MetroHealth

PROTOCOL TITLE:

Transcutaneous electrical acustimulation in automatic synchronization with breathing for treating functional dyspepsia: A phase I feasibility trial

PRINCIPAL INVESTIGATOR:

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VERSION NUMBER/DATE:

Version 1.0 02/07/2024

Version 2.0 05/10/2024

Version 3.0 3/07/2025

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	2	Adding option for subjects to complete questionnaires outside of study visit via email or text message link from REDCap after consenting in person	Y
2	3	Changed patient payment for the study from $150 to $0. Also updated expected enrollment and study completion dates.	Y

Table of Contents

1.0 Study Summary

Study Title	Transcutaneous electrical acustimulation in automatic synchronization with breathing for treating functional dyspepsia: A phase I feasibility trial
Study Design	Prospective, single-arm, open-label trial
Primary Objective	Assess the safety and usability of AutoSTEA treatment
Secondary Objective(s)	• Investigate symptom responses to AutoSTEA treatment; • Assess a diverse participant pool, especially overweight/obese and female patients
Research Intervention(s)/ Investigational Agent(s)	AutoSTEA treatment
IND/IDE #	
Study Population	Adult FD patients
Sample Size	Forty FD patients
Study Duration for individual participants	Two weeks
Study Specific Abbreviations/ Definitions	FD- Functional dyspepsia AutoSTEA- Transcutaneous electrical acustimulation in automatic synchronization with breathing TEA- transcutaneous electrical acustimulation (without synchronization with breathing) STEA- TEA manually synchronized with breathing

2.0 Objectives*

2.1 Describe the purpose, specific aims, or objectives.

- Determine the device safety when self-administrated at home by patients.
- Evaluate the device usability.
- Assess symptom responses to AutoSTEA treatment.
- Assess a diverse participant pool, especially overweight/obese and female patients.
- Assess patients' compliance of AutoSTEA treatment

2.2 State the hypotheses to be tested.

- AutoSTEA therapy is anticipated to be both safe and user-friendly, with the potential to effectively alleviate symptoms of FD.

3.0 Background* (Reference refer to Supplement 1)

3.1 Describe the relevant prior experience and gaps in current knowledge.

- FD affects up to 11.4% of the US population,[1] impairs the quality of life, and poses a high annual cost of managing the disease, exceeding $18.4 billion in the US alone.[2] Due to the limited efficacy of existing treatments, FD symptoms are challenging to treat and fluctuate with time for most patients and become a lifelong medical burden.[3-6]
- Acupuncture, electroacupuncture, and needleless transcutaneous electrical acustimulation (TEA) have been applied to attenuate FD symptoms, and improve key pathophysiologies[7-13], including impaired gastric accommodation, gastric pain/hypersensitivity, delayed gastric emptying, gastric dysrhythmia, and autonomic dysfunction.
- TEA that manually synchronizes with respiration (STEA) (Fig. 1) recently emerged as a superior acute method over non-synchronized TEA in improving FD.[14-16]

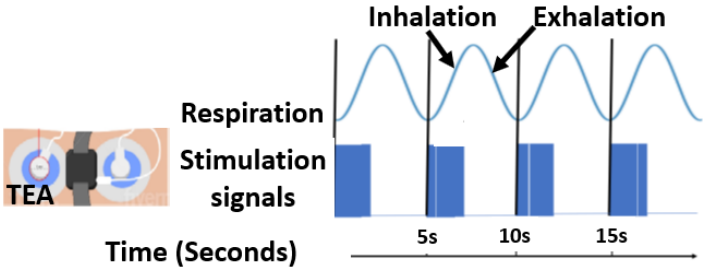

Figure 1. Transcutaneous electroacupuncture that manually synchronizes with respiration (STEA)

3.2 Describe any relevant preliminary data.

- In two clinical studies, [15,16] Dr. Song has shown that acute STEA was more potent than both sham and non-synchronized TEA. Compared to TEA, STEA further increased the normal percentage of gastric slow waves by 13%, enhanced vagal activity by 12%, and suppressed sympathetic activity by 12%. A clinical study by another group has demonstrated that acute STEA is superior to TEA in further decreasing overall dyspeptic scores by 18%, with specific symptom improvements observed for postprandial fullness, bloating, and nausea. [14] These findings suggest that STEA provides more extensive relief of FD-related discomfort compared to TEA. Moreover, STEA was found to be more effective than TEA in ameliorating impaired gastric accommodation in response to a meal by 16%, possibly through the vagal pathway. Overall, the studies provide compelling evidence for the superiority of acute STEA over TEA for FD.
- A prototype was made as shown in Fig. 2. [17] This version of the controller measures 120mm x 100mm x 30mm and weighs 228 grams, offering enhanced portability. The chest strip sensor is made with Velcro strip embedded with a strain-gauge force sensor, which is convenient for the users to wear and take off.

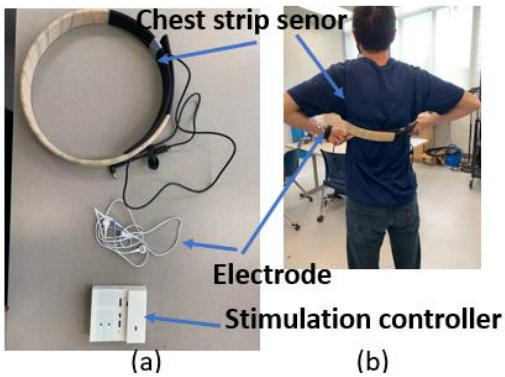

Figure 2. Prototype: (a) Overview of the device; (b) Application testing

- Benchtop experiments were conducted on three human users to verify the functionality and effectiveness of the AutoSTEA device. [17] The human users wore the respiration strip and sat in a comfortable chair, and the electrodes were connected with an artificial human impedance simulator. The testing was conducted for 5 minutes (about 75 cycles) for each user,

and each user repeated the testing three times. The results showed all the start points of the inhalation were identified. Fig. 3 shows the example result of one user. It demonstrated that the control system can synchronize respirations with neglectable delay, generate expected electrical waveforms, and provide a reliable function even with varying respiration cycles.

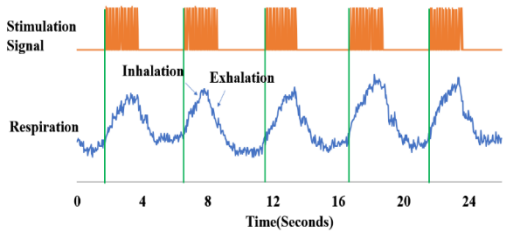

Figure 3. Benchtop testing result

3.3 Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

Functional dyspepsia (FD) also termed non-ulcer dyspepsia, is a common stomach disorder characterized by postprandial fullness, early satiety, and epigastric discomfort without an organic cause. [18-21] It affects up to 11.4% of the US population, [1] impairs the quality of life, and poses an annual management cost of over $18.4 billion in the US. [2] FD symptoms can be related to meals or unrelated, associated with impaired gastric accommodation, gastric hypersensitivity, delayed gastric emptying, gastric dysrhythmia, and autonomic dysfunction. [18,22,23] FD symptoms fluctuate over time and often become a lifelong medical burden for patients. [18]

Existing FD therapies primarily address symptoms, lose effectiveness over time, and carry substantial side effects. [18] These therapies include helicobacter pylori eradication, proton pump inhibitors (PPIs), histamine-2 receptor antagonists, antidepressants, and prokinetic agents. [18,24,25] Eradicating H. pylori may improve dyspeptic symptoms, but only one out of 14 treated patients responded positively. [7] While PPIs are moderately effective in symptomatic treatment by suppressing gastric acid production, they minimally affect FD's underlying pathophysiologies. [4] Antidepressants, considered when PPIs offer partial or no relief, improve symptoms for some patients, but studies on their pathophysiological effects are scarce, and significant side effects like drowsiness and impaired gut motor function occur. [5] Prokinetics can improve gastric motility but have limited effects on dyspeptic symptoms, and patients suffer from multiple side effects. [26] In summary, while various treatment options are available, their

therapeutic effects are limited and accompanied by multiple side effects. [3-5,26] In addition, there is a lack of integrative therapy that targets multiple pathophysiological mechanisms implicated in FD.

STEA therapy for FD. Evolving from traditional needle acupuncture and electroacupuncture, TEA that is delivered at acupuncture points via surface skin electrodes becomes a treatment of interest for gastric motility disorders. [7-12] Recently, an even more effective method STEA is emerging. The preliminary clinical studies [14-16] have demonstrated that the targeting performance of STEA is superior to that of TEA without synchronization to improve key FD pathophysiology, including amelioration of impaired gastric accommodation in response to a meal, normalization of gastric dysrhythmias, improvement of visceral hypersensitivity, and enhancement of vagal activity. No off-target mitigation/adverse effects of STEA were observed during these studies.

Limitations of STEA. Current procedure for conducting STEA treatment is mostly based on patients' manual synchronization in which the patients need to feel the start of stimulation and adjust their respiration to follow the stimulation. [14-16] This manual synchronization can generate a considerable delay or error in the synchronization and result in patients' noncompliance with chronic therapy, significantly compromising the effectiveness of this method.

A novel AutoSTEA device: To solve this issue and enhance the effectiveness of STEA in FD treatment, we have developed a novel non-invasive neuromodulation method, termed transcutaneous electrical acustimulation in automatic synchronization with breathing (AutoSTEA) (Fig 2), which automatically detects the user's respiration wave and synchronizes with the breath to deliver electrical stimulation at acupuncture points via surface skin electrodes (Fig. 3). [17] With this automated synchronization device, patients can inhale and exhale with an uninterrupted and normal respiration pace while receiving the TEA treatment, largely simplifying the treatment procedures, improving patients' compliance, and enhancing the effectiveness of the method.

Significance of the AutoSTEA therapy. (1) AutoSTEA reduces (1a) travel time and costs to acupuncture clinic, (1b) need for healthcare providers, and (1c) repeat procedure expenses, compared to traditional acupuncture/ EA. (2) AutoSTEA demonstrates superior therapeutic outcomes over non-synchronized TEA. (3) Unlike manual STEA, AutoSTEA's automation ensures uninterrupted natural respiration during treatment, simplifying procedures and improving patient experience, compliance, and feasibility and effectiveness of chronic therapy.

Scientific contribution: This project's primary objective is to evaluate the usability and safety of AutoSTEA therapy as outlined in the Phase I proposal. Success in these areas will lay the groundwork for conducting a comprehensive multi-center efficacy study in the subsequent Phase II proposal.
Clinical impact: AutoSTEA is expected to enhance and/or replace existing FD treatment and provide an integrative therapy that targets multiple pathophysiological mechanisms implicated in FD.

4.0 Study Endpoints*

4.1 Describe the primary and secondary study endpoints.

Primary Endpoint: (1) Assessment of usability will be performed at the second visit by collecting the subject's feedback using a structured questionnaire, as recommended by the IEC 60601-1-6 (Usability Standard). Each subject will grade multiple questions using a 0-to-5 scale to assess the usability, design effectiveness, satisfaction, and comfort of the device functionalities. (2) Assessment of safety includes a listing of the types, rates, and severity of AutoSTEA-related adverse events, including skin irritation, infection, or pain in the stimulation region.

Secondary Endpoint: (1) Functional Dyspepsia Symptom Diary (FDSD), an eight-item daily symptom diary, is developed according to recommendations in the FDA Patient-Report-Outcome Guidance to assess severity of FD symptoms. Each item is scored on an 11-point numeric rating scale from 0 (no symptoms) to 10 (worst imaginable symptoms). (2) Disease-Specific Quality of Life will be assessed by the short version of the Nepean Dyspepsia Index (NDI), scored from 0 to 100, with higher scores indicating a worse quality of life.

4.2 Describe any primary or secondary safety endpoints.

- Primary Safety Endpoint: The primary safety endpoint involves a comprehensive evaluation of AutoSTEA-related adverse events. This will encompass recording the incidence, type, and severity of any adverse effects directly associated with the use of AutoSTEA therapy. Specific adverse events of interest include, but are not limited to, skin irritation, infection, and pain within the area of stimulation. The severity of these events will be classified using standard grading scales, and their relationship to the AutoSTEA device will be thoroughly assessed to ensure accurate attribution.
- Secondary Safety Endpoint: As a non-significant risk device, AutoSTEA is anticipated to be well-tolerated by participants. However, secondary safety endpoints will include monitoring for

any unexpected adverse events or reactions throughout the study duration. This includes evaluating the long-term impact of treatment on functional dyspepsia symptoms, if applicable, and any other unintended outcomes related to the device's use. These assessments will be conducted through follow-up interviews and examinations, ensuring comprehensive safety monitoring beyond immediate treatment effects.

5.0 Study Intervention/Investigational Agent

1.1 Description: *Describe the study intervention and/or investigational agent (e.g., drug, device) that is being evaluated.*

According to the FDA 《Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies》, Functional Non-Invasive Electrical Neuromuscular Stimulators and Transcutaneous Electric Nerve Stimulation (TENS) Devices, excluding those used for chest pain/angina, are typically classified as non-significant risk devices (Appendix A, page 9). The AutoSTEA, which offers TEA automatically synchronized with the user's respiratory patterns, fits within this non-significant risk classification. Tailored for the management of Functional Dyspepsia (FD), the AutoSTEA mirrors the safety and functional attributes of conventional TENS devices, incorporating non-implantable features, low-power electrical stimulation, and an innovative automatic respiratory synchronization to improve user experience and comfort in treating FD, a condition that is not life-threatening. This safety and functionality equivalence is further supported by studies involving traditional TEA devices, which do not feature automatic respiratory synchronization.

The AutoSTEA device is engineered to automatically synchronize electrical stimulation with users' respiratory paces, providing non-invasive, low-power electrical stimulation to the skin. The device comprises a microstimulator with a controller, a chest strip, and standard TENS electrodes, tailored for FD patients. The AutoSTEA device is designed to be user-friendly, allowing patients to self-administer therapy.

How the device functions: A prototype was made as shown in Fig. 1. The chest strip is a non-invasive and wearable strip which is made with a Velcro strip embedded with a sensor to track the user's respiratory paces. The user wears the strip, and strategically places the reusable and disposable electrodes on the target sites, including either ST36 (leg shank) or PC6 acupoints (wrists), or both. The user will sit in a comfortable chair and turn on the stimulator. The AutoSTEA will track the user's breathing paces, and automatically deliver stimulation at each start of inhalation for 2 seconds in each respiratory cycle. The stimulation duration will be set following the

clinical trial protocol. **A video is attached to show how the device is set for use.**

The microstimulator: The latest prototype of microstimulator controller measures 4.7 inch x 4 inch x 1.2 inch and weighs 228 grams, offering enhanced portability (Fig 2), The prototype has two AA batteries to provide the power (total 3 Volts), and a power management system is established to maintain a sustainable, efficient and safe use of the power.

Electrical stimulation parameters: (1) The device allows the user to adjust the stimulation intensity up to 10 mA current through the adjustment knob. This meets the standard requirements for current commercial TENS devices. Any changes during stimulation will be logged in the stimulator memory card, and the log can be retrieved by the doctor for reviewing. (2) The generated electrical waveforms could be in the type of square or sine. This will be set by the medical professionals and recorded for future review and analysis. (3) The frequency of the waveforms can be set in the range of 1 Hz-200 Hz. And this will also be set by the medical professionals and recorded for review and analysis.

Design and manufacturing the microstimulator: (1) The cover of the latest prototype was designed in CAD software, and then additively manufactured (3d printing). The material of the cover is ABS (acrylonitrile butadiene styrene) which is the most common filament used in 3D printing. (2) The microcontroller and electronic components (e.g. resistors and capacitors) are built on a solderable printed circuit board (PCB). All these components can be operated or functional in the temperature range of -40 °C ~ 120 °C. Flexible AWG stranded electrical wires which could be operated in the temperature range of -60 °C ~ 120 °C, are used for the connection among different electronic components. (3) The PCB, battery case and relevant adapters are installed in the cover box, which is designed with engineering stands. The components are fixed on the stands with metal screws. Some parts are also further secured with silicon glue. All the components are fixed steadily to increase reliability.

Chest strip for respiration tracking: The chest strip is for tracking real-time respiration. The chest strip is embedded with a strain-gauge force sensor. The sensor is connected with the end of a power cord that has a male plug Jack on the other end. The sensor is a type of thin film and flex/bend pressure sensor that is commercially tailored for breathing sensing. The Velcro attachment method is for home use as the user can easily adjust the tightness on their own preference. The algorithm programmed in the

simulator microcontroller can guarantee the precision of the breathing tracking and avoid the influence from the tightness of installment.

Strip and sensor parameters: (1) The strip was made of double layer nylon web with 1-1/2 inch in width, 48 inch in length and 0.37 inch in thickness. If necessary, the strip size will be modified to accommodate for a wide population. The feature of Velcro is around the strip. (2) The thin film and flex pressure sensor is 23.6 inch in length, 0.6 inch in width and 0.35 mm in thickness. It can be operated in the temperature range of -20 °C ~ 60 °C. (3) The thin film and flex/bend pressure sensor works with a 3-volt power source. (4) The power cord is used to transmit the sensed electrical signal, and it has a standard 90-degree right angle male plug Jack.

Design and assembling the chest strip: (1) The thin film and flex/bend pressure sensor is soldered on one of the ends of the power cord and taped by adhesive electrical tape. (2) High adhesive electrical tape is used to fix the flex bend sensor around the strip. (3) Thin and adhesive athletic tape was wrapped around the strip to cover the sensor.

Upgraded Microstimulator for the proposed Phase I Feasibility Trial: For the proposed Phase I feasibility trial, we will employ an enhanced version of our microstimulator that retains its core functionality and stimulation parameters (refer to Fig. 4). This advanced model introduces several key improvements to optimize performance and user experience: (1) Two stimulation channels will be created so that the microstimulator can stimulate two sites simultaneously. (2) The microstimulator will be upgraded to a pager size from the protocol, with a physical dimension of approximately 4 inch x 3 inch x 1.2 inch. All the circuits and relevant electrical components will be designed in a thin PCB to achieve the dimensions. (3) A tiny display will be added so that in the stimulation mode, a count-down timer will be displayed to show the remaining stimulation time. (4) The microstimulator will be upgraded to be powered by a 3V rechargeable battery. The rechargeable battery will have an overcharge and over-discharge protection to prevent it from overheating or explosion. (5). Another layer of nylon cloth will be used to cover the sensing area of the chest strip.

These design considerations and forthcoming improvements underscore our commitment to delivering a safe, effective, and user-centered therapy solution for FD, with the AutoSTEA poised to set new standards in non-invasive neuromuscular stimulation for gastrointestinal disorders.

Figure 4: An upgraded micro-stimulator that maintains current functions and stimulation parameters for the proposed feasibility trial

5.1 Drug/Device Handling: If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

- **Storage and Security of the AutoSTEA Device:** The AutoSTEA devices will be securely stored in a locked cabinet within the Principal Investigator's (PI) office (S1-105B, Humann building), which is located in a restricted access area to ensure that access is limited to authorized study personnel only. The office is equipped with security measures including keycard access and surveillance cameras to prevent unauthorized entry and ensure the devices' safety and integrity.
- **Handling and Administration:** Only trained and authorized investigators will handle and administer the AutoSTEA devices to ensure proper use in accordance with the study protocol. Training sessions will be conducted prior to the commencement of the study to familiarize all authorized personnel with the device's operational procedures, safety features, and emergency protocols. The training will include instructions on how to correctly set up the device, adjust settings according to the study protocol, monitor participants during use, and respond to any device-related adverse events.
- **Documentation and Accountability:** A logbook will be maintained in the PI's office to record the checkout and return of each AutoSTEA device by the study personnel. The log will include the date, time, device serial number, and the name of the investigator using the device to ensure thorough tracking of device utilization and accountability. This logbook will be regularly reviewed by the PI to monitor compliance with the study protocol and handling procedures.
- **Disposal and Decontamination:** Decontamination and Reuse: Upon completion of the study or in the event of device malfunction, the AutoSTEA devices will be thoroughly decontaminated

according to established safety protocols. This process ensures the devices are safe for reuse, protecting both environmental safety and participant confidentiality. Devices will be evaluated for functionality and safety in accordance with the manufacturer's guidelines and applicable regulatory requirements. Only devices that meet these stringent standards will be reactivated for future use. Should a device not meet the necessary criteria for reuse, it will be safely deactivated and disposed of according to manufacturer guidelines and regulatory standards.

5.2 *If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:*

- *Identify the holder of the IND/IDE/Abbreviated IDE.*
- *Explain procedures followed to comply with sponsor requirements for FDA regulated research for the following:*

Regulatory Sponsor and Compliance: Athena Digital Health LLC is the designated holder of the IDE for the AutoSTEA device. *Although our IRB has preliminarily defined the proposed AutoSTEA device as non-significant risk device for the proposed study.* This week, Athena Digital Health LLC has undertaken the submission of a Q-Submission to the FDA, aimed at obtaining a Study Risk Determination. This crucial step is intended to clarify the classification of the upcoming Phase I feasibility clinical study of the AutoSTEA device — specifically, whether it will be categorized as significant risk, non-significant risk, or exempt from the regulatory requirements stipulated under IDE regulations, in accordance with 21 CFR part 812. This determination is essential for ensuring compliance with FDA regulations and guiding the study's oversight protocols.

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

6.0 Procedures Involved*

6.1 Describe and explain the study design.

Forty patients with functional dyspepsia (FD) will be enrolled in a two-week, single-arm trial to evaluate the safety and usability of the AutoSTEA treatment. Aligning with the NIH's directives to ensure a diverse participant pool, our recruitment strategy is designed to include a minimum of 15 overweight or obese patients with FD, characterized by a Body Mass Index (BMI) of 25-40. Additionally, we are committed to achieving gender balance within the study, targeting the inclusion of at least 15 female participants. This approach underscores our dedication to assessing the AutoSTEA treatment's feasibility across a broad spectrum of FD patients, with particular focus on those who are overweight/obese and female. AutoSTEA will be applied at acupuncture points ST36 and PC6 (Figs. 5&6).

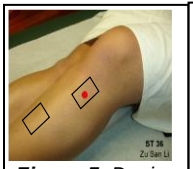

***Figure 5**. Device locations for ST36 AutoSTEA (red dot).*

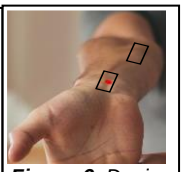

***Figure 6.** Device locations for PC6 AutoSTEA (red dot).*

6.2 Provide a description of all research procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks.

This study involves a series of structured procedures to ensure the comprehensive evaluation of the AutoSTEA treatment's safety and usability for patients with FD. Participants are scheduled for two hospital visits, marking the beginning and conclusion of the study period.

During the initial visit, participants will undergo a detailed training session. This session is designed to cover the completion of study-related questionnaires and the operation of the AutoSTEA device, including the utilization of an associated smartphone application for daily symptom tracking. To facilitate ease of use and address any potential issues during the study, this training will be recorded, providing participants with a reference. Furthermore, on-demand phone support will be readily available to assist with any inquiries or difficulties encountered during home use of the device.

Data collection and monitoring constitute a critical component of this study. Primary and secondary outcome measures will be systematically collected during hospital visits and supplemented by phone check-ins during the first week of the study. These efforts are aimed at closely monitoring participant safety and collecting valuable data on symptom progression. Furthermore, it is important to clarify that the option to complete questionnaires electronically is an additional, voluntary method available to participants. During their initial visit, all participants will be informed about and consented to this option. Those who opt-in will receive an invitation to complete the questionnaires via a secure REDCap link, delivered through their preferred method of communication, either email and/or SMS text message. This flexibility in questionnaire completion is designed to enhance participant convenience and accessibility, while rigorously maintaining the integrity and confidentiality of their responses. Additionally, the AutoSTEA device is equipped to automatically record therapy parameters as well as daily usage data, which will be stored in the device's memory. This information will subsequently be downloaded for comprehensive analysis to assess patients' adherence to the treatment protocol.

To ensure the safety of participants and minimize potential risks associated with device use, several precautionary measures will be implemented. Prior to electrode application, the skin contact area of the AutoSTEA device will be meticulously cleaned with skin prep jelly to reduce electrode-skin impedance, a crucial step for maintaining participant comfort and device efficacy. Moreover, the stimulation parameters for the AutoSTEA therapy have been carefully selected based on robust evidence of their safety and effectiveness in managing symptoms of FD.

In addition to the primary research procedures outlined, our study will incorporate the collection of historical data on the management of functional dyspepsia (FD) with traditional medical treatments, including antacids, proton pump inhibitors (PPIs), H2 blockers, and tricyclic antidepressants (TCAs), during routine clinical care. This will involve gathering demographic details, symptomatology, and treatment responses as documented in patient records. To safeguard patient privacy, all data will be de-identified and handled in accordance with HIPAA regulations and IRB-approved protocols. The integration of this historical data aims to deepen our understanding of the comparative effectiveness and outcomes of the AutoSTEA treatment relative to standard care, enhancing our analysis and enabling more informed conclusions about the AutoSTEA device's role in the FD treatment paradigm. This

comprehensive approach not only adheres to ethical standards but also contributes to the robustness of our research findings.

6.3 *Describe:*

- *Procedures performed to lessen the probability or magnitude of risks.*
    - To minimize the probability and severity of risks associated with this study, we have implemented a rigorous participant selection process. This process involves excluding individuals with pre-existing conditions that could elevate risk levels or interfere with study outcomes. The AutoSTEA device, identified as a non-significant risk investigational device by preliminary assessments, is central to our research. It is designed for the dual purposes of evaluating usability and ensuring safety within a meticulously controlled environment. Continuous and thorough monitoring of all participants for any adverse events related to the device will be conducted to promptly address and mitigate potential risks..
- *All drugs and devices used in the research and the purpose of their use, and their regulatory approval status.*
    - The AutoSTEA device, which operates on principles similar to those of a Transcutaneous Electrical Nerve Stimulation (TENS) unit, is classified as a non-significant risk device. This classification is based on its intended use and the preliminary risk assessment submitted to the FDA. In this study, the AutoSTEA device's primary function is to assess its usability and safety among participants with functional dyspepsia, under controlled conditions. Continuous monitoring for any adverse events will be rigorously maintained to ensure participant safety and compliance with regulatory standards.
- *The source records that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.)*
    - Data will be collected from structured questionnaires, symptom diaries, and quality of life indices. These instruments have been chosen for their relevance to the study's objectives and their established validity in similar research contexts.

6.4 What data will be collected during the study and how that data will be obtained.

- Data collected will include usability feedback, adverse event reports, FD symptom diaries, and quality of life assessments. These will be obtained through direct input from participants into the provided questionnaires and diaries, as well as through objective measurements recorded during hospital visits. Furthermore, it is important to clarify that the option to complete questionnaires electronically is an additional, voluntary method available to participants. During their initial visit, all participants will be informed about and consented to this option. Those who opt-in will receive an invitation to complete the questionnaires via a secure REDCap link, delivered through their preferred method of communication, either email and/or SMS text message.

6.5 If there are plans for long-term follow-up (once all research related procedures are complete), what data will be collected during this period.

- While no long-term follow-up is planned post-study, any significant findings related to safety during the trial will be reported to the IRB and participants will be provided with appropriate care recommendations.

6.6 For Humanitarian Use Device (HUD) uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

- This section is not applicable as the AutoSTEA device is not being considered for HUD use in this study. It is being evaluated under a Q-Submission to the FDA to determine its risk classification and is not yet approved or exempted under IDE regulations.

7.0 Data and Specimen Banking*

7.1 If data or specimens will be banked for future use, describe where the specimens will be stored, how long they will be stored, how the specimens will be accessed, and who will have access to the specimens.

- As this study does not involve the collection of biological specimens, there will be no specimen banking. However, data generated from the study will be securely stored in a HIPAA-compliant cloud data server, encrypted and password-protected. Access to this data will be restricted to authorized study personnel only, with rigorous controls in place to ensure confidentiality and integrity.

7.2 List the data to be stored or associated with each specimen.

- The data to be stored will include de-identified participant information, device usability and safety data, FD symptom data, and device parameter data in the device memory. This approach ensures participant privacy while facilitating future research and analysis.

7.3 Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

- Given the absence of specimen banking and the strict privacy protections in place, requests for data release will be handled on a case-by-case basis, requiring approval from the principal investigator. Release will be contingent upon the scientific merit of the request and compliance with all applicable privacy laws and regulations. Data released for approved requests will include only de-identified information to protect participant confidentiality.

8.0 Sharing of Results with Subjects*

8.1 Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how the results will be shared.

- Results are not going to be shared

9.0 Study Timelines*

9.1 Describe:

- *The duration of an individual subject's participation in the study.*
    - A 2-week duration.
- *The duration anticipated to enroll all study subjects.*
    - 12 months
- *The estimated date for the investigators to complete this study (complete primary analyses)*
    - 02/26/2027

10.0 Inclusion and Exclusion Criteria*

10.1 Describe how individuals will be screened for eligibility.

Adult patients exhibiting symptoms of functional dyspepsia, who either have normal esophagogastroduodenoscopy (EGD) results or

EGDs indicating mild gastric or duodenal inflammation that does not account for their dyspeptic symptoms, will be considered for screening.

10.2 Describe the criteria that define who will be included or excluded in your final study sample.

- Inclusion criteria: We will recruit men and women aged 18 years and older who meet the Rome IV criteria for functional dyspepsia. Participants must be willing and able to attend the two-week trial, understand the study procedures, complete questionnaires, and provide informed consent.
- Exclusion criteria: Patients with dyspeptic symptoms fully resolved by antisecretory, antidepressants, or prokinetics therapy will be excluded. However, those on a stable dose of PPIs, antidepressants, or prokinetics who experience only partial symptom resolution may be included. We will not enroll individuals with a history of active use of NSAIDs, unhealed esophagitis, unhealed ulcer disease, or other organic upper gastrointestinal diseases that explain dyspepsia, nor those with a history of upper GI surgeries, GI cancers, uncontrolled diabetes (types 1 or 2), severe psychiatric conditions, uncontrolled medical disorders, total knee replacement, or above-the-knee amputation. Additionally, individuals with positive H. pylori infection without confirmed eradication are excluded.

10.3 Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of the above populations as subjects in your research unless you indicate this in your inclusion criteria.)

- Adults unable to consent- will be excluded
- Individuals who are not yet adults (infants, children, teenagers)- will be excluded
- Pregnant women- will be excluded
- Prisoners- will be excluded

11.0 Vulnerable Populations*

11.1 If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

- Not indicated. Vulnerable populations will not be included in the study.

12.0 Local Number of Subjects

12.1 Indicate the total number of subjects to be accrued locally.

- The primary source for recruitment for this study will be the MetroHealth outpatient clinic. About 1,000 FD patients are seen annually at the MetroHealth outpatient clinic.

12.2 If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

- We plan to recruit 40 subjects who meet the eligibility criteria to ensure that 30 participants will complete the study, conservatively assuming a 25% attrition.

13.0 Recruitment Methods

13.1 Describe when, where, and how potential subjects will be recruited.

Recruitment will occur at the MetroHealth outpatient clinic, targeting patients with FD. Gastroenterology specialists will identify eligible patients during clinic visits, supplemented by study flyers and social media outreach.

13.2 Describe the source of subjects.

Subjects will be sourced from the outpatient GI clinic patient population, specifically those diagnosed with FD.

13.3 Describe the methods that will be used to identify potential subjects.

Potential subjects will be identified by clinic gastroenterologists based on eligibility criteria, with the study coordinator facilitating further screening and enrollment processes.

13.4 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Recruitment materials include flyers posted in clinics and IRB-approved ads on social media platforms, offering study information and coordinator contact details.

13.5 Describe the amount and timing of any payments to subjects.

There will not be any sort of payment or financial compensation for participants. Due to the study not being funded by the NIH or other external source, payments will not be available at any stage.

14.0 Withdrawal of Subjects*

14.1 *Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.*

Subjects may be withdrawn involuntarily under circumstances like non-compliance with study procedures or if continuing poses a health risk.

14.2 *Describe any procedures for orderly termination.*

An orderly termination process will involve a final assessment and discussion of the withdrawal's implications for the study's outcomes.

14.3 *Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.*

Upon withdrawal, subjects may choose to discontinue all study activities or permit ongoing data collection from completed procedures. The team will respect participant decisions, ensuring a clear communication path for any concerns or withdrawal requests.

15.0 Risks to Subjects*

15.1 *List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.*

The primary foreseeable risk to participants involves potential allergic reactions to the adhesives used in ECG electrodes. While such reactions are generally mild and localized, involving symptoms like skin irritation or rash, they are considered low in probability and magnitude. The discomfort is typically short-lived and reversible upon removal of the electrodes. No significant physical, psychological, social, legal, or economic risks are anticipated from participating in this study.

15.2 *If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.*

Currently, no procedures are anticipated to pose unforeseeable risks to the subjects.

15.3 *If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.*

This study will not include pregnant women, thus eliminating the risk to embryos or fetuses.

15.4 *If applicable, describe risks to others who are not subjects.*

There are no expected risks to individuals who are not subjects of the study.

16.0 Potential Benefits to Subjects*

16.1 Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits.

Individual subjects participating in this research may experience improvements in their symptoms of FD, leading to enhanced quality of life. While the primary aim of the study is to evaluate the safety and usability of the AutoSTEA treatment, symptom relief as a result of the therapy could offer significant personal benefits to participants. The probability and magnitude of these benefits, although optimistic, will vary among subjects, and any improvements in symptoms are anticipated to persist for the duration of the study and potentially beyond, depending on individual responses to the treatment.

16.2 Indicate if there is no direct benefit. Do not include benefits to society or others.

This study is designed to provide direct benefits to participants through potential symptom relief and improved quality of life.

17.0 Data Management* and Confidentiality

17.1 Describe the data analysis plan, including any statistical procedures or power analysis.

Descriptive statistics will be calculated for all variables, with appropriate tests applied based on data distribution. Continuous variables will undergo the Kolmogorov-Smirnov test to confirm normality, followed by the paired t-test or the Wilcoxon rank-sum test as applicable. Categorical variables will be analyzed using Pearson's χ^2 test.

17.2 Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

Data will be securely stored RedCAP, accessible only by the PI and research assistant, ensuring compliance with FDA 21 CFR Part 11 through password protection and encryption.

17.3 Describe any procedures that will be used for quality control of collected data.

Data collection accuracy will be ensured by providing participants with questionnaire instructions and by having trained personnel collect stimulation/parameter data in the memory card of the AutoSTEA device.

17.4 Describe how data or specimens will be handled study-wide:

- *What information will be included in that data or associated with the specimens?*

  Data, including questionnaire and device stimulation/parameter information, will be stored in RedCAP. The data will be retained for up to five years post-study, with access limited to the PI and research assistants. The research assistant will manage data receipt and transmission.

- *Where and how data or specimens will be stored?*

  Stored in secured MHS network drive in RedCAP, accessible only by the PI and IRB approved members of the study team, ensuring compliance with FDA 21 CFR Part 11 through password protection and encryption.

- *How long the data or specimens will be stored?*
  - Up to 5 years after the research concluded
- *Who will have access to the data or specimens?*
  - PI and research assistants
- *Who is responsible for receipt or transmission of the data or specimens?*
  - Research assistant
- *How data or specimens will be transported?*

  For this study, data and specimens will not require physical transportation as there are no tangible specimens collected, and all data will be digitally managed and stored. Any transfer of digital data will be conducted securely via encrypted electronic means, ensuring compliance with confidentiality and data protection standards. This approach eliminates risks associated with physical transport and aligns with modern data management practices in clinical research.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

This section is required when research involves more than Minimal Risk to subjects.

N/A, as this is a non-significant risk study.

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

To protect the privacy interests of participants, confidentiality will be rigorously maintained by all investigators, staff, sponsors, and their agents. This includes clinical information related to study participants. Strict confidentiality will be ensured for the study protocol, documentation, data, and all generated information. Any shared data or records will be de-identified, removing all Protected Health Information (PHI) and replaced with a unique study identifier. Information will only be released with participant consent or for regulatory oversight by entities such as the IRB, FDA, OHRP, or safety committees, to ensure study safety, monitor side effects, and facilitate outcome analysis.

19.2 Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

To ensure participants feel comfortable and respected throughout the research process, we will adopt a sensitive and respectful approach when asking questions and performing procedures. This involves framing questions in a non-judgmental manner and explicitly seeking consent before any examinations or procedures are conducted. Additionally, we will provide clear explanations about the purpose and nature of each question and procedure, allowing participants to feel informed and in control of their participation. This respectful engagement aims to minimize any sense of intrusiveness and foster a trusting environment.

19.3 Indicate how the research team is permitted to access any sources of information about the subjects.

Access to subject information will be strictly regulated within the research team. The study coordinator, tasked with data collection and management, will utilize Case Report Forms (CRFs) for documenting participant visits and ensuring data completeness. These CRFs will undergo a review process for completeness by the study coordinator before confirmation. Additionally, to maintain rigorous oversight, the primary investigator or co-investigators will conduct bi-annual reviews of the CRFs. This structured approach ensures that only designated research personnel have access to

participant information, safeguarding privacy and maintaining data integrity.

20.0 Compensation for Research-Related Injury

20.1 If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

- The research involved minimal risk to subjects

20.2 Provide a copy of contract language, if any, relevant to compensation for research-related injury.

- N/A

21.0 Economic Burden to Subjects

21.1 Describe any costs that subjects may be responsible for because of participation in the research.

Participants may incur some costs due to their involvement in the research, primarily related to travel to the clinic and parking fees. These are the anticipated direct out-of-pocket expenses for subjects.

22.0 Consent Process

22.1 Indicate whether you will you be obtaining consent, and if so describe:

- *Where will the consent process take place*

  The consent process will be conducted in a flexible and accessible manner. Identified subjects will be approached by the PI or designated research investigators either in the clinic setting or via telephone, ensuring convenience and consideration for the participant's preferences and circumstances. This approach facilitates a thorough and personalized consent discussion, allowing for any questions or concerns to be addressed promptly and effectively.

- *Any waiting period available between informing the prospective subject and obtaining the consent.*

  While no specific waiting period is mentioned, it's critical to ensure that participants have enough time to consider their participation fully. If a waiting period isn't mandated, ensuring participants understand they can take the time they need before consenting is important.

- *Any process to ensure ongoing consent.*

Highlighting that participants may withdraw at any time emphasizes respect for autonomy and ongoing consent, a cornerstone of ethical research.

- *Whether you will be following the IRB's SOPs for the consent process (Chapter 12, Section d). If not, describe:*

  Confirming adherence to the IRB's Standard Operating Procedures for the consent process reassures that the study will follow established ethical guidelines, ensuring participant rights and welfare are prioritized throughout the study

Non-English Speaking Subjects

- *Not indicated*

Waiver or Alteration of Consent Process and Waiver or Alteration of HIPAA Authorization (consent and HIPAA Authorization will not be obtained, required information will not be disclosed, or the research involves deception)

- *Not indicated*

Subjects who are not yet adults (infants, children, teenagers)

- *Not indicated*

Cognitively Impaired Adults

- *Not indicated*

Adults Unable to Consent

- *Not indicated*

23.0 Process to Document Consent in Writing

23.1 Describe whether you will be following the IRB's SOPs on written documentation of consent (Chapter 12, Section e). If not, describe whether and how consent of the subject will be documented in writing.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the

study participants and their families. Consent forms (written in non-technical language) describing in detail the study interventions/products, study procedures, and risks are given to the study participant and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB-approved and the study participant will be asked to read and review the document. Upon reviewing the document, the study team member will explain the research study to the study participant and answer any questions that may arise. The study participant will sign the informed consent document prior to any procedures being done specifically for the study. The study participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The study participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the study participants for their records. The rights and welfare of the study participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

24.0 Setting

24.1 Describe the sites or locations where your research team will conduct the research.

- *Identify where your research team will identify and recruit potential subjects.*

  The primary source for recruitment for this study will be the MetroHealth outpatient clinic. About 1,000 FD patients are seen annually at the MetroHealth.

- *Identify where research procedures will be performed.*

  The research procedures will be performed in the outpatient clinic or GI function unit.

- *Describe the composition and involvement of any community advisory board.*
  - *N/A*
- *For research conducted outside of the organization and its affiliates describe:*
  - *N/A*

25.0 Resources Available

25.1 *Describe the resources available to conduct the research: For example, as appropriate:*

- *Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?*

  Given that approximately 1,000 FD patients are seen annually at the MetroHealth outpatient clinic, the recruitment goal appears feasible. Assuming a conservative interest and eligibility rate, even a small percentage of this patient pool would be sufficient to meet the study's recruitment targets within the specified period. This approach, anchored in an existing, high-volume clinical setting, provides a solid foundation for achieving the required sample size, ensuring the study's feasibility and success.

- *Describe the time that you will devote to conducting and completing the research.*
  - Dr. Kurin and his research team, including clinical coordinator will have designated time of the week to perform the study.
- *Describe your facilities.*
  - Outpatient clinic or GI function unit will be used to perform the study.
- *Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.*
  - *Dr. Kurin and research assistant will be available to provide medical advice if needed.*
- *Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.*

  To ensure all research personnel are thoroughly familiar with the study protocol, procedures, and their specific roles, we will conduct regular team meetings. During these sessions, responsibilities will be clearly outlined and assigned, ensuring each team member understands their duties and the importance of adherence to the study protocol. This structured approach promotes a cohesive and informed research environment, essential for maintaining the study's integrity and ethical standards.

26.0 Multi-Site Research*

The research will be conducted across two sites, including the MetroHealth Main Campus and the Parma Campus. This two-site approach will enable us to access a broader participant base, enhancing the study's diversity and statistical power.