Neuromodulation with Percutaneous Electrical Nerve Field Stimulation for Adults with Irritable Bowel Syndrome: A Randomized, Double-Blind, Sham-Controlled Pilot Study

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Project Title: Neuromodulation with Percutaneous Electrical Nerve Field Stimulation for Adults with Irritable Bowel Syndrome: A Randomized, Double-Blind, Sham-Controlled Pilot Study

Principal Investigator: Lin Chang, MD[1, 2]

Co-Investigator: Adrienne Lenhart, MD[2]

Research Coordinators: Eileen Liu[1,2], Cathy Liu[1,2], Ariela Khandadash[1,2]

Affiliation: [1]G Oppenheimer Center for Neurobiology of Stress and Resilience, [2]Vatche and Tamar Manoukian Division of Digestive Diseases, Department of Medicine, David Geffen School of Medicine at UCLA

A. SUMMMARY:

Irritable bowel syndrome (IBS) has a worldwide prevalence of 11.2%[1] and is characterized by chronic or recurrent abdominal pain associated with altered bowel habits[2]. Visceral hypersensitivity and dysfunction within the autonomic nervous system (ANS) and immune function are important components contributing to the pathophysiology of irritable bowel syndrome (IBS). Despite recent advances in medical therapies for IBS, a significant subgroup of patients fails to experience satisfactory relief of abdominal pain. Given evidence of anti-inflammatory and anti-nociceptive components of vagal nerve pathways, peripheral field stimulation of the vagus nerve may help reduce visceral sensitivity in IBS patients. Percutaneous electrical nerve field stimulation (PENFS) administered via the IB-Stim device (Innovative Health Solutions, Versailles, IN, USA) has been shown to be efficacious in pediatric patients with abdominal-pain-related functional GI disorders[3]. PENFS was associated with a greater reduction in their worst abdominal pain and overall composite pain scores compared with a sham device after three weeks of treatment. These effects were sustained over an extended follow-up period with minimal to no side effects. This IB-Stim is the first device to be approved by the Food and Drug Administration (FDA) for the treatment of functional abdominal pain in adolescents aged 11-18 with IBS. However, the efficacy of PENFS in adults with IBS is not unknown. We propose to perform a double-blind, randomized, sham-controlled pilot study evaluating the efficacy of PENFS using IB-Stim for the treatment of IBS symptoms in adult patients with IBS.

B. HYPOTHESIS AND SPECIFIC AIMS:

Hypotheses:
In adult patients with IBS, compared to sham therapy, PENFS therapy will be associated with:

1. A greater reduction in IBS Severity Scoring System (IBS-SSS) scores after 4 weeks of treatment and at extended follow-up (8 weeks) compared to baseline in adult patients with IBS
2. An increased proportion of abdominal pain responders after 4 weeks of treatment
3. A greater improvement in weekly average worst abdominal pain score after 4 weeks of treatment and at extended follow-up (8 weeks) compared to baseline.

4. A greater improvement in weekly average bloating scores after 4 weeks of treatment and at extended follow-up (8 weeks) compared to baseline.
5. A greater reduction in cardiosympathetic/vagal tone as measured by heart rate variability (HRV)
6. A greater improvement in disease-specific health related QOL (IBS-QOL).

Primary Aim:

1. To compare the efficacy of PENFS therapy versus sham therapy on the improvement of IBS symptom severity in adult IBS patients after 4 weeks of treatment compared to baseline, measured by the mean change in the IBS-SSS.

Secondary Aims:

To compare the efficacy of PENFS therapy versus sham therapy on:

1. the change in mean IBS-SSS at week 8 compared to baseline.
2. the proportion of adult patients with IBS who experience at least a 50-point reduction on the IBS-SSS after 4 weeks of treatment and at the extended follow up period at week 8. These patients are considered clinical responders.
3. the proportion of adult patients with IBS who experience an improvement of ≥30% from baseline in weekly average of the daily worst abdominal pain scores after 4 weeks of treatment. These participants are considered a responder.
4. the change in mean weekly average of the daily worst abdominal pain scores after 4 weeks compared to baseline in adult patients with IBS.
5. the change in average weekly abdominal pain symptoms after 4 weeks of treatment and at extended follow-up (8 weeks) compared to baseline, assessed through the PROMIS Gastrointestinal Belly Pain Scale.
6. the change in average daily stool consistency after 4 weeks of treatment compared to baseline, assessed using the Bristol Stool Form Scale (BSFS).
7. the change in average weekly bowel habits after 4 weeks of treatment and at extended follow-up (8 weeks) compared to baseline, assessed through the PROMIS Gastrointestinal Constipation Scale and Gastrointestinal Diarrhea Scale.
8. the change in average weekly bloating symptoms after 4 weeks of treatment and at extended follow-up (8 weeks) compared to baseline, assessed through the PROMIS Gastrointestinal Gas and Bloating Scale.
9. the change in IBS-QOL in adult patients with IBS after 4 weeks of treatment and at extended follow-up (8 weeks) compared to baseline.
10. the change in resting cardio-autonomic tone, i.e. HRV, over 4 weeks of treatment compared to baseline.
11. the safety and tolerability of PENFS therapy versus sham therapy in adult patients with IBS.

C. RESEARCH STRATEGY:

Background and Clinical Significance:

1. Irritable bowel syndrome:

IBS is a chronic, functional gastrointestinal disorder (GI) disorder characterized by recurring episodes of abdominal pain, bloating, and changes in stool form and frequency. It represents one of the most commonly

diagnosed GI disorders, with a prevalence around 11% worldwide[1]. IBS can negatively affect QOL, reduce work productivity, and lead to increased health care costs and expenditures of health care resources[4]. The pathogenesis of this disorder is complex and likely multifactorial, secondary to abnormalities in intestinal motility, visceral sensitivity, intestinal permeability, immune activation, the microbiome, and brain-gut interactions involving the afferent ascending and the efferent descending pathways[2].

Visceral hypersensitivity contributes to an intensified severity of abdominal pain in a large proportion of IBS patients, with an estimated prevalence ranging from 33-90% in different studies[5-7]. This phenomenon refers to altered sensation or enhanced perception of physiologic stimuli within the GI tract, which are interpreted as inducing pain or discomfort. It encompasses the notions of bothr hyperalgesia, which is defined as an intensified response to stimuli which typically induce pain, and allodynia, which denotes heightened nociception in the setting of benign stimuli. Although the pathophysiology of visceral hypersensitivity in IBS is not completely elucidated, proposed mechanisms include low grade mucosal inflammation, disturbed GI motility, and peripheral and central sensitization of the visceral afferent neuronal pathways[8,9].

The interactions between the gut and the central nervous system (CNS) are also exceedingly sophisticated and are responsible for modulating physiologic GI tract homeostasis[10]. The brain-gut axis encompasses both an intrinsic enteric nervous system primarily responsible for gut motility and peristalsis, as well as an extrinsic neural network made up of the vagus nerve (cranial nerve X) and spinal primary afferents that deliver sympathetic and parasympathetic innervation[11-15]. The vagus nerve represents one of the main components of the parasympathetic nervous system, conveying both afferent and efferent sensory information between the digestive tract and the CNS. Recent studies have also identified the vagus nerve as a potential modulator of intestinal immune function, exerting anti-inflammatory capabilities through the hypothalamic pituitary axis (HPA), the splenic sympathetic anti-inflammatory pathway, and the cholinergic anti-inflammatory pathway[16]. The vagus nerve is also believed to elicit anti-nociceptive effects, primarily through its projections to the nucleus tractus solitarius, which acts as a relay station to the rostral ventral medulla, hypothalamus, amygdala, and spinal cord, as well as through induced activation of the descending noradrenergic and serotonergic systems in the spinal cord that inhibit second order nociception neurons[17-19]. The amygdala is an integral part of the limbic system, involved in fear conditioning, motivation, reward learning and emotional response to pain[20]. Interestingly, brain imaging studies have demonstrated altered functional connectivity between the amygdala and dorsal anterior insula within the default mode network in hypersensitive IBS[21].

An imbalance in autonomic nervous system (ANS) function in IBS patients may contribute to heightened visceral sensitivity and altered motility in response to stressors. Indicators of ANS dysfunction, include low vagal tone and increased sympathetic drive, in IBS patients compared to controls[22-26]. Cardio-vagal autonomic tone, expressed as heart rate variability (HRV), has therefore been utilized as a measure of overall as well as GI specific ANS function, with lower HRV associated with poorer autonomic health[27]. We and others have measured HRV in IBS compared to healthy controls. Studies have also shown that HRV correlates with rectal mucosal blood blow and colonic transit and may be attenuated in patients with IBS compared to healthy controls[28]. Different components of HRV can be used to describe function of the ANS, with power in high frequency (HF) signifying cardiovagal or cardiac parasympathetic activity, and the ratio of low-frequency (LF) power to HF power (LF/HF) representing cardio-sympathetic balance[23,29-33].

Modulating central pain pathways through electrical stimulation of deep brain structures, the vagus nerve, and the spinal cord has also recently gained increased interest in the treatment of chronic pain syndromes, including IBS[34,35]. However, these aforementioned procedures are quite invasive, limiting their utility in many patients. Rather, a more ideal approach to treating chronic pain in IBS patients may be to potentially access central pain and vagal nerve pathways through peripheral, non-invasive techniques. A study in a rat model of post-inflammatory hyperalgesia showed that PENFS attenuated baseline firing of amygdala and lumbosacral spinal cord neurons, resulting in decreased visceral and somatic hypersensitivity[36]. This intriguing observation subsequently led to a pilot study in humans that demonstrated that a short course of PENFS targeting cranial nerves V,VII, IX, and X, could rapidly and effectively decrease the signs and symptoms of opioid withdrawal without the use of pharmacotherapy[37]. More recently, Kovacic et al conducted a double-blind, randomized, sham-controlled trial evaluating PENFS in children with abdominal-pain-related functional GI disorders[3]. Children in the PENFS group, who effectively underwent peripheral vagal nerve stimulation, had a greater reduction in their worst abdominal pain and overall composite pain scores compared with sham after three weeks of treatment. These effects were sustained over an extended follow-up period with minimal to no side effects.

Despite the promise that PENFS has shown in the treatment of adolescents with IBS, there are currently no studies of PENFS in adult IBS patients. The discovery of non-pharmacologic options for adult IBS patients is paramount, because despite recent advances in dietary and medical therapies for IBS, a high percentage of patients do not completely respond to currently available treatments. For instance, in a randomized controlled trial evaluating the efficacy of a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), around 50% of IBS patients did not report clinically significant reductions in IBS severity scores[38]. Linaclotide and plecanatide are both guanylate cyclase agonists that increase intracellular levels of cGMP, activating the cystic fibrosis transmembrane conductance regulator, which leads to secretion of chloride, bicarbonate, and fluid into the intestinal lumen and ultimately accelerates intestinal transit[39]. In animal models, linaclotide also reduces the firing of afferent pain fibers, presumably decreasing visceral hypersensitivity[40]. However, in a phase 3 randomized controlled trial of linaclotide in constipation predominant IBS (IBS-C) patients, 63.4% of patients failed to meet the criteria for endpoint abdominal pain response (improvement of ≥ 30% from baseline in average daily worst abdominal pain scores)[41]. In addition, 48% of patients receiving linaclotide failed to demonstrate clinically meaningful improvement in IBS-related QOL (IBS-QOL)[41]. Similarly, in two trials comparing different doses of plecanatide, between 69.8% and 78.5% of IBS-C patients did not achieve the combined endpoint of a ≥ 30% reduction from baseline in worst abdominal pain plus an increase in ≥1 complete spontaneous bowel movement[42].

The percentage of patients with diarrhea predominant IBS (IBS-D) who reported a clinically significant improvement in abdominal pain was slightly higher in trials of eluxadoline, a peripherally acting mixed μ-opioid receptor agonist, -δ-opioid receptor antagonist, and κ-opioid receptor agonist. However, after 12 weeks of therapy, between 49.0% and 57.5% of patients still did not meet the endpoint response for improvement in abdominal pain[43]. In addition to low clinical response rates, many of these medications approved for IBS elicit undesirable side effects, which limit their use in certain individuals. Cognitive behavior therapy (CBT) has also been utilized successfully in IBS patients through targeting of the psychological factors that contribute to GI symptoms[44,45]. However, only a small proportion of IBS patients are actually referred for CBT, largely secondary to barriers including cost, therapist and resource availability, and underlying stigmas.

Overall, the high prevalence of IBS in adults, the negative effect of this disorder on QOL, and the lack of medications that successfully alleviate abdominal pain symptoms illustrate the need to develop effective, non-pharmacologic therapies to better treat IBS patients. Given evidence of anti-inflammatory and anti-nociceptive components of vagal nerve pathways, peripheral field stimulation of the vagus nerve may help reduce the visceral sensitivity component of abdominal pain in IBS patients. This technique of PENFS has already been successfully demonstrated in adolescents with functional abdominal pain, but trials in adults are lacking. If successful, PENFS could represent a favorable, non-pharmacologic treatment option for adult patients with debilitating IBS related abdominal pain and other symptoms.

Innovation:

Percutaneous Electrical Nerve Field Stimulation (PENFS)

An FDA-approved auricular device, IB-Stim, that utilizes the concept of PENFS to alleviate pain has recently been developed by Innovative Health Solutions (Versailles, IN, USA). This device uses discontinuous frequencies of stimulation to target central pain pathways through branches of cranial nerves V, VII, IX, and X that innervate the external ear and project to certain brainstem nuclei, including the nucleus tractus solitarius[46-49]. As previously mentioned, Kovacic et al recently conducted a double-blind, randomized, sham-controlled trial evaluating PENFS in 115 children with abdominal-pain-related functional GI disorders[3]. Children in the PENFS group had a greater reduction in their worst abdominal pain and overall composite pain scores compared with sham after 3 weeks of treatment, and these effects were sustained over an extended follow-up period of 8-12 weeks.

Children in the PENFS group also had a reduction in their worst pain of ≥ 30% from baseline to 3 weeks of treatment compared with children in the sham group. Additionally, children in the PENFS group had greater scores on the Symptom Response Scale (median score of 3) compared to children in the sham group (median score of 1) at the end of 3 weeks; however, these effects were no longer significant at extended follow-up. Patients who received PENFS also showed significant improvement in functional disability at extended follow-up compared to the sham group. Side effects from the therapy were minimal (6 patients reported ear discomfort, 3 reported an adhesive allergy, and 1 reported syncope from needle phobia) and no serious adverse events were observed. This is consistent with a previously published retrospective cohort study of over 1,200 patients that reported minimal to no side effects with PENFS used for other indications[50]. In June 2019, the FDA approved the use of Innovative Health Solutions' device, IB-Stim, to treat functional abdominal pain associated with IBS in adolescent patients between the ages of 11 and 18 years old. Again, there are currently no trials of PENFS in adult IBS patients.

Smart Watch Technology

In collaboration with a UCLA research group led by Dr. Ramenzani (IRB IRB#16-000166) participants will have the option to be given a SmartWatch system. This system includes ambient location and activity sensors, wireless data transmission, specialized software application, and analytic engine for functional and performance measurement. This platform allows for the detection and classification of patient motion and position with an accuracy of over 85%. In this study, we want to be able to monitor subject activity and abdominal pain in real time. Data will also be collected to measure HRV. With collected of HRV data in a standard manner with each in-person visit, we will be able to validate SmartWatch measurements of HRV.

Research Approach:

1. Trial Design and Participants

We will perform a prospective, double-blind, randomized, sham-controlled pilot study evaluating the efficacy of PENFS for the treatment of adult patients with IBS. Patients will be recruited from the outpatient GI clinics within the Vatche and Tamar Manoukian Division of Digestive Diseases at UCLA, as well as through community advertisements for physiologic or treatment related clinical trials and research studies by the UCLA G. Oppenheimer Center for Neurobiology of Stress and Resilience. New IBS patients or returning IBS patients who have continued abdominal pain even in the presence of medical therapy will be identified for participation in the study. The study will be approved by the institutional review board at UCLA.

An informed consent form will also be approved by the UCLA institutional review board and will be signed by all eligible patients prior to participation in the study (consent will be conducted via telephone and patients will bring signed consent form to the first visit). Patients will be compensated $25 each time they participate in device placement and/or questionnaires (total compensation $175). Parking will be provided at the Ronald Reagan UCLA Medical Center for each visit. Driving compensation will also be provided for eligible participants. $50 will be compensated to participants if they live greater than a 10 mile distance from UCLA and $75 will be compensated to participants if they live greater than a 25 mile distance. Driving compensation will be provided through either a gift card or through addition to the subject's stipend, via the participant's preference.

Patients will be allowed to continue any medication regimens that they are on prior to enrollment in the study as long as the doses are stable, meaning there can be no changes to medication doses that have been shown to relieve abdominal pain within 60 days of enrollment in the trial and to all other medications within 30 days. The use of all medications will be carefully monitored each week to ensure that patients maintain consistent medication doses during the entire study. The initiation of new medications or non-pharmacologic treatment for abdominal pain or other IBS symptoms will not be permitted during the trial period.

Allowed concomitant therapy will include:

- Fiber supplements (i.e. psyllium)
- Polyethylene glycol (PEG)
- Lactulose
- Milk of magnesium
- Magnesium hydroxide
- Bisacodyl
- Sennosides
- Lubiprostone
- Linaclotide
- Plecanatide
- Loperamide
- Eluxadoline
- Cholestyramine, colestipol, colesevelam
- Alosetron
- Rifaximin
- Dicyclomine

- Hyoscyamine
- Peppermint oil (i.e. IBgard)
- Tricyclic antidepressants (i.e. amitriptyline, nortriptyline, imipramine, desipramine)
- Selective serotonin reuptake inhibitors (i.e. citalopram, paroxetine, fluoxetine)
- Selective norepinephrine reuptake inhibitors (i.e. duloxetine)
- Probiotics

During the consent call, participants will be introduced to the option of the SmartWatch system. The system includes a watch and sensors. The watch interacts with the passive Bluetooth sensors to track the wearers activity. If participants elect to use the SmartWatch system, they will receive a daily question on the watch related to abdominal pain. This will allow researchers to track abdominal pain in real time. If participants do not elect to use the SmartWatch, they will complete this same daily abdominal pain question via an online questionnaire.

2. ***Mandatory inclusion criteria:***
    a. Adults, aged 18-60 years, who are able to provide written, informed consent
    b. Patients must meet Rome IV criteria for IBS[2], confirmed by a gastroenterologist who specializes in functional GI disorders. Any of the IBS bowel habit subtypes (diarrhea, constipation, mixed bowel habits, unclassified) will be allowed.
    c. Average daily worst abdominal pain score between 4 and 8 (on a 0-10-point rating scale).
    d. Minimum of 2 days of abdominal pain/week prior to starting trial.
    e. At least moderate IBS symptom severity with an IBS-SSS ≥175 (total score range 0-500).
3. ***Preferred, but not mandatory, inclusion criteria:***
    a. Ability to wear SmartWatch on the upper extremity (left or right wrist)
    b. Willingness to have SmartWatch system sensors installed in home (30-60 minute process)

4. ***Mandatory exclusion criteria:***
    a. Patients under the age of 18 years or over the age of 60 years
    b. Patients who cannot provide informed consent or do not speak English
    c. Comorbid, organic medical conditions associated with abdominal pain, including:
        i. Inflammatory bowel disease, chronic liver disease, peptic ulcer disease, celiac disease, diverticulitis, appendicitis, colorectal cancer, endometriosis, pregnancy, other intestinal or extra-intestinal malignancies
        ii. Patients with overlapping functional GI disorders (i.e. functional dyspepsia) will not be excluded as long as IBS is their predominant disorder
    d. History of surgery involving CN V, VII, IX, or X. History of abdominal surgeries other than appendectomy or cholecystectomy at least 6 months before entry into trial.
    e. Patients on chronic opioids, benzodiazepines, or with illicit substance use
    f. Patients with underlying neurologic conditions, including history of:
        i. Seizures, CVA, uncontrolled migraines, traumatic brain injury, multiple sclerosis
    g. Patients with underlying psychiatric conditions
    h. Patients with dermatologic conditions affecting the ear, face, or neck region (i.e. psoriasis), or with cuts or abrasions to the external ear that would interfere with needle placement
    i. Patients with hemophilia or other bleeding disorders

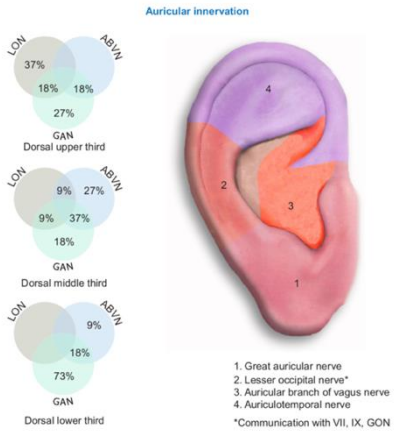
j. Patients with any implanted electrical device
k. Patients who are pregnant or breastfeeding
l. Movement disorder

5. Preferred, but not mandatory, exclusion criteria:

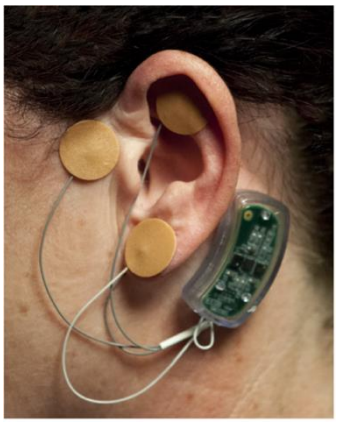
a. Unwillingness to wear the SmartWatch on upper extremity (left or right wrist) or have SmartWatch sensors installed in their home.

6. Technology

The IB-Stim/PENFS device consists of a battery activated generator and wire harness that connects to the generator. Four leads are also attached to the generator, each with a sterile 2 mm, titanium needle. Prior to device placement, the patient's ear is cleaned with alcohol wipes and the ear is trans-illuminated to identify neurovascular bundles that are avoided during needle placement. The generator is attached with adhesive to the skin behind the patient's ear, just above the mastoid process. Each of the 2 mm needles are inserted into the dorsal and ventral aspects of the ear, within 1-1.5 mm of the visualized vascular branches to create a field effect. The PENFS device settings are standardized and deliver 3.2 volts with alternating frequencies (1 ms pulses of 1 Hz and 10 Hz) every 2 s. This stimulation targets central pain pathways through branches of cranial nerves V, VII, IX, and X, which innervate the external ear. The PENFS device generator has a battery life of 5 days and delivers stimulations in 2-hour cycles. Patients remove the device at home on day 6 of treatment. Original protocol from Kovacic et al[3].



Patient with PENFS device



Figures taken from Roberts et al (2016)[50]

SmartWatch Software:

Each SmartWatch contains a proprietary web-based application that is able to record, analyze and transmit activity data.

Environmental Sensors/Beacons

Sensors are 2.4 GHz radio using Bluetooth 4.0 Smart, also known as BLE or Bluetooth low energy beacons. These beacons are similar to small lighthouses that use only radio waves to communicate with any smart device in the range of 40-50 meters. . Smart devices, such as smartwatches, can receive the beacons' signals and estimate the distance by measuring the received signal strength.

7. Study Protocol

Randomization and Masking:

Patients who meet study eligibility criteria will be randomly assigned (1:1) in blocks of two and four, using a code generated by a randomization program to 4 weeks of stimulation with an active or inactive (sham) PENFS device. Allocation will be concealed, and all physicians, statisticians, participants, and research coordinators will be unaware of device codes. One research coordinator who has no patient contact (CL) will be unblinded and handle allocation and storage of devices.

The sham devices will be identical to the active devices but will not administer electrical charges. Per manufacturer design and patient anecdotal experience from previous studies, both active stimulation and sham are below detectable sensation threshold. Per report from previous studies, some patients may experience a sensation around the ear after percutaneous needle placement; however, this sensation can occur with equal likelihood in the active or sham device[3]. All subjects will be asked if they believe they were randomized to the active PENFS therapy arm or the sham therapy arm at the end of 4 weeks of treatment, and these results will be analyzed.

Assessments and Questionnaires:

Administration of questionnaires throughout the study is shown in Table 1 and Figure 2.

Patients will provide telephone consent for enrollment into the study. During the this phone call, the investigator will obtain the participant's medical and medication history to check eligibility. After enrollment, patients will complete an online daily questionnaire to assess daily stool consistency (7-point Bristol Stool Form Scale [BSFS])[51] and a daily question pertaining to daily worst abdominal pain (measured using an 11-point scale) that will be delivered by the smart watch, for one week prior to device placement. If patients do not elect to use the SmartWatch, then they will complete the daily question pertaining to daily worst abdominal pain via an online questionnaire. The questionnaires will provide a baseline for daily worst abdominal pain and stool consistency. In order to be enrolled into the study, patients must have an average daily worst abdominal pain score between 4 and 8, have a minimum of 2 days per week of abdominal pain, and have completed at least 4 out of 7 of the daily worst abdominal pain questionnaires.

If enrollment criteria are met, patients will then present to the UCLA G. Oppenheimer Center for Neurobiology of Stress and Resilience one week after enrollment for their first visit, where they will get a physical examination, complete additional questionnaires, undergo a measurement of HRV, and have the initial PENFS device placed by a trained health care professional (LC, AL, EL). After initial device placement, patients will be instructed to return to UCLA every 7 days (leeway of +/- 2 days in each direction will be allowed) for a total of 4 visits for device replacement and completion of additional questionnaires. Four different devices will be placed in total (at the start of weeks 1, 2, 3, and 4).

Although the IB-Stim device is currently FDA approved for use for 3 consecutive weeks, children in the original study by Kovacic et al actually received 4 consecutive weeks of device treatment[3]. The authors chose to analyze the data after 3 consecutive weeks as children did not return to the clinic after the 4th week of treatment. However, we will analyze IBS symptom severity, abdominal pain, bloating, and bowel habits after the completion of the 4th week of treatment. Again, actual stimulation time is 5 days per week with 2

days off during each of the 4 consecutive weeks. The device is not waterproof and should be protected from water exposure. Patients will be instructed to either place a washrag in a small bowl and hold it over the ear while showering or will be provided with dry shampoo.

Bowel Habit Classification:

Bowel habits, defined by IBS-C, IBS-D, IBS-mixed type (IBS-M), and IBS-unclassified (IBS-U) will be assessed at baseline using the Rome-IV questionnaire.

Bowel Symptom Questionnaire (BSQ):

The BSQ evaluates general abdominal symptoms, GI tract specific symptoms, and bowel habits. It measures the severity of abdominal pain over the preceding week using a numerical scale ranging from 0-20, with 0 representing no pain and 20 representing the most intense pain imaginable. This questionnaire will also evaluate bloating and the severity of overall IBS symptoms over the previous week, again using numerical rating scales from 0-20, with 0 corresponding to "no sensation/symptoms" respectively, and 20 referring to the "most intense sensation/symptoms imaginable". The BSQ will be measured at visit 1 for each patient in the trial.

UCLA CNSR Participant Demographics:

The UCLA CNSR Participant Demographics questionnaire will collect demographic information from study participants. The CNSR Participant Demographic questionnaire will be completed at visit 1 for each participant.

Primary Endpoint:

IBS Severity Scoring System (IBS-SSS)

The primary aim of this study is to compare the efficacy of PENFS versus sham therapy on the improvement of symptom severity after 4 weeks of treatment in adult patients with IBS, using the IBS-SSS. The primary endpoint is the mean change in IBS-SSS at the end of week 4 compared to baseline. This questionnaire is a validated measure of IBS symptom severity and has been shown to be responsive to treatment in different studies[38,52-56]. It assesses severity of abdominal pain, frequency of abdominal pain, severity of abdominal distention, dissatisfaction with bowel habits, and interference of IBS with daily life over a 10-day period. Each of the five categories will receive a score from 0-100, and the total IBS-SSS is calculated by taking the sum of these categories (total score range 0-500). Patients will complete the IBS-SSS at week 1, after week 4 of treatment, and at extended follow-up (after 8 weeks). The IBS-SSS will be completed in person at visit 1 and via an online survey at the end of week 4 and during the extended follow-up period at week 8. The online survey will be emailed to the patients the day it is to be completed, and a reminder email will be sent if the survey is not submitted. Improvement in symptom severity will be assessed using a mean change in IBS-SSS score from baseline to 4 weeks after treatment and from baseline to 8 weeks after treatment.

Secondary Endpoints:

IBS-SSS Responder Rate

In addition, one secondary endpoint of this study will be to assess the proportion of clinical responders, using the IBS-SSS. Clinical responders at the end of 4 weeks and at extended follow-up will be defined as those that have ≥ 50-point decrease on the IBS-SSS score from baseline. This is based upon a study by

Francis et al that demonstrated that a reduction in 50-points correlated with clinically meaningful improvement[52]. Another secondary endpoint is the mean change in IBS-SSS at the end of the extended follow up period at week 8 compared to baseline.

Daily Worst Abdominal Pain

Other secondary endpoints of this study is the change in weekly average of the daily worse abdominal pain after 4 weeks of treatment compared to baseline and the proportion of patients with a ≥30% reduction from baseline in the weekly average of the daily worst abdominal pain scores after 4 weeks of treatment. A ≥30% reduction in worst abdominal pain score is a recommended primary endpoint by the Food and Drug Administration for IBS treatment trials and has been used in multiple clinical trials[57]. As previously mentioned, if participants elect to use the SmartWatch system, the watch will deliver one question assessing daily worst abdominal pain to each participant's watch for one week prior to device placement to obtain a baseline. This daily worst abdominal pain will be measured using an 11-point numeric rating scale. The smart watch will then deliver the same question assessing daily worst abdominal pain for the duration of the study. If the participant elects to not use the SmartWatch system, then this same question pertaining to daily worst abdominal pain will be completed via an online questionnaire, for the duration of the study.

Patient Reported Outcomes Measurement Information System (PROMIS)[58]

The PROMIS Gastrointestinal Belly Pain Scale is a validated questionnaire that assesses the severity of abdominal pain in adult patients over the previous 7 days. This scale incorporates aspects of abdominal pain intensity, discomfort, location, frequency, predictability, and extent to which the pain is bothersome.

The PROMIS Gastrointestinal Gas and Bloating Scale assesses the frequency and intensity/severity of bloating, the appearance of abdominal swelling, flatulence, and abdominal gurgling/rumbling, and the degree to which bloating is bothersome or interferes with daily activities over the past 7 days.

The PROMIS Gastrointestinal Constipation Scale will be used to assess the frequency and intensity of incomplete evacuation, rectal pain, straining, and hard stools. This scale will measure the extent to which constipation is bothersome or interferes with daily activities over the past 7 days. The PROMIS Gastrointestinal Diarrhea Scale will be utilized to evaluate the frequency and severity of loose to watery stools and urgency during the previous 7 days.

Each of the above PROMIS GI scales will be scored using percentile scores that are based on the general population. In order to accurately obtain percentile scores, the scale of each PROMIS question will be converted from 1-5 to 0-4. PROMIS questionnaires assessing bowel habits and the severity of abdominal pain and bloating will be assessed at baseline (visit 1), after each week of treatment (after weeks 1-4), and at extended follow-up. The questionnaires will be completed in person at baseline (visit 1) and after weeks 1-3 (visits 2-4), and via online surveys after 4 weeks and 8 weeks. Response will be assessed by the change in composite abdominal pain scores, bloating scores, constipation scores, and diarrhea scores from baseline to 4 weeks after treatment and from baseline to 8 weeks (extended follow up) after treatment.

Daily Bowel Habits:

Baseline daily stool consistency will be assessed for one week prior to device placement (using 7-point BSFS). Daily stool consistency will again be assessed for one week after the 4th device placement. We will then compare the 4-week change-from baseline in stool consistency between patients who received the PENFS therapy compared to sham therapy.

IBS Quality of Life (IBS-QOL)

Health-related QOL will be assessed using the IBS-QOL, a validated IBS specific survey containing questions that assess disease-specific QOL over the past 30-days, with lower scores indicative of poorer health-related QOL (score range 1-100). Patients will complete the IBS-QOL at baseline/visit 1 (in person) and at extended follow-up (week 8) using an online survey questionnaire.

Hospital Anxiety and Depression Scale (HADS) and Visceral Sensitivity Index (VSI)

Psychological symptoms will be evaluated using the HAD scale for depression and anxiety (each with a score range from 0-21). GI symptom related anxiety will be measured using the VSI. This questionnaire contains statements regarding how individuals may potentially react with anxiety, worry, or fear to different GI symptoms. Patients respond with how strongly they agree or disagree with each statement (0-strongly disagree to 5-strongly agree), with total scores ranging from 0-90. Patients will complete both the HADS and VSI at baseline/visit 1 and will also complete the VSI after 8 weeks of extended follow-up using online survey questionnaires.

Heart Rate Variability (HRV)

HRV will be assessed at baseline/visit 1 and at the end of weeks 1, 2, and 3 (visits 2, 3, and 4 respectively) of treatment, with the goal to determine if HRV (cardio-autonomic tone) changes over 4 weeks of PENFS treatment vs. sham treatment and if HRV predicts response to PENFS. The previous protocols used for HRV analysis have previously been published by members of our research group and are summarized below[59]. HRV will be recorded for 5-minute intervals using a 2-lead electrocardiogram (ECG) attached to patients' upper chest. ECG data will be collected using the BioPac recording system (MP100A-CE; BioPac Inc., Santa Barbara, CA, USA) and will be manually screened for artifacts. The AcqKnowledge peak detection algorithm (V3.8.2; BioPac, Inc.) will be used to determine intervals between adjacent QRS complexes. The interbeat (R-R) interval data will be used for HRV analysis (Kubios HRV 2.0, Biosignal Analysis and Medical Imaging Group, Dept. of Physics, University of Kuopio, Finland). Autoregression (AR) frequency analysis and Fast Fourier transform (FFT) analysis were performed on one continuous 2-minute segment (epoch) of data to avoid inclusion of artifacts, which can distort HRV data[60]. The AR and FFT analyses should yield measures of HF power in normalized power based on a frequency band of 0.15-0.4 Hz and the LF/HF ratio with LF power defined as the interval between 0.04 and 0.15 Hz. A model order of 16 will be used in the AR analysis with no spectral factorization. FFT analysis will use Welch's periodogram method with a window width of 256 s and window overlap of 50%.

The timing of device placements, questionnaires, and HRV assessment is further outlined in Table 1 and Figure 2.

Table 1: Timing of PENFS vs Sham Interventions, Questionnaires, and HRV

	Daily	Baseline	Screening (Visit 1)	End of Week 1 (Visit 2)	End of Week 2 (Visit 3)	End of Week 3 (Visit 4)	End of Week 4	8-week follow up
Consent + Enrollment		X						
History		X						
Daily Worst Abdominal Pain (via Smart Watch)	X	X (daily for 1 week)		X (daily during week 1)	X (daily during week 2)	X (daily during week 3)	X (daily during week 4)	
Daily BSFS		X (daily for 1 week)					X (daily during week 4)	
Physical			X					
PENFS vs Sham Device Placement			X	X	X	X		
Rome IV		X						
Bowel Symptom Questionnaire (BSQ)			X					
UCLA CNSR Participant Demographics			X					
IBS-SSS		X	X	X	X	X	X	X
PROMIS Questionnaires			X	X	X	X	X	X
IBS-QOL			X				X	X
HAD			X					
VSI			X				X	
Heart Rate Variability			X	X	X	X		

8. Data Collection and Monitoring

Demographic data and medical history information including co-morbid illness and medication history will be collected and recorded on password protected Excel documents. Questionnaire data collected at different visits will also be stored on password protected Excel documents. We will also monitor for and document any adverse events that occur during this trial. Patients will be given a phone number to call if any questions, concerns, or symptoms related to the device occur.

Secure Data Analytics For SmartWatches:

As is the case in IRB #16-000166, data collected from the SmartWatch sensors and radio frequency beacons will be encrypted and transmitted through secure socket protocol (SSL). The SSL guarantees encryption and secure data transmission from patient's home or rehab center to the server. Servers hosting the data are HIPAA compliant machines located on UCLA campus.

9. Statistical Considerations

Sample Size Calculation

Power calculations determined that at least 22 patients would be needed in each arm in order to achieve 95% power to detect at least a 30% reduction in worst daily abdominal pain scores. This power calculation was based on a study by Krasaelap et al[61], which evaluated the efficacy of PENFS on at least a 30% reduction of worst abdominal pain severity in adolescents with IBS.

We will aim for a sample size that will surpass the number needed to achieve at least 95% power, with a goal of 35 patients in each arm. We will also aim to enroll an additional 5 patients in each arm to account for potential dropouts or losses to follow-up. We will perform an interim analysis about one year after study enrollment has started or when each group has achieved completion of 22 subjects, whichever occurs first (will compare group data but not break the code). An estimate of the study profile is presented in Figure 1.

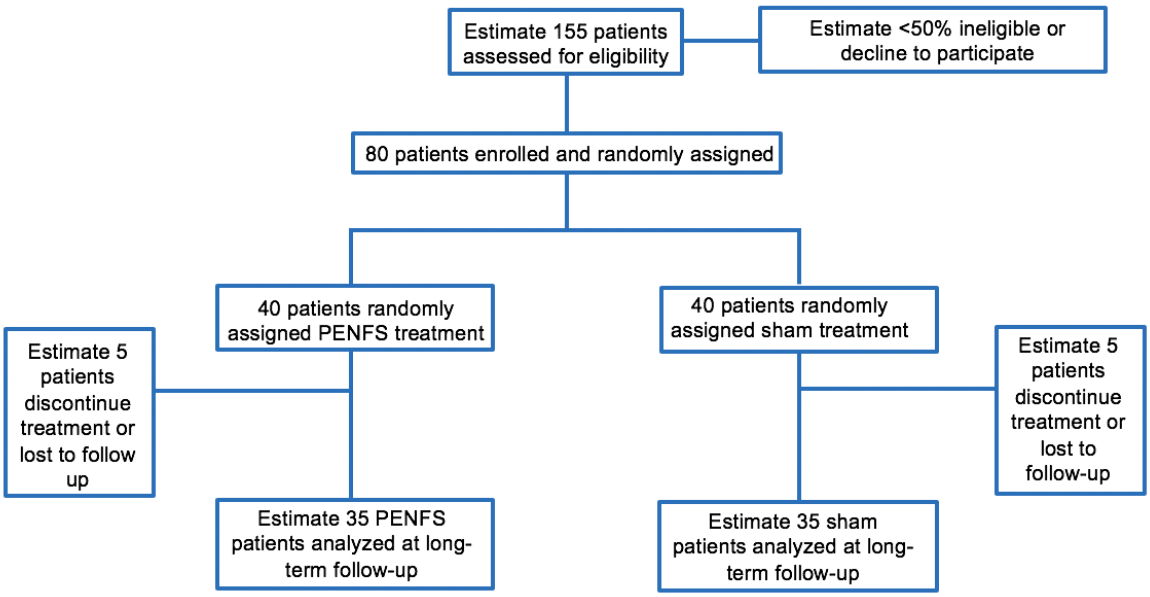
Statistical Analysis

Fisher tests will be used to evaluate for differences in categorical variables and a 2-tailed t-test and Mann-Whitney-U (MWU) test will be used for assessing differences between normally distributed continuous data and non-normally distributed continuous data, respectively. The data will be analyzed using R statistical analysis software.

The change in IBS-SSS score from baseline will be computed using a generalized linear mixed effect model. We will include treatment, time, and treatment x time as covariates. Tukey's honestly significant difference will be used for multiple comparisons. Data will be analyzed based on a modified intention-to-treat approach. Specifically, patients with less than one full week of data will be excluded from the study.

For all the secondary Aims, a simple 2-sample analysis (T-, MWU or Fisher's) test for changes in outcomes will be performed.

Figure 1. Study Profile



BUDGET AND JUSTIFICATION

IHS budget and devices

We are requesting the supply at least 150 PENFS devices and 150 sham devices, by Innovative Health Solutions (IHS). Each completed subject will use 4 devices. We estimated the average number of devices used for a subject who drops out of the study to be 2. The breakdown for each group is the following:

35 completed PENFS subjects x 4 PENFS devices per subject = 140 active devices
35 completed sham subjects x 4 sham devices per subject= 140 sham devices
5 PENFS dropouts x 2 PENFS devices per subject = 10 active devices
5 sham group dropouts x 2 sham devices per subject = 10 sham devices

Total number of devices is 300 with 150 PENFS devices and 150 sham devices.

We are also requesting $100 payment per each completed patient (n=70) from IHS. This does not include the indirect cost associated with the direct cost.

IHS Budget

IHS will also provide $100 stipend reimbursement for 70 subjects (35 subjects/group)	
Direct Costs	$7,000

Indirect Costs	$1,820
	$8,820

Direct Costs ($7,000)

IHS will also provide $100 stipend reimbursement for 70 subjects (35 subjects/group)

Indirect Costs ($1,820)

University of California, Los Angeles federally negotiated indirect cost rate is 26.0% of modified total direct costs (excluding tuition, equipment, and subaward amounts over $25,000) per our F&A Rate Agreement with DHHS.

UCLA budget and costs

The remaining costs of the personnel, equipment, patient stipends, and statistical support will be provided by the PI and Division of Digestive Diseases. This will include a research coordinator to assist with patient recruitment and coordination for this project. Equipment to measure HRV is also available through the UCLA G. Oppenheimer Center for Neurobiology of Stress and Resilience at no additional cost. Budget is outlined in Table 2.

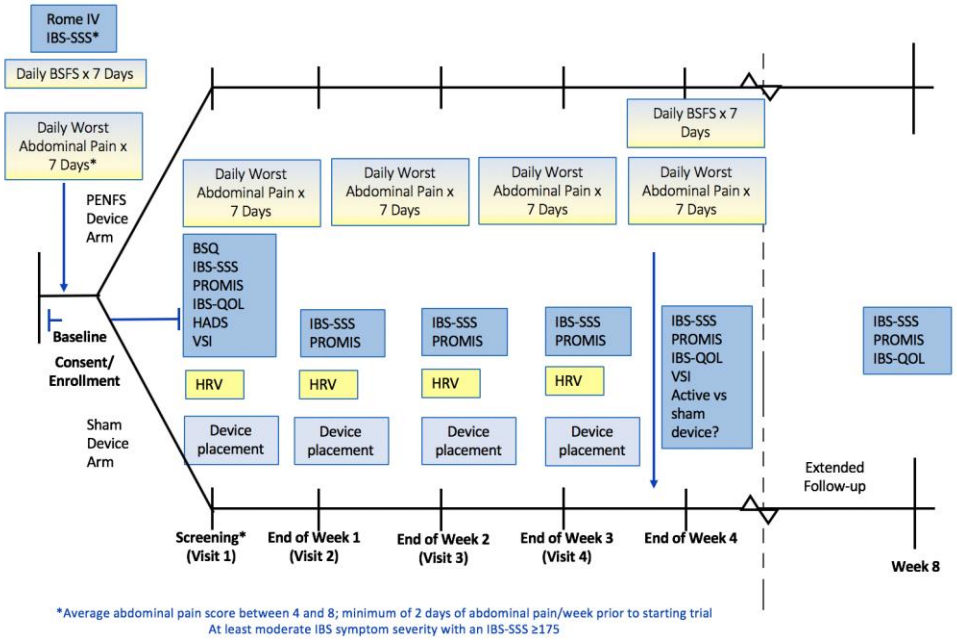
Human Subject Stipends. Patient stipend payments include parking. Parking rate at UCLA is $13 per in-person visit, each subject will have 4 in-person visits ($52/subject total). Patients will be paid stipends of $25 per set of questionnaires and we expect each subject to complete 7 sets of questionnaires not including the daily abdominal pain questionnaire (baseline, 4 visits, week 4 follow-up, week 8 follow-up). This equates to $175/subject, making the total payment per subject to be $227 with an additional driving compensation if applicable.

Table 2. Budget and Justification

Number subjects needed to meet "n" (15% drop out)			**N=35 per group + 5 estimated dropouts per group (n=80 total)**
Supplies	$/unit	#/subject	
Dry Shampoo	$4.19	4	$1,357.56
Urine Pregnancy Tests	$2.00	4	$648
PENFS Devices	$0	4	$ -
Sham Devices	$0	4	$ -
Subject Payments			
Questionnaires	$25.00	7	$14,175.00

Parking	$13.00	4	$4,212.00
Total Cost			**$20,392.56**
Funds from IHS (direct cost)	$100	70	$7,000.00
Remaining Cost to PI/UCLA			**$13, 392.56**

Figure 2. Timeline of Interventions and Questionnaires and Associated Cost



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