Optimization of TEA Modalities for Treatment of IBS-C
A Phase 1 25 Study participant Clinical Trial of Transcutaneous Electrical Acustimulation (TEA) in Study participants with IBS-C

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A Phase 1 25 Study participant Clinical Trial of Transcutaneous Electrical Acustimulation (TEA) in Study participants with IBS-C

HUM00189911

Principal Investigator:
Primary Investigator: Dr. Jiande Chen
Co-Investigators: Dr. William Chey, Dr. Borko Nojkov, Dr. Chung Owyang
Statistician: Jonathan Troost

Supported by: The National Institute of Health: HEAL Transfer Home-based for abdominal pain

Study Intervention Device Provided by: Transtimulation Inc.

Version Number: 1

Date: 2/10/2021

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- NIH Clinical Terms of Award
- The University of Michigan

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Study participants Protection Training.

SIGNATURE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations.

Primary Investigator:*

Signed:  Date: 1/5/2021

Name: Jiande Chen
Title: Professor of Medicine

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Abbreviations

TEA: Transcutaneous electrical acustimulation

EA: Electrical acustimulation

IBS-C: Irritable Bowel Syndrome with Constipation

PC6: acupuncture point three finger widths below the wrist

ST36: acupuncture point four finger widths below the knee

EA: Electro acupuncture

CRF: Case report form

SOP: Standard of procedure

PROTOCOL SUMMARY

Title:	Optimization of TEA Modalities for Treatment of IBS-C: A Phase I 25 Study participant Clinical Trial of Transcutaneous Electrical Acustimulation (TEA) in Study participants with IBS-C
Précis:	This study aims to discern whether Transcutaneous Electrical Acustimulation (TEA) at acupuncture points ST36 and/or PC6 will relieve the abdominal pain associated with IBS-C. Each study participant will have 5 research visits at the Michigan Medicine GI physiology lab. During these visits, they will undergo a procedure similar to Anal Rectal Manometry performed by the GI physiology lab staff. TEA is similar to this procedure as it is uses the barostat device and is performed by the GI physiology lab staff. This device has a rubber catheter that will be inserted 5-15 cm into the rectum of the study participant. Then the GI physiology staff will inflate the catheter. They will ask the study participant when they can sense the catheter. Then the GI physiology staff will continue to inflate the catheter and the study participants feel discomfort (described as the 'urge to defecate'). Then the study participant will be asked to pass the balloon (like they would pass a bowel movement). The difference between ARM procedure and the study procedure is that there will be stimulation of acupuncture point ST36 which is below the knee cap or stimulation of acupuncture point PC6 which is just above the wrist. At each visit there will be stimulation of only one of the points at either 100Hz or 25Hz. These are the potential combinations: ST36 100Hz, ST36-25Hz, PC6-100Hz, PC6-25Hz, Sham-TEA. The frequency and position combination (or sham visit) is randomly assigned. The randomization determines the order in which the study participant moves through the study. Every study participant will, in the end, complete one visit at each frequency and a sham visit. The study participant will also complete surveys at the appointment. Study participants will be compensated for their participation and given a parking pass.
Objectives:	Primary: Determine the best stimulation point and frequency for relieving the abdominal pain in study participants with IBS-C. Secondary: Collect measurements of visceral hypersensitivity in study participants with IBS-C.
Population:	25 study participants, male and females, age ≥18 years, IBS-C satisfying Rome IV criteria
Phase:	1

Number of Sites:	1, Michigan Medicine, University of Michigan
Study Duration:	24 Months
Study participant Participation Duration:	Each visit will be 120 minutes long. There will be 5 visits total. The maximum amount of time between visits is 3 weeks. The minimum amount of time between visits is 1 week
Description of Intervention:	The device being studied, the Transcutaneous Electrical Acustimulation (TEA) will give stimulation similar to electro acupuncture at two specific acupuncture points (ST-36 and PC-6) known to impact pain perception. The study team would like to access if TEA is safe for study participants and will impact the pain perception in study participants with IBS-C.
Estimated Time to Complete Enrollment:	12 Months

Schematic of Study Design:

Table 1: Arm of the study

This study has 1 cohort all study participants are in 1 arm	Sample size: 25 study participants	Intervention: Transcutaneous Electrical Acustimulation (TEA)	Randomization: The order of TEA will be randomized for each study participant.

See appendix A for the schedule of events table.

1 KEY ROLES

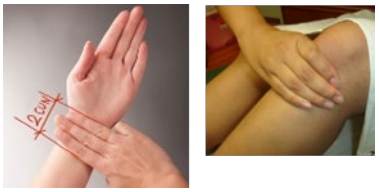
For questions regarding this protocol, contact Jiande Chen PhD. at 734-647-9252

Individuals:	**Principal Investigator:** Jiande Chen PhD. responsible for conducting the study. **Emergency Contact:** William Chey M.D. will be responsible for evaluation and connecting the study participant to treatment options. **Co-Investigators:** Chung Owyang and Borko Nojkov serve will help the PI in recruiting study participants and clinical research study design. **Lead Statistician:** Jonathan Troost will be the lead statistician.
Institutions:	University of Michigan (Michigan Medicine) 1500 E Medical Center Drive, Ann Arbor MI 48109 **Contact person**: Jiande Chen 734-647-9252 cjiande@umich.edu

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

- In this project, **we will use a novel transcutaneous electrical acustimulation (TEA) device for treatment of chronic abdominal pain in study participants with Irritable Bowel Syndrome with Constipation (IBS-C).** This is a device that has stimulating electrodes. The electrodes are placed on acupuncture points that previous studies demonstrate relieve pain related to constipation.
- This therapeutic strategy is called **Neuromodulation**. The process of preforming acupuncture via electrical stimulation in place of traditional acupuncture methods is called **electroacupuncture, EA**. The two acupuncture points, acupoints, that have been found to improve autonomic functions impaired in animal models of IBS are points ST-36 and PC6.
- In the human **PC6 is three finger widths above the wrist**. In the human **ST-36 is four finger widths below the knee**.
- The motivation behind this study is to access the impact of TEA on pain and motility in study participants with IBS-C. If successful, TEA could serve as a non-opioid treatment for pain related to IBS-C.



Left: image of acupuncture point PC6. Right: image of acupuncture point ST-36.

- The **barostat** is a FDA approved **device (K99 1288)** used in clinical practice and research to study the function and activity of the motor and sensory functions of the gastrointestinal tract. This is a common method used to measure gastric motility (or the movement of food from the mouth through the pharynx (throat), esophagus, stomach, small and large intestines and out of the body). It can monitor volume changes while maintaining a set constant pressure and deliver controlled distensions of gastrointestinal organs. The controlled distension is completed by the device's ability to inflate at the tip of the catheter. In this study, the device will be used in the rectum. This device does not use electricity to stimulate the rectum.
- This device is not being studied. Rather it is used to collect measurements. In this case, we will use the barostat device to monitor the activity in the rectum. The rectum of the GI track thought to be have abnormal activity in study participants with IBS-C, contributing to their symptoms.

Top: Image of the rectal barostat balloon, partially inflated. Bottom: Image of the barostat device, control panel.

2.2 Rationale

- The aim of the study is to determine the best TEA stimulation point and parameters for treating the abdominal pain in study participants with IBS based on a well-established measurement of motility, the barostat and the study participant's survey responses.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The immediate risks involved with barostat inflation and subsequent rectal distension include:

- Discomfort during the balloon insertion
- Sensation (discomfort) with the balloon inflation which is a variable of the study. The likelihood of this risk is common, up to 100% of participants will experience discomfort. The study team will make the study participant aware of this before consenting to the procedure. The study participant has the right to stop the procedure at any time.
- Bleeding at the site of balloon inflation (in the rectum). The likelihood of this risk is rare, approximate incidence of <1%.

However, the duration of rectal distention is brief and the distention can be immediately terminated upon intolerable pain or discomfort.

The long range risk of barostat inflation is:

- Perforation of the rectum into the peritoneal space, the likelihood of this risk is rare, approximate incidence of <1%.

The risks of electrical stimulation via TEA are:

- Possible allergic reaction to the stimulation electrodes and sensation of electrical stimulation. The likelihood of this risk is rare, approximate incidence of <1%.

However, the stimulation output will be set at a level that is well tolerated by the participant. In very rare occasions, the participant might experience rash or minor infection at the stimulation point that can be treated locally if needed.

The risk involved with the ECG recording:

- Allergic reaction of ECG electrodes. The likelihood of this risk is rare, approximate incidence of <1%

The researchers will try to minimize these risks by having an experienced investigators and lab personnel performing the barostat studies with particular care. The study investigators and our GI Physiology lab staff are well versed in doing these type of procedures. In addition, one of gastroenterologist-physician study investigators will be present/perform the studies or will be readily available on site for consultation/evaluation in case of any study complications or questions.

The rationale behind these risks is that the risks are unlikely and the study participant would receive care

immediately. Moreover, the study team would not be able to collect this data without study participants enduring the risks. Alternative procedures would not provide the same understanding of the influence of TEA for IBS-C study participants.

2.3.2 Known Potential Benefits

A potential benefit for study participant is a reduction in pain related to their IBS-C.

3 Objectives

3.1 Study Objectives

The objectives of this study are as follows:

- To understand the impact of TEA on study participants with IBS-C (reduction of pain related to IBS-C)
- Access the safety of TEA in study participants with IBS-C
- Refine which (if any) TEA stimulation and location combination delivers the greatest reduction in pain associated with IBS-C

3.2 Study Outcome Measures

The barostat device and study participant survey responses will measure the study outcomes.

3.2.1 Primary Outcome Measures

The barostat device will measure the volume changes in the rectum during controlled distension of the gastrointestinal organs. If the TEA is successful, the study participant's maximum tolerance should increase after TEA compared to their first maximum tolerance of the visit. This will be defined by comparing their maximum tolerance pre and post TEA.

3.2.2 Secondary Outcome Measures

A secondary outcome of the study will be reviewing the volume and pressure measurements from the barostat device. The surveys will also be reviewed to see if the study participants have a change in their symptoms.

4 Study Design

This is a placebo-controlled trial. The placebo is the sham-TEA visit. The study will recruit 25 study participants with IBS-C. These study participants will be recruited from the UM Health Research Recruiting Registry (UM HealthResearch.org), Michigan Bowel Control Program (MBCP), Functional Bowel Disease (FBD), and the study team will screen the gastroenterology clinic schedules via MiChart.

This is a phase 1 trial. This is study will only occur at the University of Michigan. There is only one group/arm of study participants. The study team plans to complete enrollment within 12 months of beginning to the study. Study participant participation will be at a minimum 5 weeks (1 week between

visits) and at a maximum 15 weeks (3 weeks between each visit). The test agent is the novel TEA device.

4.1 Schedule of Events for Each Visit

Every visit is the same and will follow the steps detailed below, with the exception of the first visit which will include the informed consent process. At visit one, the study team will randomly generate the stimulations schedule unique to each study participant; this is the order of locations and currents by using a random generator. For example, ST36-100Hz, ST36-25Hz, PC6-100Hz, PC6-25Hz and Sham-TEA.

48 Hours prior to the visit: The study participants will not take any medications known to affect the gut or pain perception.

8:00 pm on the night before the visit: The study participants begin fasting for their visit the next day. Study participants can still drink water. Study participants cannot drink coffee, tea, juices or eat any food items.

Day of the Visit:
Study participants will come to the study location, the Gastrointestinal Physiology Lab in University of Michigan. The visit will take place in one of the private rooms within the lab. **If the study participant is a women of child bearing potential:** She will complete a pregnancy test provided by the study team. If her pregnancy test is positive, she will be excluded from further participation in the study and will not complete the visit.

Rome IV Criteria for Irritable Bowel Syndrome: Upon arrival for every visit, the study participant will complete the Rome IV Criteria for Irritable Bowel Syndrome survey.

Enema: The study participant will be given a rectal enema to clean the rectum. Then the study participant will undress from the bottom down and be given a gown and sheets for comfort and privacy.

Position the study participant: The study participant will be asked to lie down on the medical examination table on one side and bring his or her knees up to the chest, similar to the fetal position. The table has rails that will protect the study participant from falling. The staff may use pillows to adjust and secure the study participant as well as for comfort.

Electrode Placement: The GI physiology laboratory staff will place two electrocardiogram (ECG) electrodes from of the TEA device on the subject's skin, one on the wrists at location PC6 and the other on upper leg below the knee at location ST36. These two electrodes will be used for delivering weak electrical current stimulation. The electric current and stimulating electrode location is determined by that study participant's randomized stimulation schedule. Electrodes will be placed at both locations at each visit.

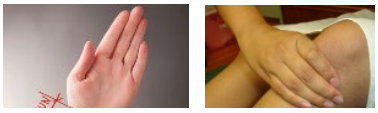


Fig.1: Locations of PC6 and ST36.

An additional three ECG electrodes connected to the ECG machine will be placed on the study participant's skin, one on the manubrium of sternum, one above the breastbone and one on the study participant's right chest. These three electrodes will be used for recording the ECG. Before the placement of each of the 5 electrodes, the skin area where the electrodes to be placed will be carefully cleaned using skin-prep materials.

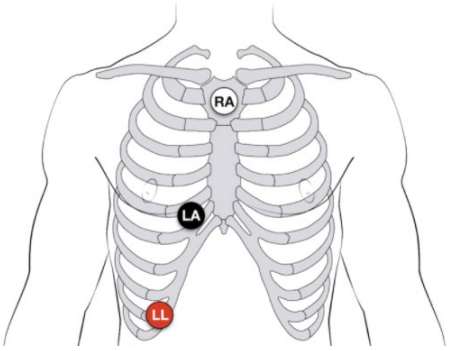


Fig.2: Locations of ECG electrodes to read electrocardiogram.

Baseline data collection with the Barostat:
The Barostat is an FDA-Approved device that measures pressure in the rectum. The device has a thin and flexible polyvinyl catheter (PVC) will be placed 5-15 cm into the study participant's rectum. Once placed, this catheter will be in the rectum for the reminder of the visit.

Rest - 15 Minutes
While the study participant is at rest, baseline data will be collected for 15 minutes.

Inflation with the Barostat:
The GI physiology lab staff will inflate a small balloon at the tip of the catheter and ask the study participant to assess the sensation. During this period, the study participant will be asked to take a note of their first sensation, urge to defecate and maximum tolerance; meanwhile, the study participant will also be asked to report the scale of pain or discomfort during the process of the balloon distention. The study participant will complete the Visual analog Scale Pain Score during inflation.

Maximum Tolerance:
Once the maximum tolerance is reached, the inflation will stop and the air will be removed.

TEA – 15 minutes
One of the randomly assigned TEA methods (or sham-TEA) will be performed for 15 minutes.

Inflation with the Barostat and TEA:
Then the inflation process described above will be repeated while applying the TEA. The study participant may sense the weak electrical stimulation. If the stimulation intensity is uncomfortable for the study participant, the stimulation will be set a level where the study participant feels comfortable. This will be noted in the visit summary. The study participant will complete the Visual Analog Scale Pain Score during inflation.

During the entire period, the ECG signal will be recorded from the three chest ECG electrodes. Once the inflation with barostat and TEA is completed, the study participant's visit will end.

5 Study Enrollment and Withdrawal

Eligibility Criteria:

5.1 Study participant Inclusion Criteria

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

- Male or female, aged 18 to 99
- Willing to comply with all study procedures and be available for the duration of the study
- Diagnosed with IBS-C satisfying Rome IV criteria
- Have symptoms present for at least the last 3 months
- Have abdominal pain that is not adequately relieved at the time of screening and the time of randomization
- Has a VAS pain score of >3 (on 0-10 score)

5.2 Study participant Exclusion Criteria

A potential study participant who meets any of the following exclusion criteria at baseline will be excluded from participation in this study if:

- Have an unrelated active disorder which may involve abdominal pain, such as inflammatory bowel disease, diabetes, unstable thyroid disease
- Have history of abdominal surgery other than cholecystectomy (gallbladder removal) or appendectomy
- Are taking anticoagulants or antispasmodic, antidiarrheal, or opioids or other pain relief medications and cannot stop these medications for three consecutive days before each study visit
- Are pregnant or breastfeeding; women of child bearing potential complete a pregnancy test at each visit
- Have known allergic reactions to components of the ECG electrodes
- Received treatment with an investigational drug or other intervention within 6 months of the date of consent
- Anything that, in the opinion of the investigator, would place the study participant at increased risk or preclude the study participant's full compliance with or completion of the study
- Are unable to provide informed consent

5.3 Strategies for Recruitment and Retention

Recruitment: Co-investigators, Drs. Chey, Owyang and Nojkov, and physician colleagues seeing study participants at Michigan Bowel Control Program (MBCP) and Functional Bowel Disease (FBD) will refer potential study participants to the study team. MiChart schedule screening may also be used for identifying possible study participants.

The study team will also post the study on the UM Health Research Portal. According to NIH guidelines, we will also post the study on clinicaltrials.gov.

Retention: The study team hopes to retain study participants in the study by allowing a flexible time period between visits; as short as one week and as long as 3 weeks between visits.

5.4 Treatment Assignment Procedures

5.4.1 Randomization Procedures

Prior to the first visit, the order of TEA stimulation at the visits will be randomly assigned to each study participant. Every study participant will undergo every TEA combination (For example, ST36-100Hz, ST36-25Hz, PC6-100Hz, PC6-25Hz and Sham-TEA).

5.4.2 Reasons for Withdrawal

A study participant will be discontinued from participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, intercurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the study participant.
- The study participant meets any exclusion criteria (either newly developed or not previously recognized).

Study participants are free to withdraw from participation in the study at any time upon request.

5.4.3 Handling of Withdrawals

This study may be prematurely terminated if, in the opinion of the investigator or the sponsor, there is sufficient reasonable cause. Written notification, documenting the reason for study termination, will be provided to the investigator or sponsor by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to study participants.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Plans to modify, suspend, or discontinue the development of the TEA device.

If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

6 Study Intervention/Investigational Device

6.1 Study Device Description

The TEA device is about 4x3cm. It is similar to a TENS (transcutaneous electrical nerve stimulation) unit that is classified by FDA as a non-significant risk device. For this study, two regular ECG electrodes will be placed on the skin surface on the preferred location as shown in Fig.1 and connected to the TEA device. This device will deliver a specified weak electrical signal. The device is powered by a small rechargeable battery and the charging will take place only when the device is not in use. The maximum current output is 10mA.

7 Study Schedule

7.1 Screening

Once a candidate is identified, a member of the study team will speak with the study participant to explain the study. The study participant may be contacted via phone and the study team member will follow the phone script and go through the pre-screen questions if interested. If the study participant is determined to be ineligible or not interesed via the pre-screening contact, he or she will be excluded in the study and logged as pre-screened and ineligible or not interested.

If the study participant is eligible and interested the study team will set up the first study visit. The study participant will go through the informed consent process at the first study visit.

7.2 Visit Schedule of Events

see section 4.1 Schedule of Events for Each Visit and Appendix A for a Table Describing the Schedule of Events

7.3 Visit Compensation

Subjects in this study will receive $200.00 per visits 1-3 and $350.00 per visits 4 and 5.

This totals to $1,300.00 once all study activity is completed.

The compensation is set at such a high value based on the lengthy duration of the study visits (120 minutes), the strong likelihood of discomfort due rectal dilation (the balloon inflation with the barostat procedure) and the sensitive nature of the study.

The additional payment in visits 4 and 5 is to encourage study participants to complete all five visits. It is crucial to the study design that the study participant completes all five visits.

8 Study Procedures/Evaluations

8.1 Surveys

The study participant will complete the Rome IV criteria for Irritable Bowel Syndrome at the beginning of every visit. The study participant will complete the Visual Analog Scale Pain Score twice, once during both inflations, at every visit.

9 Assessment of Safety

9.1 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.1.1 Adverse Events

Adverse Event: AE is defined as any untoward medical occurrence in a study participant or clinical investigation study participant administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include MD, DDS, DMD, PA, Nurse Practitioner, or DO), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the study participant is screened will be considered as baseline and not reported as an AE. If a pre-existing condition or illness, which is not expected to exacerbate or worsen, deteriorates at any time during the study it should be reported as an AE.

All AEs must be graded for severity and relationship to study product.

Severity of Event: All AEs will be assessed by the clinician using a protocol defined grading system. For events not included in the protocol defined grading system, the following guidelines will be used to quantify intensity.

- **Mild:** Noticeable to the study participant, but does not interfere with study participant's expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study.
- **Moderate:** Interferes with the study participant's expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.
- **Severe:** Extremely limits the study participant's daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolved. Severe events are usually incapacitating.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed.

Relationship to Study Products: The clinician's assessment of an AE's relationship to test article (study drug) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study product assessed using the terms: associated or not associated. To help assess, the following guidelines are used.

- **Associated** – The event is temporally related to the administration of the study product and no other etiology explains the event.
- **Not Associated** – The event is temporally independent of study product and/or the event appears to be explained by another etiology."=

9.1.2 Expected Adverse Reactions

It is expected that study participants may discover they have an allergy to the adhesives used during on the ECG electrodes during the study.

9.1.3 Serious Adverse Events

Serious Adverse Event (SAE): An SAE is defined as an AE that meets one of the following conditions:

- Death during the period of protocol-defined surveillance
- Life-threatening event (defined as a study participant at immediate risk of death at the time of the event)
- An event requiring in study participant hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the study participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in study participant hospitalization, or the development of drug dependency or drug abuse/overdose or cancer.

All SAEs will be:

- recorded on the appropriate SAE Report Form and CRF
- followed through resolution by a study clinician. The study clinician for this study is Dr. William Chey. The PI is a PhD. And not an MD. As an MD, Dr. William Chey will serve as the emergency contact person for the study. He is the lead of the GI physiology lab.
- reviewed and evaluated by a study clinician.

9.1.4 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to study participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the study participant population being studied;
- related or possibly related to participation in the research (in the guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places study participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in order to protect the safety, welfare, or rights of study participants or others. Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

- changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to study participants
- modification of inclusion or exclusion criteria to mitigate the newly identified risks
- implementation of additional procedures for monitoring study participants
- suspension of enrollment of new study participants
- suspension of research procedures in currently enrolled study participants
- modification of informed consent documents to include a description of newly recognized risks
- provision of additional information about newly recognized risks to previously enrolled study participants.

Unanticipated problems will be recorded and reported throughout the study.

9.2 Reporting Procedures

9.2.1 Serious Adverse Events

The study will comply with IRB and FDA reporting requirements and guidelines.

9.2.2 Regulatory Reporting for Studies Not Conducted Under IND

All AEs and SAEs will be reported to the University of Michigan IRB Med.

9.2.3 Other Unanticipated Problems

Incidents or events that meet the OHRP criteria for unanticipated problems require the completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem."

9.2.4 Reporting of Pregnancy

If a study participant is pregnant she will be excluded from the study. If a study participant becomes pregnant during the study she will excluded from the remainder of the study.

9.3 Type and Duration of Follow-up of Study participants after Adverse Events

All AEs will be followed until resolved or considered stable. Follow up will be conducted by Dr. William Chey. He will determine the rate of contact by accessing the severity of the AE. The reporting of AEs to IRB Med will be conducted by the study coordinator.

9.4 Safety Oversight

Data and Safety Monitoring Board (DSMB)
The first DSMB meeting will occur one month after recruitment begins. In addition to reviewing Serious Adverse Events (SAEs), the first DSMB meeting will focus on over all safety of the trial and study agent and will make a determination as to whether or not the study should proceed. The DSMB will then meet once every 6 months throughout the remainder of the study and at any time during the study in which an unexpected and possibly related SAE occurs.

The DSMB will be composed of the following members:

Irene Sarosiek, MD: a Gastroenterologist and Professor of Medicine from the Division of Gastroenterology, Texas Tech University Health Science Center. Dr. Sarosiek is an established clinical investigator in the field of functional gastrointestinal diseases. She will serve as the Chair of the committee.

Thomas Abell, MD: a Gastroenterologist and Arthur M. Schoen, M.D., Chair in Gastroenterology Gastrointestinal Motility Clinic from the Division of Gastroenterology at the University of Louisville. Dr. Abell is an expert in functional gastrointestinal diseases and has extensive experience in clinical trials and clinical research. He will serve as a member of the committee.

Gengqing Song, MD, PhD: an Assistant Professor of Medicine and Director of Gastrointestinal Motility, Division of Gastroenterology and Hepatology MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio. He will serve as a member of the committee

Blair Richards: a lead statistician from University of Michigan, Michigan Institute for Clinical & Health Research. He has over 15 years of experience on translational and health research projects across various disease area. He will serve as a member of the committee.

10 Statistical Considerations

Analysis of variance (ANOVA) will be performed to investigate the difference in each of the outcomes among 4 different sessions. Tukey's test will be used for study the differences in each of the measurements between two stimulation points (same stimulation parameters) and between two stimulation parameter sets (same stimulation points). The Pearson correlation analysis will also be performed to investigate the correlation between each of HRV parameters and the pain score or sensation threshold

. 10.1 Study Hypotheses

TEA at acupoints ST36 (a point below the knee cap) or PC6 (a point in the wrist) will be effective in reducing abdominal pain induced by rectal distention in patients with IBS-C. This hypothesis is based on published literature and our Dr. Jiande Chen's experience with EA and TEA at the Johns Hopkins. Dr. Chen's previous experience with EA and TEA includes: animal studies in which electrical acupuncture at ST36/PC was shown to reduce abdominal pain in a rodent model of IBS and functional dyspepsia and preliminary clinical study in patients with IBS-C showing the reduction of overall symptoms of IBS, including abdominal pain.

10.2 Sample Size Considerations

The study team plans for a 20% participant dropout or incompletion rate. For this reason, they will enroll 25 study participants when in actuality they need 20 study participants to complete the study. If 20 study participants complete the study and there are still 5 active participants, the active participants will still complete the study.

This is **not** a clinical trial to investigate the efficacy of the therapy for the treatment of IBS-C. Instead, this is a pilot study to determine which method of TEA (4 different modalities and 1 placebo) is more effective in treating abdominal pain in patients with IBS-C by studying patients' sensation to rectal distention with different methods of treatment. The findings of this pilot study will be used to determine which treatment to use in a future clinical trial. No preliminary data are available for the calculation of the sample size. The simple size stated in this study was based the PI's experience in other neuromodulation studies involving methodological optimization.

10.2.1 Safety Review

Study enrollment and/or study visits will halt to at if the study team feels the study is unsafe. This would include if study participants are experiencing serious adverse events. The DSMB will meet every 3 months during the study enrollment/study visit period. If needed, the DSMB will meet more frequently to monitor the study.

This is an acute study involving 5 sessions on separate days. No treatment or intervention will be given in between sessions.

The risks involved in the study include rectal distention (a clinically approval procedure) and delivery of weak electrical current via skin surface electrodes. Any acute study session will be terminated if the patient is not tolerable to the procedure or decides to withdraw. If the safety is a concern, the remaining

study sessions will be cancelled for that particular subject. The study enrollment will be halted if serious adverse events are reported.

Safety outcome measures will include 1) pain/discomfort level during rectal distention, 2) any signs or symptoms of possible perforation or rupturing of the rectum during insertion of the rectal catheter and during rectal balloon distention, 3) any side effects due to weak electrical stimulation, such as rash or discomfort in the area of stimulation.

10.2.2 Efficacy Review

This pilot study does not assess efficacy of the proposed TEA treatment.

The study outcomes include rectal sensation and pain during rectal distention, autonomic functions noninvasively assessed from the ECG.

10.3 Final Analysis Plan

Analysis of variance (ANOVA) will be performed to investigate the difference in each of the outcomes among different sessions. Tukey's test will be used for study the differences in each of the measurements between two stimulation points (same stimulation parameters) and between two stimulation parameter sets (same stimulation points). The Pearson correlation analysis will also be performed to investigate the correlation between each of autonomic function parameters and the pain score or sensation threshold.

11 Source Documents and Access to Source Data/Documents

Only members of the study team will have access to source data. This includes: all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

12 Quality Control and Quality Assurance

- The study team will be present for each visit and follow the visit CRFs. The study team will go through the procedures with the GI physiology lab staff members to ensure that there is adherence to the protocol.
- The study team will sign the bottom of each study CRF at the end of the visit.

13 Ethics/Protection of Human Study participants

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Study participants of Research, as drafted by the US National Commission for the Protection of Human Study participants of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46; 62 Federal Regulations 25691 (1997) and the Declaration of Helsinki and Good Clinical Practice (GCP).

13.2 Institutional Review Board

The TEA device is similar to a TENS unit which is a non-significant risk but is not approved by the FDA.

As the device is not approved by the FDA the study team will have it reviewed by the Clinical Engineering Department for them to check into the safety. I have the device now. It is similar to a TENS device (non-significant risk) but not FDA approved.

The study will be reviewed for IRB approval. The study will not begin until IRB approval is granted.

13.3 Informed Consent Process

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.

13.4 Exclusion of Women, Minorities, and Children (Special Populations)

This study will exclude women who are pregnant. This is for their safety and the safety of their fetus(es).

The study also excludes children. This is because the population being studied are adults with IBS-C.

13.5 Study Participant Confidentiality

Study participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating study participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence.

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be de-identified of any protected health information (PHI) and replaced with study identifier to maintain study participant confidentiality. Information will not be released without written permission of the participant , except as necessary for monitoring by IRB, the FDA, OHRP and/or any other government officials, safety monitors/committees that may need the information to make sure that the study is done in a safe and proper manner, learn more about side effects, and/or analyze the results of the study.

13.6 Study Discontinuation

In the event that the study is discontinued:

- The study participants will not be able to continue with TEA.
- The study will not compensate study participants for incomplete visits.

14 Data Handling and Record Keeping

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Dark ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

14.1 Data Management Responsibilities

The study coordinator will be responsible for data collection and management. The study coordinator will use the CRFs to document study participant visit. They will also review data for completeness prior to signing the bottom of the CRF. Periodically, every six months, the primary investigator or co-investigators will review the CRFs and for completeness. The barostat measurements will be saved as part of the research file by the GI physiology lab staff at the end of each visit.

14.2 Types of Data

Data for this study will include safety, barostat measurements, and survey results.

14.3 Timing/Reports

The primary investigator will review the study documents with the study coordinator every six months.

14.4 Study Records Retention

Study documents should be retained for a minimum of 3 years after the final study publication.

14.5 Protocol Deviations

Protocol deviations will be documented in a deviation log kept on the shared drive with all other study documents. Deviations will be reported to the IRB for review as required.

15 PUBLICATION POLICY

Following completion of the study, the investigator is expected to publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov**, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For grants and cooperative agreements, it is the Institution's responsibility to register the trial in an acceptable registry. In addition, *NIH Public Access Policy* requires the principal investigator to submit journal articles that arise from NIH funds to the digital archive *PubMed Central*.

The ICMJE defines a clinical trial as any research project that prospectively assigns human study participants to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., Phase I trials), would be exempt from registering trials in a public registry such as ClinicalTrials.gov.

SUPPLEMENTS/APPENDICES

Appendix A: Schedule of Events

APPENDIX A: SCHEDULE OF EVENTS

A detailed schematic describing all visits and assessments.

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Informed consent	X				
Documentation of current IBS-C symptoms via the IBS (GSRS-IBS)	X	X	X	X	X
Documentation of current laxative and/or antispasmodic use	X	X	X	X	X
Rectal Enema	X	X	X	X	X
Baseline 15 minutes	X	X	X	X	X
Experimental Protocol – Example of randomized TEA	ST36-100Hz	ST36-25Hz	PC6-100Hz	PC6-25Hz	Sham-TEA
Pregnancy Test (if participant is a woman with child bearing potential. If the woman is not on a birth control method)	X	X	X	X	X