Wearable Transcutaneous Electrical Acustimulation for Gastroparesis

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Version Number: 1

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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: B. Nojkov Date: 9/18/21

Name: Borko Nojkov, MD
Title: Assistant Professor of Medicine

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Abbreviations

TEA: Transcutaneous electrical acustimulation

PC6: acupuncture point three finger widths above the wrist

ST36: acupuncture point four finger widths below the knee

EGG: electrogastrogram

ECG: electrocardiogram

GCSI-DD: Gastroparesis Cardinal Symptoms Index-Daily Diary

CRF: Case report form

PROTOCOL SUMMARY

Title:

Wearable Transcutaneous Electrical Acustimulation for Gastroparesis

A Phase I 60 Study participant Clinical Trial of wearable Transcutaneous Electrical Acustimulation (TEA) in Study participants with gastroparesis

Précis:

The aims of this project are to study the effects of wearable TEA at acupuncture points ST36 and PC6 on gastrointestinal symptoms, gastric motility and possible mechanisms related to autonomic functions. After the enrollment, each study participant will come to the clinic for two times at the Michigan Medicine GI physiology lab. During these visits, the participant will undergo the following procedures: 1) completion of questionnaires related to GI symptoms and quality of life; 2) a gastric emptying breath test performed by the study team member; 3) simultaneous recordings of the electrogastrogram (EGG) and the electrocardiogram (ECG) before and after a w*ater* drink test performed by both the GI physiology lab staff and the study team member. During the first visit, the participant will also be trained to use the TEA device system (the electrodes, stimulator, charger and a smartphone), including adjusting the amplitude and the use of the pre-installed app for questionnaire completion and submission. After the first visit, the participant will perform the home-based treatment twice daily for 8 weeks with symptoms to be reported through the smartphone app. The participant will return to the clinic after the 8-week treatment and the same tests performed at baseline will be repeated for evaluating treatment effects. After the second visit, there will be an open-label treatment/follow-up period of 4 weeks during which the sham-TEA group will be treated using TEA at ST36 and PC6, and the TEA group will be taken off the treatment. During this 4-week period, only main symptoms will be assessed by questionnaire and phone and no office visit will be needed. At the end of the 4-week period, the patient will be asked to send back the questionnaire and the TEA devices.

Since home-based treatment will be required, the participant will be trained to locate acupuncture points ST36, PC6 and sham acupoints used in the sham-TEA group. During the first visit, the study team member will mark the ST36, PC6 or sham acupoint locations with sharpie marker pen and take pictures using the smartphone, train the participant to find the right locations by tracing the markers and the picture.

The smartphone in which patient information is stored will not be connected to any internet services and no data on the smartphone will

	be transmitted to any other locations. It will be returned to the study team during the second visit. The study will also recruit 40 healthy control subjects to undergo simultaneous recordings of the electrogastrogram (EGG) and the electrocardiogram (ECG) before and after a w*ater* drink test. Study participants will be compensated for their participation and given a parking pass.
Objectives:	Primary: to study the effects of wearable TEA on GI symptoms in patients with gastroparesis. Secondary: to study the effects of wearable TEA on gastric motility including gastric emptying, gastric accommodation and gastric slow waves, and possible mechanisms involving autonomic functions.
Population:	100 study participants, male and females, age ≥18 years, 60 diabetic gastroparesis subjects and 40 healthy control subjects
Phase:	1
Number of Sites:	1, Michigan Medicine, University of Michigan
Study Duration:	24 Months
Study participant Participation Duration:	Gastroparesis Subjects: Each visit will be of 2 days. Day 1: completion of questionnaire and a gastric emptying test, lasing about 5-6 hours. Day 2: a w*ater* drink test together with the recordings of the EGG and ECG, lasting about 3-4 hours. The participant will be asked to stay at a nearby hotel for one night if he or she is from out of town.here will be 2 visits in total; the interval between the two visits is 8 weeks. Healthy Controls: There will be one visit where subjects undergo a water drink test with EGG and ECG recordings which will take about 3-4 hours.
Description of Intervention:	Gastroparesis Subjects: The device being studied, the Transcutaneous Electrical Acustimulation (TEA) will give stimulation similar to transcutaneous electrical nerve stimulation (TENS) at two specific acupuncture points (ST-36 and PC6) with stimulation parameters known to improve gastrointestinal motility. The study team would like to access if wearable TEA is safe for study participants and will impact the GI symptoms and gastric motility in study participants with gastroparesis. Healthy Controls: There is no intervention.
Estimated Time to Complete Enrollment:	12 Months

Schematic of Study Design: See appendix A for the schedule of events table.

Table 1: Arm of the study

Two-arm, parallel, double-blinded	Sample size: 60 diabetic gastroparesis participants	Intervention: Transcutaneous Electrical Acustimulation (TEA)	Randomization: TEA or sham-TEA will be determined prior to the study by the collaborating statistician.
One arm, no blinding	Sample size: 40 healthy controls	No intervention	No randomization

1 KEY ROLES

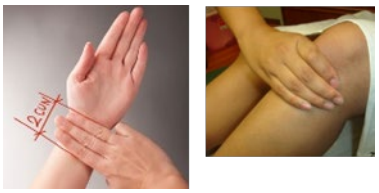
For questions regarding this protocol, contact Borko Nojkov. at 734-846-6747

Individuals:	**Principal Investigator:** Borko Nojkov, MD, responsible for conducting the study. **Emergency Contact:** Borko Nojkov M.D. will be responsible for evaluation and connecting the study participant to treatment options. **Co-Investigators:** Jiande Chen will help the PI in recruiting study participants and clinical research study design as well as data analysis and interpretation. **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**: Borko Nojkov, MD 734-846-6747 bnojkov@med.umich.edu

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

- In this project, **we will use a novel wearable transcutaneous electrical acustimulation (TEA) device for treatment of GI symptoms such as nausea, early satiety, postprandial fullness, upper abdominal pain and vomiting in study participants with diabetic gastroparesis.** This is a device that has stimulating electrodes. The electrodes are placed on acupuncture points that are known to improve gastric motility in functional GI disorders.
- The process of preforming needleless acupuncture via electrical stimulation in place of traditional acupuncture methods is called **transcutaneous electrical acustimulation or TEA**. Two acupuncture points, previously known to improve autonomic functions in both basic and clinical studies, are points ST36 and PC6.
- In the human, **PC6 is three finger widths above the wrist**. In the human, **ST36 is four finger widths below the knee cap**.
- The motivation behind this study is to access the impact of TEA on GI symptoms and gastric motility in study participants with gastroparesis. If successful, the proposed wearable TEA could serve as innovative and non-invasive treatment option for gastroparesis.



Left: image of acupuncture point PC6. Right: image of acupuncture point ST36.

- The gastric emptying breath test (**GEBT**) is a noninvasive FDA-approved method for assessing gastric emptying. GEBT $T_{1/2}$ is a continuous measurement representing the calculated time to empty from the stomach into the small intestine half of a ^{13}C-labeled, 230kcal test meal (27g of rehydrated, pasteurized scrambled egg mix containing a dose of 43mg of ^{13}C [provided by approximately 100mg of 13C-Spiruina], 6 saltine crackers, 180mL water, and consisting of 29.9% kcal as carbohydrates, 25.5% as protein, and 44.6% as fat). The breath samples will be collected at baseline, 45, 90, 120, 150, 180 and 240 minutes after the test meal, and then shipped to Cairn Diagnostics for analysis.
- **3-in-1 gastric functional test:** A 3-in-1 noninvasive method will be used to assess three major pathophysiologies of gastroparesis, including gastric accommodation, visceral sensitivity and gastric slow waves. The method is a combination of the electrogastrogram (EGG, for noninvasively assessing gastric slow waves), electrocardiogram (for assessing autonomic function) and a modified water drink test for gastric accommodation. During the visit, the 4-channel electrogastrogram (EGG) and an one-channel electrocardiogram (ECG) will be recorded for 30 minutes, then a water drink test will be performed during which the patient will be asked to drink as much water as they can in 5 minutes, or until reaching the maximum tolerable volume (MTV), after that, another 30 min EGG and ECG recording will be performed during the postprandial period. The postprandial symptoms of dyspepsia will be assessed at 10 , 20 and 30 min after completing the drink test with the patient scoring symptoms of bloating, fullness, nausea and pain using a visual analogue scale (VAS) with 100 mm lines and the words “unnoticeable” (0 mm) and “unbearable” (100mm) at each end.

2.2 Rationale

- The aim of the study is to study the effects of wearable TEA stimulation on GI symptoms and gastric motility and possible mechanisms on autonomic functions in patients with gastroparesis

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

- Electrode pad placement on the skin: there is a possibility of allergic immune response to the electrode pad. The likelihood of this risk is low, approximate incidence of <1%.

- Current flow through the skin during TEA therapy: during TEA therapy application, there is a possibility of uncomfortable sensation or pain at the skin, abnormal or involuntary movements (chorea, dystonia, dyskinesia), gastrointestinal disturbances or nausea. 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 likelihood of this risk is low, approximate incidence of <1%.

- Gastric emptying breath test: A natural, stable isotope carbon-13 will be used to collect gastric emptying data; it is noninvasive and does not impose any risk.

- Water drink test for assessing gastric accommodation is noninvasive; patients will drink as much water as they are able to over a 5 minute period or until they reach the maximum tolerable volume. Patient may have the feeling of fullness and nausea after the test, which usually goes away spontaneously.

- Electrogastrogram and electrocardiogram: Both electrogastrogram and electrocardiogram recordings are noninvasive via body surface electrodes. The skin where the electrodes to be placed will be well cleaned that may result in redness, which should go away quickly. The likelihood of this risk is low, approximate incidence of <1%.

- Privacy and confidentiality: risk of compromised confidentiality is associated with analysis and sharing of medical data. The likelihood of this risk is low, approximate incidence of <1%.

Hypoglycemia. Subjects will be asked to fast before each study visit which may lead to hypoglycemia in diabetic subjects. Symptoms of hypoglycemia may present as excess sweating, excessive hunger, fainting, fatigue, lightheadedness, anxiety, blurred vision, headache, irritability, pallor, palpitations, sensation of pins and needles, sleepiness, slurred speech, tremor, or unsteadiness. To reduce the likelihood of developing low blood sugar, we will discuss the possibility of adjusting blood-sugar lowering medications before the fast associated with the in-person study visits. Subjects will also be given an information sheet that describes preprocedure management.

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 wearable TEA for gastroparesis participants.

2.3.2 Known Potential Benefits

A potential benefit for study participants is the improvement of their dyspeptic symptoms. There are no potential benefits to healthy control subjects

3 Objectives

3.1 Study Objectives

The objectives of this study are as follows:

- To study the effects of wearable TEA at ST36 and PC6 on symptoms and pathophysiologies of gastroparesis.
- To study the possible mechanisms involving autonomic functions in patients with gastroparesis.
- To compare the gastric accommodation, visceral sensitivity and gastric slow waves of healthy control subjects to subjects with diabetic gastroparesis

3.2.1 Primary Outcome Measures

The primary outcome will be The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptoms Index-Daily Diary (ANMS GCSI-DD), consisting a 24-hours recall period and five symptoms related to delayed emptying from the stomach: nausea, early satiety, postprandial fullness, upper abdominal pain, and vomiting.

3.2.2 Secondary Outcome Measures

The secondary outcome will be gastric emptying, quality of life and gastric accommodation. The exploratory endpoints will be gastric slow waves and possible mechanisms related to autonomic functions.

4 Study Design

Diabetic gastroparesis subjects: This is a randomized, double-blinded, sham-controlled, parallel-group study design.

The study will recruit 60 study participants with diabetic gastroparesis. These study participants will be recruited from the UM Health Research Recruiting Registry (UM HealthResearch.org), and the study team will screen the gastroenterology clinic schedules via MiChart.

This is a phase 1 trial. This study will only occur at the University of Michigan. There are two-arm study participants. The study team plans to complete enrollment within 12 months of beginning to the study. Study participant participation will have a 2-week phase-in period, an 8-week TEA/sham-TEA treatment, and a 4-week open label follow-up period.

We are not using cross-over design due to concern for a carry-over effect from the TEA therapy. Since this is a parallel design (not cross-over) we are having the second TEA treatment period to

provide potential therapeutic benefits for patients who were in the sham-TEA group (this data will not be used scientifically but is for potential patient benefit).

The test agent is the novel TEA device.

Healthy Control Subjects: This is a single arm, non-randomized study with no treatment component. The study will recruit 40 healthy control subjects. These study participants will be recruited from the UM Health Research Recruiting Registry (UM HealthResearch.org), These subjects will participate in a single visit where they will undergo a 3-in-1 gastric functional test.

4.1 Schedule of Events for Each Visit

Diabetic Gastroparesis Subjects: There will be two visits after the enrollment. The visits are 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 treatment options; a sealed envelope with assigned treatment (TEA or sham-TEA) group will be given to the participant, and opened by the study team member after the participant signs the consent form.

12:00 am on the night before the visit: The study participants begin fasting for their visit the next day, no solid food for 8 hours. The participant may allow to drink 120ml plain, unflavored water up to 1 hour before the test.

Day 1 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.

GEBT: The participant should sit quietly, completed the required information in to GEBT Requisition Form. Two pre-meal breath samples will be collected by the study team member before the GEBT meal. The meal must be consumed within 10min and record time on GEBT Requisition Form. Post-meal breath samples will be collected **45, 90, 120, 150, 180** and **240** minutes from time of completion of the meal. The patient can sit in the waiting room during the 4 hour period after the meal.

Questionnaires: Will be completed during GEBT between two breath samples collection.

At the completion, the patient can go home or stay at a nearby hotel and can have regular foods and drinks.

12:00 am on the night before the visit: The study participants begin fasting for their visit the next day, no solid food for 8 hours. The participant may 120ml plain, unflavored water up to 1 hour before the test.

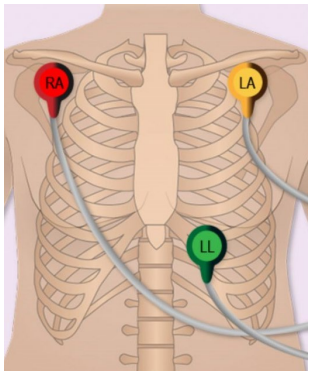


Fig.1: Locations of electrodes for the ECG recording.

Day 2 of the Visit:

In the morning, the participants are required to come to the same lab. The **3-in-1 gastric functional test** (water drink test, ECG and EGG, as described in Background Information) will be performed. The detailed methods of the ECG and EGG are described as follows:

The ECG recording: Three ECG electrodes will be placed on the study participant's skin as shown in Figure 1 and connected to an ECG device. The skin area where the electrodes to be placed will be carefully cleaned using skin-prep materials.

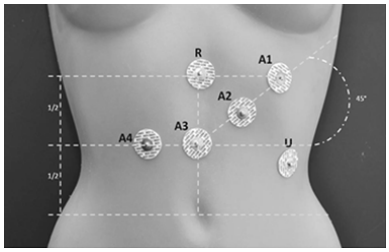


Fig.2: Locations of electrodes for the EGG recording.

The EGG recording: Six ECG electrodes connected to the EGG machine will be placed on the study participant's abdominal skin: a reference electrode (R) will be located at the xiphoid process, a grounding electrode (U) is at the lower edge of the left rib arch; electrode A3 is at the midpoint of the xiphoid and the umbilicus, A4 is at 4-6 cm on the right to the horizontal right of A3; A2 is at 5cm to the upper-left of A3, and A1 is at 5cm to the upper-left of A2. The skin area where the electrodes to be placed will be carefully cleaned using skin-prep materials and conductive gel will be applied to reduce skin-electrode impedance.

As described in the Background Information, the participant will be firstly recorded both EGG and ECG for 30 minutes in the fasting state, then the water drink test will be performed by the study team member. After that, EGG and ECG will be recorded for another 30 minutes, the postprandial dyspeptic symptoms of bloating, fullness, nausea and pain will be assessed at 10, 20, and 30min during the recording.

Training on the use of TEA device: At the completion of the above test, the study participant will be trained to find the location of stimulation and the operation of the TEA device.

Placement of the TEA device: The study team member will show the participant how to place the patch TEA electrodes (sticky and bottom part of the TEA device) on the subject's skin, at ST36 (one side of the body) and PC6 (one other side of the body) for the TEA group or on the sham points S1 and S2 for the sham-TEA group (Figure 3). These electrodes will be used for delivering weak electrical current stimulation via the stimulators snapped on them. Picture will be taken using a smartphone (to be provided to the participant on the placement of the devices so that the participant could use the pictures to localize the right stimulation positions.

Fig.4: Patch-like TEA device. Left: the size of the device in comparison with a quarter; right: storage of the device.

Operation of the TEA Device: After the device placement, electrical stimulation will be performed for a period of a few minutes (5-10 min) so that the patient can feel and learn how to operate the device. The stimulation parameter on the leg will be 25Hz, 0.5ms, 2s-on, 3s-off and current amplitude based on the maximal tolerance of the subject. On the wrist, the 100Hz will be used. The stimulation duration will be 45min. These parameters will be set by the study team member and the patient is only able to adjust the stimulation strength within a safe range. The TEA device is of a weight of 11g and operated by a 3.7v battery (see Fig.4). The participant will also be taught how to store and charge the device when it is not in use. The storage box can also be used as a charging unit.

Training on the use of the app installed on a smartphone: in addition to the TEA device, the participant will also be provided with a smartphone. A special app is installed in the smartphone to record daily symptoms and the usage of the TEA device. The participant will be trained to use the app and input daily symptoms on the smartphone. To avoid any potential leakage of patient information, the remote access function will be disabled. We will plan to call subjects once per week phone call to participants to remind them/assure they are entering data in their apps. Our smartphone app will alert patients to complete any forms that are needed for any specific day. If any items are missing for that day, the app will alert the patient to complete them.

During the 8-week period between visit 1 and visit 2, as well as after visit 2 and until week 12, subjects will be called once per week to ensure the surveys are being completed. During this phone call, the study coordinator will also ask if the subjects are experiencing any symptoms or if any adverse events have occurred.

After visit 2, patients will return home to complete another four weeks of the same surveys that were completed during the first 8 weeks. Those randomized to sham stimulation for the first 8 weeks will be offered treatment at the test (treatment) points for the last 4 weeks. At visit 2, subjects will be given a pre-labeled shipping container to mail the devices (stimulators and smartphones) back to the study team.

Healthy Control Subjects: These subjects will be consented before any study activity occurs (prior to fasting as described below). On the day of the visit, subjects will undergo a single visit which will entail a questionnaire and a 3-in-1 gastric functional test.

12:00 am on the night before the visit: The study participants begin fasting for their visit the next day, no solid food for 8 hours. The participant may allow to drink 120ml plain, unflavored water up to 1 hour before the test.

Visit timeline:

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.

The **3-in-1 gastric functional test** (water drink test, ECG and EGG, as described in Background Information) will be performed. The detailed methods of the ECG and EGG are described as follows:

The ECG recording: Three ECG electrodes will be placed on the study participant's skin as shown in Figure 1 and connected to an ECG device. The skin area where the electrodes to be placed will be carefully cleaned using skin-prep materials.

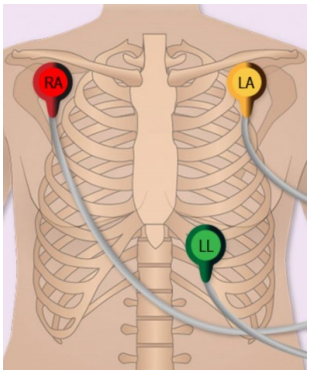


Fig.1: Locations of electrodes for the ECG recording.

The EGG recording: Six ECG electrodes connected to the EGG machine will be placed on the study participant's abdominal skin: a reference electrode (R) will be located at the xiphoid process, a grounding electrode (U) is at the lower edge of the left rib arch; electrode A3 is at the midpoint of the xiphoid and the umbilicus, A4 is at 4-6 cm on the right to the horizontal right of A3; A2 is at 5cm to the upper-left of A3, and A1 is at 5cm to the upper-left of A2. The skin area where the electrodes to be placed will be carefully cleaned using skin-prep materials and conductive gel will be applied to reduce skin-electrode impedance.

As described in the Background Information, the participant will be firstly recorded both EGG and ECG for 30 minutes in the fasting state, then the water drink test will be performed by the study team member. After that, EGG and ECG will be recorded for another 30 minutes, the postprandial dyspeptic symptoms of bloating, fullness, nausea and pain will be assessed at 10, 20, and 30min during the recording. The study team will ask the subject to rate each symptom and will record the answers on a paper form.

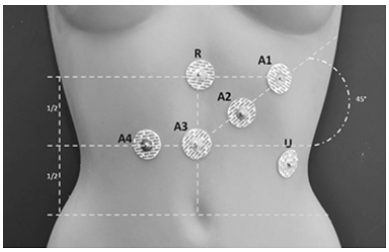


Fig.2: Locations of electrodes for the EGG recording.

Upon completion of the second recording period, the study will be completed and the healthy control subject will be free to leave the study center.

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:

Diabetic Gastroparesis Subject Inclusion Criteria:

- Male or female, aged 18 to 80 years
- At least a 3-month history of diabetic gastroparesis symptoms on an on-going basis; at least one severe gastroparetic symptom or two moderate gastroparetic symptoms (e.g. vomiting, nausea, early

satiety, bloating, or epigastric or abdominal pain) during the screening. A minimal Gastroparesis Cardinal Symptom Index (GCSI) score of 2.2.

- Documented delayed gastric emptying.
- Stable concomitant medications, defined as no changes in regimen for at least 2 weeks prior to the experiment (daily adjustments of insulin doses are permitted if patient has diabetes)
- Able to provide written informed consent prior to any study procedures and willing and able to comply with study procedures;

Healthy Control Eligibility Criteria

- Male or female, age 18-75 without gastrointestinal symptoms or history of gastrointestinal disease
- Willing to comply with all study procedures and be available for the duration of the visit

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:

Diabetic Gastroparesis Subject Exclusion Criteria:

- Currently receiving parenteral feeding or presence of a nasogastric or other enteral tube
- History of gastric surgery such as fundoplication, gastrectomy, or vagotomy
- Symptoms suggestive of gastroparesis with no diagnosis of diabetes
- Pregnancy or expect to conceive during the course of the study
- Any other conditions, which in the opinion of the investigator would impede compliance or hinder the completion of the study
- Uncontrolled diabetes mellitus (HbA1c > 11%).
- Failure to give informed consent
- With any implanted medical device, such as cardiac pacemaker or Entera device

Healthy Control Exclusion Criteria:

- 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: Dr. Nojkov and physician colleagues seeing study participants at Michigan Medicine Clinics 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 by the treatment benefit from this study.

5.4 Treatment Assignment Procedures

5.4.1 Randomization Procedures

Prior to the first visit, either TEA treatment or sham-TEA treatment will be randomly assigned to each study participant with diabetic gastroparesis. Healthy control subjects will not undergo any randomization

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 wearable TEA device (see Fig.4) is of a weight of 11 g and a dimension of 50x28x11mm. it is operated by a Li-ion 3.7V rechargeable battery. The maximal output is 10mA (well within the safety limit). It is similar to a TENS (transcutaneous electrical nerve stimulation) unit that is classified by FDA as a non-significant risk device. The maximum current output of a TENS device is 80mA, whereas our device is designed to have a maxium output of 10mA – more information can be found in the following link: *http://www.electrotherapy.org/modality/transcutaneous-electrical-nerve-stimulation-tens*. The TEA device is wireless: the stimulator is snapped on the top of the electrodes (ECG-like electrodes). The energy delivery is calculated as follows: E = current x voltage x frequency x pulse width = 0.005 (A) x 5 (V) x 25 /s x 0.0005s = 0.0003125 (w) = 0.3mw

The TEA device can be connected to a smartphone with the functions of programing and reporting symptoms. The smartphone will be given to each study participant and collected at the end of the 8-week treatment. For data safety, the smartphone and the app are both password protected, and the cellphone functions (wifi and cellular communications) are disabled.

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 interested 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

Diabetic Gastroparesis Subjects: will receive a total of $500 and an additional $200 if they use overnight housing and are greater than 70 miles from Ann Arbor. The payment will be issued at the completion of the first visit (30%), second visit (30%) and end of the follow-up period (returning of the TEA device and symptom forms) (40%). Subjects will not be paid for visits not completed. Local subjects will receive $150 after each study visit and $200 following the return of the TEA device. Subjects greater than 70 miles from Ann Arbor will receive $250 after each study visit and $200 following the return of the TEA Device. The compensation is set at such a value based on the duration of the study (8 weeks) and length of each visit (need to stay at the hotel for a night), and the sensitive nature of the study.

Healthy Control Subjects: will receive $75 for their participation. If not all study procedures are completed, subjects will receive $25

8 Study Procedures/Evaluations

8.1 Surveys

Diabetic gastroparesis study participants will complete several questionnaires during each visit: GCSI-DD for dyspeptic symptoms, Quality of Life questionnaire, Hospital Anxiety and Depression Scale and Visual Analog Scale Pain Score, and food dairy. In addition, the participant will need to complete the questionnaire from home through the smartphone from the TEA device system either daily or every 2 weeks or every 4 weeks depending on the form schedule.

Healthy control subjects will undergo one survey at the time of screening and at the visit which will assess their gastrointestinal symptoms over the previous two weeks.

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. Borko Nojkov. The PI is a PhD. And not an MD. As an MD, Dr. Borko Nojkov will serve as the emergency contact person for the study.
- 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. Borko Nojkov. 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 semi-annually 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

We will first review data for completeness and consistency, and examine missing data due to non-response for non-randomness; imputation of missing data will be explored for sensitivity analyses as appropriate. We will use general descriptive analyses for all variables. Means and standard deviations and distributions will be examined, and t-tests will be used to assess differences between the TEA and sham-TEA groups. We will test all continuous variables for normality and transformed as needed. For examination of categorical variables, we will use contingency table arrays and the $\chi 2$ statistic and nonparametric statistics to assess group differences.

10.1 Study Hypotheses

Wearable TEA at acupoints ST36 (a point below the knee cap) or PC6 (a point in the wrist) will be effective in improving dyspeptic symptoms in patients with gastroparesis. This hypothesis is based on published literature and Co-investigator, Jiande Chen's experience with EA and TEA during his previous research, which have been shown that electrical acupuncture at ST36/PC6 improves impaired gastric emptying, gastric accommodation and gastric slow waves. Dr. Chen's previous research also indicated that the improvement may be attributed to the enhancement of vagal activity.

10.2 Sample Size Considerations

The study team plans for a 20% participant dropout or incompletion rate. For this reason, they will enroll 60 study participants when in actuality they need 50 study participants to complete the study. If 50 study participants complete the study and there are still 10 active participants, the active participants will still complete the study.

The patient number per group is estimated by the power analysis based on the preliminary study in 18 patients, where the fullness score before and after 4-week TEA treatment were 4.2 and 3.2 (correspondingly) with the standard deviation of 1.0. Based on a desired power of 0.8 and a desired alpha value of 0.05, the sample size per group was calculated as n = 25, using the sample size calculator at www.stat.ubc.ca/~rollin/stats/ssize/n2.html. Conservatively accounting for a possible 20% attrition, the adjusted patient number per group is n = 30.

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 6 months during the study enrollment/study visit period. If needed, the DSMB will meet more frequently to monitor the study.

This is a chronic study involving 2 visits with 8-week duration in between two visits. In addition to the two visits, the participant will perform either TEA or sham-TEA treatment at home with the TEA device twice daily for 8 weeks, 45 minutes each time. After the 8-week treatment, the participant in the sham-TEA group will be offered for 4-week TEA treatment. During the 8-week treatment period, the participant can report the symptoms or any adverse event through the provided smartphone app.

The risks involved in the study include delivery of weak electrical current via skin surface electrodes. The study will be terminated if the patient is not tolerable to the procedure or decides to withdraw. The study enrollment will be halted if serious adverse events are reported.

Safety outcome measures will include any side effects due to weak electrical stimulation, such as rash or discomfort in the area of stimulation.

10.2.2 Efficacy Review

The efficacy of TEA on symptoms of dyspepsia, the quality of life and gastric motility measurements including gastric emptying, gastric accommodation and gastric slow waves will be assessed.

The autonomic mechanisms recorded by ECG will also be reviewed.

10.3 Final Analysis Plan

We will first review data for completeness and consistency, and examine missing data due to non-response for non-randomness; imputation of missing data will be explored for sensitivity analyses as appropriate. We will use general descriptive analyses for all variables. Means and standard deviations and distributions will be examined, and t-tests will be used to assess differences between the TEA and sham-TEA groups. We will test all continuous variables for normality and transformed as needed. For examination of categorical variables, we will use contingency table arrays and the $\chi 2$ statistic and nonparametric statistics to assess group differences.

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. The TEA Device is not intended for use as an implant, it will not be used to sustain human life, it will not be used as a diagnostic or curative device, rather, it will be in an attempt to alleviate pain associated with dysmotility. Failure of the device will not result in injury to the subject. The device has a max output lower than a TENS unit. More information can be found in section 6.1.

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.

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 diabetic gastroparesis.

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 ECG and EGG measurements will be saved as part of the research file by the study team member at the end of each visit.

14.2 Types of Data

Data for this study will include safety, gastric emptying assessment, gastric accommodation assessment, gastric slow wave recording, ECG recording, 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 two visits and assessments.

Assessment	**V1**	**V2**	**F1**
	Week 0	**Week 8**	**Week 12**
Informed Consent	X		
Pregnancy test (if participant is a woman with child bearing potential. If the woman is not on a birth control method)	X	X	
Inclusion/Exclusion Criteria	X		
Medical History	X		
Vital Signs	X	X	
GCSI-DD	X	X	X
SF-36 (QoL)	X	X	X
HADS	X	X	X
GEBT	X	X	
Gastric Accommodation	X	X	
Abdominal Pain	X	X	
EGG	X	X	
ECG	X	X	
Adverse Events	X	X	X