%	4.00%	11.00%

Same subscript letter denotes a subset whose column proportions do not differ significantly from each other at the .05 level.

Author Disclosure Information:

I. Franco,
GoGoBand Management position, Chief Science O! cer.
J. Coble,
Gogoband Employment, Management position, CEO.
M. Kohonowski,
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S. Zyglowicz,
gogoband Employment, Management position, Chief Technology O! cer.
Category (Complete): Bowel/ Bladder Dysfunction/ Urinary Tract Infection/ Vesicoureteral Reflux
Presentation Preference (Complete): Podium Presentation

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2.2 Background/prevalence of research topic

Urologic literature recognizes that enuresis alarm treatment for nocturnal enuresis is a form of behavioral therapy. It works in conjunction with both positive reinforcement and aversive negative experiences and has been shown to be effective after Mowrer and Mowrer introduced it in 1938. Unfortunately, the literature, using the current effectivity standard of maintaining four weeks of dry nights criteria from the International Children's Continence Society consensus document, reveals that it is not as effective as it is stated. Using the new standard, there are few publications that have success rates that exceed 50%[2, 3]. When the published abandonment rates (~30%) and relapse rates (~50%) are taken into consideration, the effectivity of current enuresis alarm treatment is further reduced to only 25-33%. Innovation in enuresis alarm treatment for pediatric enuresis has been stagnate for the last 30 years and clearly a better method of enuresis alarm treatment in children is necessary.

There is evidence that there is a disequilibrium in the sympathetic/parasympathetic balance in enuresis subjects utilizing heart rate variability (HRV) monitoring[4-6]. For urination to occur there must be a deactivation of the sympathetic and activation of parasympathetic flow. There are numerous other studies indicating that subjects with bladder over-activity also have a predominance of low frequency signals based on HRV analysis.[7-9] This data coincides with our own pilot work where we have seen that an HRV spike is evident prior to an enuresis event. We therefore hypothesis that there should be a predictable change in HRV parameters that signal sympathetic/parasympathetic activity and balance, utilizing real time monitoring of subjects with nocturnal enuresis prior to an accidental voiding event. Our modeling indicates that we can predict an event by identifying an changes in heart rate as well as ultra-low frequency HRV signal utilizing signal processing in a patented method that allows for the real-time analysis of HRV to identify these specific signals. Artificial intelligence in our web-based database develops hundreds of thousands of models and selects the best one to predict a urination event. As time moves along the machine learning continues to modify the signaling parameters as the child's bedwetting improves. In the weaning phase the system gradually eliminates alarming episodes in a controlled fashion and as the children continues to progress it will eliminate all alarming. Once this stage is completed and the child remains dry for a week consecutively, they are deemed cured. This process can last a few days to several months with some children using the alarm remaining dry on day one and never having another accident without the alarm going off and others remain in need of the system to continue to wake them and keep them dry.

3 Rationale/Significance

3.1 Problem Statement

At the present time we have no side-by-side comparison studies of GoGoband® vs SNEA. Since many of the prior studies were conducted using variable outcome parameters that makes direct comparisons of studies difficult it would be beneficial to obtain comparable data from the 2 groups and compare dry night rates for the 2 devices.

3.2 Purpose of Study/Potential Impact

Our preliminary quality improvement data indicates that the GoGoband® is more efficacious than both medication and SNEA in an uncontrolled environment when deidentified data was analyzed off our servers. Our present database does not allow us to discern if patients are MNE or NMNE. Without this ability as well as for controlling for behavioral and academic problems which are known to affect outcomes in nocturnal enuresis studies, we are not able to compare our results definitively and accurately to other treatment modalities.

3.2.1 Potential Risks

Risks associated with the alarms:

- The risk of electric shock is minimal since the whole system is a battery operated low voltage system, the only part in contact with the patient is a heart rate monitor which is an approved Photoplethysmography (PPG). PPG technology is presently ubiquitous today in most smart watches and heart rate monitors. Similarly, the risk of shock from detachment of the wired ends in the regular alarm is minimal since it is low voltage battery system.
- As the device is being installed and during usage, cord entanglement is a possibility, and mitigated by wearing a shirt over the cord.
- Choking can be a hazard if any of the associated components are placed in the mouth. The age for this study is 6 or above which would minimize this risk, additionally we do not allow for the enrollment of children with developmental or behavioral disabilities which should further minimize this risk.
- If the user chooses to attach the alarm unit using a safety pin, use of a secure pin that does not come loose easily will mitigate this risk.
- The child may become disoriented by the sound of the alarm. To mitigate this a soft rug or padding at the bedside will help prevent injury should your child roll out of bed upon awakening. Minimizing the elevation of the bed above the floor is advisable.
- There may be no benefit from either alarm therapy
- Some children may be startled by the alarm and may not wish to continue to use the device, if so, they will exit the study.
- There is a risk that internet service at the home may be inadequate for proper functioning of the GoGoband® alarm, if so, they will need to exit the study.

3.2.2 Potential Benefits

Nocturnal enuresis is a source of depression, social isolation, and has even been linked to teenage suicide, and physical abuse of children. It is also significant financial and emotional drain on parents and families. Current enuresis alarm treatments are marginally effective requiring parents to seek specialist medical advice, which may not be readily available, and to spend large amounts of money on drug therapy and diapers. Many parents have an aversion to giving their children medications such as DDAVP or Imipramine to manage their enuresis

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because of potential side effects, even though rare. A mechanism that allows for early warning of an impending urination event to the patient and parent is a boon for society and to the patients' own self-esteem and the families economic well-being. Our non-invasive, home-based, predictive alarming system will help satisfy these treatment needs by providing a superior conditional enuresis alarm therapy while keeping the child dry at a fraction of the cost of drug therapy or diapers with virtually no negative side-effect risk.

4 Study Objectives

4.1 Hypothesis

Our hypothesis is that the GoGoband® is more effective than SNEA and Desmopressin in the treatment of Nocturnal Enuresis

4.2 Primary Objective

The primary objective of this study is to determine whether the GoGoband®] is as effective or more effective in comparison to children who use SNEA in a population of MNE patients with no underlying ADHD in a 3 month period.

4.3 Secondary Objectives (if applicable)

To ascertain if familial incidence of nocturnal enuresis has an effect on outcomes

5 Study Design

5.1 General Design Description

We propose the following study in patients who have been evaluated for primary nocturnal enuresis in our Yale New Haven Clinics.

- All patients to be evaluated for nocturnal enuresis will undergo standard evaluation and initial treatment for nocturnal enuresis which includes:
- Assessment Of Bowel Habits,
- Fill Out A Questionnaire To Evaluate For Voiding Dysfunction
- Treatment with routine bedwetting protocol of:
  1. Stopping drinks 1 HR before bedtime, meals at least 3 hrs before bedtime, eliminating milk and ice cream from dinner and on, making sure that bowel movements are occurring 4 times per week and treating appropriately if necessary.
  2. On return visit bedwetters and parents will be given the option of using medication , no further treatment, or alarm therapy.
  3. If patients choose alarm therapy, they will be asked if they wish to participate in the Randomized study comparing GoGoband® vs SNEA.
  4. Alarms will be provided to the patients free of cost to participants
  5. Patients in the alarm group will be treated for 3 months continuously.
  6. Patients in the SNEA group will record nightly if they wet their clothes and the report will be recorded and reviewed weekly
  7. GoGoband® patients' data will be automatically saved on the HIPPA Compliant servers and subsequently reviewed at the end of the week.

5.1.1 Study Date Range and Duration

Each patient will be in the study for 90 days. The study duration will be 2 years to accrue enough patients willing to participate in the study and 1 year for data analysis and publication

5.1.2 Number of Study Sites

Study sites include:
Yale New Haven Children's Hospital clinic WP2
Yale New Haven Children's Hospital Longwharf Clinic
Yale New Haven Children's Hospital Trumbull clinic
Yale New Haven Children's Hospital Norwalk clinic
Yale New Haven Children's Hospital Greenwich Clinic

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

Variables:
Wetting event: Dry or Wet
Did patient wear the device: yes or no used to measure compliance
Did patient take the medication: yes or no used to measure compliance
Is the patient considered cured (dry 29/30 nights) : yes or no
Is the patient partially better (improvement of 50% or more compared to pre treatment)
Does the patient show no improvement (<50% improvement compared to Pre treatment)

5.2.2 Secondary and Exploratory Outcome Variables (if applicable)

Did parents wake to assist child when alarm goes off: yes or no (2 nd measure of compliance)
What is the role of parental assistance in Dry night rates.
Evaluate parental nocturnal enuresis rates as children and cessation of enuresis and compare to final success outcomes of participants.

5.3 Study Population

1. Any patient seen in clinic for nocturnal enuresis in our clinic is eligible as long as they wet the bed a minimum of 2 times per week and are over 6 years and under 21 years of age
2. All patients will have filled out a DVQ and found not to have daytime voiding issues
3. All patients will not have evidence of hyperactivity or learning difficulties as measured by the DVQ
4. All patients will have a post void residual test prior to randomization. If residual is greater than 30 cc they will be excluded from participation based on the possibility of dysfunctional voiding problem.

5.3.1 Number of Participants

Number of participants: 100 total, 50 in each group GoGoband®, SNEA,
Number to be screened: 200

5.3.2 Eligibility Criteria/Vulnerable Populations

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study

3. Male or female, aged 6 to 21 years
4. In good general health as evidenced by medical history and diagnosed with MNE
5. Ability to and be willing to adhere to the treatment regimen.
6. Subjects to be eligible for the Trial need to have functioning WiFi at home utilizing a home network and not a cellular tethering connection.

An individual who meets any of the following criteria will be excluded from participation in this study:

1. No patient may have had treatment of MNE in the past 6 months whether with medications or alarms
2. Current use of on ADHD medications, Tricyclics, SSRI's, NRI's or any antipsychotic medications.
3. Presence of Autistic Spectrum disorder, ADHD, genetic syndrome associated with developmental or learning disabilities
4. Treatment with another investigational drug or other intervention within last 6 months
5. Any form of Diabetes Mellitus or Diabetes Insipidus
6. No patient with known Chronic renal disease with moderate to severe renal impairment (defined as a creatinine clearance below 50mL/min).
7. No patient with known hyponatremia or a history of hyponatremia.

6 Methods

6.1 Treatment – Device

6.1.1 Intended Use for Device (provide the following information for each device being investigated in the study)

Generic bedwetting alarms

Generic bedwetting alarms which are commercially available and are an FDA class II device
See below the FDA documentation on enuresis alarms

[Code of Federal Regulations]
[Title 21, Volume 8]
[Revised as of April 1, 2020]
[CITE: 21CFR876.2040]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H - MEDICAL DEVICES

PART 876 -- GASTROENTEROLOGY-UROLOGY DEVICES

Subpart C - Monitoring Devices

Sec. 876.2040 Enuresis alarm.

(a) *Identification.* An enuresis alarm is a device intended for use in treatment of bedwetting. Through an electrical trigger mechanism, the device sounds an alarm when a small quantity of urine is detected on a sensing pad. This generic type of device includes conditioned response enuresis alarms.

(b) *Classification.* Class II (special controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to § 876.9.

[48 FR 53023, Nov. 23, 1983, as amended at 63 FR 59228, Nov. 3, 1998]

GoGoband® is a FDA class II device

GoGoband® is a biometric, artificial intelligence and machine learning powered wearable bedwetting alarm uses of heart rate data, heart rate variability (HRV) analysis and real time monitoring that combines the use of algorithms developed with machine learning to learn the individual profile of each patient. Each device consists of a photoplethysmography (PPG) heart rate sensor worn on the calf, a beside tablet, a Bluetooth moisture sensor and a parent app that can alarm the parent that a wetting even is eminent or has occurred.

6.1.2 Device Administration and Schedule

SNEA: Device Will be provided to the patient

1. Instruction will be provided on how to set up the device and use it
2. The device will be worn consecutively for 3 months.
3. The alarm use will be terminated if they have been dry for 3 months consecutively.

GoGoband®: Device Will be provided to the patient

1. Instruction will be provided on how to set up the device and use it
2. The device will be worn consecutively for 3 months
3. The device will follow the built in algorithm in the device to decide when to begin the weaning process.
4. The weaning process will occur automatically until there no more nights in which the system will sound impending urination alarms

Non-compliant patients will be removed from the study. Alarms will not be requested back from the participants.

Reasons for noncompliance will be the following

1. Not taking medication
2. Not using device
3. Not filling in and submitting biweekly logs.

If a bedwetting alarm breaks or is nonfunctional the device will be replaced, and the study will proceed from the last active day

Method of Assignment/Randomization (if applicable)

Randomization will be accomplished by having 100 envelopes with 50 SNEA and 50 GoGoband® choices. The envelopes will be distributed to the sites and pulled randomly at each site.

Age matching:
After 50% enrollment in any group the average age and standard deviation of the group will be calculated and an effort to adjust enrollment so groups are age matched will be made.

6.1.3 Device Calibration
No device calibration is necessary

6.1.4 Storage Conditions
No specific storage conditions are necessary

6.1.5 Concomitant therapy
1 Use of any of the prior medications described in the 5.3.2 exclusions is to be avoided.

2 Use of acetaminophen is acceptable

3 Ibuprofen or any ANSAID may be used but it's use for any reason renders that day as a non-compliant day

3.1.1 Restrictions
no restrictions

3.2 Assessments
3.2.1 Efficacy

SNEA: Device Will be provided to the patient
1. A log will be kept document that the patient wore the device that night
2. Mark if they were wet or dry that morning
3. if the alarm sounded that night
4. whether the device was on the patient in the morning
5. A log will be kept if the patient took ibuprofen or any Ansaid that day

GoGoband®: Device Will be provided to the patient
1. A log will be kept identifying that the patient wore the device that night
2. Mark if they were wet or dry that morning
3. if the alarm sounded that night
4. whether the device was on the patient in the morning
5. A log will be kept if the patient took ibuprofen or any ansaid that day

3.2.2 Safety
Any safety events will be reported to the investigators by the parent or patient at follow up visit or via direct call to the PI on the phone number provided on the consent. Any reportable event which in this case is considered to be a skin injury due to pressure or a burn or if a choking hazard occurred due to a cable or swallowing a portion of the device are considered serious reportable events.

Events such as refusal to wear alarm due to fear of alarm, or startling patients are not considered serious events and do not warrant reporting, but this data will be recorded and reported in the final causes for exit from the study.

3.2.3 Adverse Events Definition and Reporting

The principal investigator or the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project via email as they are reviewed by the principal investigator. The protocol's research monitor(s), IRB study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies will be informed of skin injuries due to worn device or choking incidents. adverse events within 5 days of the event becoming known to the principal investigator."
"The principal investigator or the Institutional Review Board (IRB) or have the authority to stop or suspend the study or require modifications.

3.2.4 Pharmacokinetics (if applicable)

No testing will be performed

3.2.5 Biomarkers (if applicable)

3.3 Study Procedures

3.3.1 Study Schedule

Total study time is 3 months exclusive of prestudy visit which should be within 2 months of start of study.
Prestudy entry:

- all Nocturnal enuresis patients are all evaluated with physical examination and post void residual check.
- DVQ questionnaire is administered
- Inclusion and exclusion criteria evaluated
- treated with standard urotherapy previously described.

Visit 1:

- Confirm that patient has no daytime voiding symptoms identifying patient has MNE and qualifies for study
- Offer the patient treatment Choices:

    - medical treatment if so no longer candidate for study
    - Alarm therapy: If Alarm therapy is chosen: randomize into SNEA or GoGoband®
- Conset to be signed
- Dispense alarm that day or have patient return within a week to have the alarm demonstrated and how to setup and to take home.
- Subject log is given along with alarm.

Visit 2:

- 1 month virtual or in person to follow progress,
- log is handed in, scanned into my chart, faxed or emailed
- new log dispensed

Visit 3:

- 2 month virtual or in person to follow progress
- log is handed in, scanned into my chart, faxed or emailed
- a new log dispensed

Visit 4:

- 3 months virtual or in person to close out study,
- log is handed in, scanned into my chart, faxed or emailed.
- Patients are informed that they can keep the alarm and continue to use it if they wish.

3.3.2 Informed Consent

Informed consent will be obtained from all participants, including assents from appropriately aged minors.

3.3.3 Screening

Screening will be performed at the initial visit by members of the research staff with the use of the DVQ which will confirm a diagnosis of MNE or NMNE.
Other exclusion questions will be ascertained on the initial visit as part of the usual evaluation

3.3.4 Enrollment

The person performing the initial screening and evaluation of the patient will be the person in charge of enrolling the patient

3.3.5 On Study Visits

Study visit 1: enrollment and study logs will be handed out along with alarms
Study visit 2: review of progress
review logs
Identify issues with compliance and correct them if possible
Identify any safety issues

Study visit 3: review of progress
review logs

Identify issues with compliance and correct them if possible
Identify any safety issues

Study visit 4: review of progress
review logs
Identify issues with compliance
Identify any safety issues
Close out study

3.3.6 End of Study and Follow-up

Patients who withdraw from the study due to lack of efficacy of the treatment will then be allowed to continue regular treatment options afforded to patients with MNE.

Patients that failed alarm therapy will be candidates to start treatment with desmopressin and if they fail that they can proceed to the addition of additional medications such as imipramine, atomoxetine, guanfacine or oxybutynin

3.3.7 Removal of subjects

Non-compliant patients will be removed from the study. Alarms will not be requested back from the participants.
Reasons for noncompliance will be the following

1. Not using device
2. Not filling in and submitting monthly logs.

3.4 Statistical Method

3.4.1 Statistical Design

This is a prospective randomized case study comparing outcomes between 2 groups of patients.
Descriptive statistics will be performed on patient characteristics such as age, and sexual make up amongst the participants.
Outcomes will be evaluated between the 2 groups using crosstab analysis of the data
Logistic regression analysis may be performed on the incremental wet dry data vs time to achieving dryness

3.4.2 Sample Size Considerations

A power calculation was performed using
http://powerandsamplesize.com/Calculators/Compare-2-Proportions/2-Sample-1-Sided
A 2 proportion 1 sided power analysis was performed A proportion of 0.5 was used for the SNEA and an expected outcome of 0.8 for the GoGoband® the sampling ratio is 1, the power was set to 0.8 and type 1 error rate of 5%. This gives a sample size of 29 participants.

3.4.3 Planned Analysis

3.4.3.1 Primary Analyses

Outcomes will be evaluated between the 2 groups using crosstab analysis of the data for the following data :
Wetting event: Dry or Wet
Did patient wear the device: yes or no used to measure compliance

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Did patient take the medication: yes or no used to measure compliance
Is the patient considered cured (dry 29/30 nights) : yes or no
Is the patient partially better (improvement of 50% or more compared to pretreatment)
Does the patient show no improvement (<50% improvement compared to Pretreatment)
Logistic regression analysis may be performed on the incremental wet dry data vs time to achieving dryness

3.4.3.2 Secondary Objectives Analyses

Crosstab analysis of Did parents wake to assist child when alarm goes off: yes or no (2 nd measure of compliance)
Logistic regression analyses of What is the role of parental assistance in Dry night rates
Role of familial nocturnal enuresis in treatment outcomes
Logistic regression analysis of spontaneous age remission of enuretic parents to the success of the alarm therapy.
Crosstab analysis of Parents comparing enuretic parents vs non enuretic parents and success with alarms.

3.4.3.3 Safety

The likelihood of safety issues is minimal with bedwetting alarms. Any major safety events will be reported. Also patients who drop out due to excess startling or unwillingness to continue to wear the alarm will be considered failures and included as such in the data analysis.

3.4.3.4 Analysis of Subject Characteristics

Age and sex of patients in each group
Dvq scores of each group

3.4.3.5 Interim Analysis (if applicable)

interim analysis will be done a midpoint to evaluate ages of groups so we can make adjustments to have an age matched cohort.

3.4.3.6 Health economic evaluation

The cost of therapy with SNEA vs GoGoband® over a 3 month period will be evaluated

3.4.3.7 Other

3.4.4 Subsets and Covariates

3.4.5 Handling of Missing Data

Patients who drop out of the study will be considered failures for purposes of the study with regards to success vs partial or failure analysis
Dry /wet night rates will be maintained for the overall analysis of overall dry/wet ratios regardless of the patient ceases participation

4 Trial Administration

4.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

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4.2 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol or study team will require an approved IRB amendment before implementation. The IRB will determine whether informed consent and HIPAA authorization are required.
The IRB will conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year.
A study closure report will be submitted to the IRB after all research activities have been completed.
Other study events (e.g. data breaches, protocol deviations) will be submitted per [Yale Universtiy IRB's policies.

4.3 Subject Confidentiality

Subject confidentiality is held in strict trust by the research team. Subject medical record review will be limited to the just the elements needed to complete the study. Only authorized HIPAA and GCP trained study team members will be allowed to extract research data from medical records and enter it into **Randomized Study Of Novel Enuresis Alarm Vs Standard Bedwetting Alarm** which will be maintained in a yale secure hippa compliant box drive. No direct subject identifiers will be entered into **Randomized Study Of Novel Enuresis Alarm Vs Standard Bedwetting Alarm.** Each subject will be assigned a unique study number. A master list linking the unique study number to the human subject will be maintained in a locked drawer in FMP 308 the principal investigators office in a locked cabinet within a locked office .

4.4 Deviations/Unanticipated Problems

If the study team becomes aware of an anticipated problem (e.g. data breach, protocol deviation), the event will be reported to the IRB by e mail.

4.5 Data Collection

Data will be collected at each visit, entered by the principal investigator and then sent back to be scanned and entered into the patient's epic chart.

4.6 Data Quality Assurance

Data quality consists of data logs which need to be maintained by the patients. Other than reminding patients that the data needs to be entered we are constrained by lack of being able to record events if the patient does not. The GoGoband® system has a built in system of recording wet dry events therefore this data will be available consistently as long as the patients use the device.

4.7 Study Records

Study records will consist of the medical record which is maintained in epic
DVQ which is entered into epic routinely
Logs which will be transferred to database and then retained in epic

4.8 Access to Source

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Source documents such as the log forms will be entered by the principal investigator Adam Hittelman, MD, PhD into a dedicated spreadsheet which will be deidentified and maintained on a yale university protected box drive. Once data is entered the documents will be scanned and entered to epic as media files as per routine protocol for the department of urology.

4.9 Data or Specimen Storage/Security
As mentioned before the logs and DVQ along with the medical record will be in epic.

4.10 Retention of Records
Records will be maintained as per law for pediatric patients and as per the guidelines set forth by Yale/New haven Health and the state of Connecticut

4.11 Study Monitoring
Study monitoring will be conducted internally

4.12 Data Safety Monitoring Plan
The risk assessment is minimal

4.13 Study Modification
No modifications are expected

4.14 Study Discontinuation
Discontinuation of the study is only expected if grant money is not forthcoming

4.15 Study Completion
We expect the study to last 2 years and and will allow for 1 year for data analysis and submission of data for publication. Once competed we will notify the irb by e mail.

4.16 Conflict of Interest Policy
The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.
All investigators will follow the applicable conflict of interest policies.

4.17 Funding Source
Alarms will be provided to the patients by GoGoband® Inc. via a grant awarded to them from SouthWest Pediatric Device Consortium and American Academy Pediatrics Section of Urology Pediatric Urology Device Prize

4.18 Publication Plan
Once the study is completed the study will be presented at the American Urological Association and later published in the Journal of Urology

5 Appendices

Appendix #	Title	Section	Topic
1	flowchart		
2	alarm log		
3	email to pediatricians for recruitment		
4	Prescreening questions for Care center for patients calling in regarding the study		
5			

6 List of Tables