Transcutaneous Electrical Acustimulation (TEA) as a Treatment Modality for Symptoms of Distention/Bloating in Participants with Systemic Sclerosis

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Transcutaneous Electrical Acustimulation (TEA) as a Treatment Modality for Symptoms of Distention/Bloating in Participants with Systemic Sclerosis

Principal Investigator:
Dinesh Khanna MD, MSc
Department of Internal Medicine
Division of Rheumatology
University of Michigan
khannad@med.umich.edu

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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)
- 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.

Protocol Summary

Title:	Transcutaneous Electrical Acustimulation (TEA) as a Treatment Modality for Symptoms of Distention/Bloating in Participants with Systemic Sclerosis (SSc) A Pilot Open Label Feasibility Study
Synopsis:	The aim of this study is to investigate the feasibility of TEA in alleviating symptoms and improving gastric motility in participants with SSc. In this project, we will investigate the impact of active treatment with TEA on the distension/bloating in participants with SSc. This is a pilot open label study in which all participants will be screened using the UCLA SCTC GIT 2.0 Questionnaire to assess participants with symptoms of distension/bloating. After enrollment, all participants will complete a gastric emptying study for both solids and liquids, unless completed in the last 6 months. All study participants with symptoms will undergo TEA treatment for 4 weeks, regardless of gastric emptying study results. Participants with an abnormal baseline gastric emptying study will repeat gastric emptying study at the end of the trial to observe any changes. The treatment will be home-based and last for a period of 4 weeks. After the enrollment, each eligible study participant will come to the clinic at Michigan Medicine and undergo the following procedures: 1) Completion of the UCLA SCTC GIT 2.0 Questionnaire ; 2) Gastric Emptying Study (unless it was done in the last 6 months before the screening visit) 3) Blood draw for biomarkers; 4) Training on how to use the TEA device system (the electrodes, stimulator, charger), including adjusting the amplitude; and 5) The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptoms Index-Daily Diary (ANMS GCSI-DD). Then will return to the clinic after the 4-week treatment and the same procedures except the training on the use of the TEA device performed at baseline will be repeated for evaluating treatment effects. Only participants with an abnormal baseline gastric emptying study will repeat study to observe any changes. Participants will also be called by the study team weekly to assure compliance with assigned therapies and assess for potential side effects and plan to have a week 2 telephone visit with study physicians. Since home-based treatment will be required, the participant will be trained to locate the acupuncture point— ST36. During the first visit, the study team member will mark the ST36 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. A similar protocol has been approved by UM IRB HUM00217301.
Objectives:	Primary: to evaluate the acceptability of transcutaneous electrical acustimulation (TEA) as an intervention for alleviating

	symptoms of distension and bloating in individuals diagnosed with SSc. Secondary: 1) to investigate the efficacy of TEA in alleviating the symptoms of distention/ bloating in SSc using the GCSI. 2) To assess the effect of TEA on the gastric motility in participants with scleroderma-related gastroparesis. 3) To assess the effect of TEA on distention/ bloating on the GIT 2.0.distention scale 4) To evaluate the safety and tolerability of TEA in participants with scleroderma-related GI symptoms.
Population:	Up to 16 study participants, male and females, age ≥18 years.
Phase:	Pilot Open Label Feasibility Study
Number of Sites:	1, Michigan Medicine, University of Michigan
Study Duration:	14 months
Study Participant Participation Duration:	After signing an IRB approved consent form. Study participants will complete a two-week phase-in period during which they will complete daily online surveys to assess baseline ANMS GCSI-DD scale. After the phase-in period they will come in for visit 1. Each visit will be on a single day, lasting about 2-3 hours and up to 7 hours for those who need the gastric emptying study. During visit 1, participants will complete questionnaires, blood draw and TEA device administration training. Participants will receive weekly calls by study coordinator and a telephone/ Zoom follow visit with study physician at 24. These visits will assess the compliance with the TEA and assess for any adverse events. Visit 2 (week 4): completion of questionnaires, evaluation for potential side-effects, and return of the device. There will be 2 in person visits; the interval between the in person visit 1 and visit 2 is approximately 4 weeks. Participants that are of childbearing age will be asked to do a pregnancy test during visit 1 prior to gastric emptying study. If the test is positive, they be withdrawn from the study and not undergo the procedures. If participant is of childbearing potential, the study team will recommend the use of some form of contraception during the study.
Description of Intervention:	Transcutaneous Electrical Acustimulation (TEA) at one specific acupuncture points (ST-36) with stimulation parameters known to improve gastrointestinal motility.
Estimated Time to Complete Enrollment:	12 months

Background

Systemic sclerosis (SSc) is a systemic autoimmune disease that affects multiple organs and is associated with significant morbidity and mortality. The disease is characterized by endothelial dysfunction, vasculopathy, dysregulated immunity and subsequent end organ damage and fibrosis. Nearly all participants with SSc are negatively affected by dysfunction in the gastrointestinal tract, and the severity of gastrointestinal disease in SSc correlates with high mortality. The clinical complications of this dysfunction are heterogeneous and include gastro-esophageal reflux disease, gastroparesis, small intestinal bacterial overgrowth, intestinal pseudo-obstruction, malabsorption and the requirement for total parenteral nutrition. The abnormal gastrointestinal physiology that promotes the clinical manifestations of SSc gastrointestinal disease throughout the gastrointestinal tract are diverse and present a range of therapeutic targets. (1)

Distention/ bloating is common in SSc and can be multifactorial. Common causes including gastroparesis and small intestinal bacterial overgrowth syndrome (SIBO). Gastroparesis is defined as delayed gastric emptying in the absence of mechanical obstruction. Gastroparesis can be debilitating and may be caused due to SSc or medications. A mainstay of treatment includes lifestyle changes, antiemetics, prokinetic agents, and in rare instances, invasive surgical options. Patients present with nausea, vomiting, early satiety, fullness and abdominal pain or discomfort. SIBO is characterized by an increase in the number and/or an abnormal type of bacteria in the small intestine. Symptoms associated with SIBO include diarrhea, abdominal pain, flatulence, abdominal distension and malabsorption of nutrients. In gastroparesis, although gastric prokinetic drugs are considered first-line therapy, their use is limited by either adverse effects or tachyphylaxis. (1)

Non-pharmacological approaches such as Implantable and transcutaneous neuromodulation methods have been applied to treat various gastrointestinal motility disorders. An example of implantable neuromodulation methods is gastric electrical stimulation. It has been applied for treating nausea and vomiting in gastroparesis. Because these methods are invasive and involve the use of an implantable pulse generator, they have not been applied in SSc. Non-invasive transcutaneous neuromodulation methods have been applied to treat gastrointestinal motility disorders, including transcutaneous auricular vagal nerve stimulation, transcutaneous cervical vagal nerve stimulation, transcutaneous electrical acustimulation (TEA) and transcutaneous electrical nerve stimulation (TENS). TEA applied at acupuncture points ST36 (leg) and PC6 (wrist) to treat gastric complications in patients with SSc was reported to improve gastric slow-wave rhythmicity and coupling by enhancing vagal efferent activity with concurrent suppression of vasoactive intestinal peptide and the pro-inflammatory cytokine IL-6. Such a method has also been noted to improve constipation in a few with SSc. TEA has been reported to improve gastro-esophageal reflux and constipation; it remains to be investigated whether TEA is also effective in treating gastrointestinal complications of SSc. (1)

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive peripheral stimulation technique commonly used to treat chronic pain. TENS is usually applied to nerve dermatomes or areas of muscle pain. Similarly to TEA, TENS may also be applied to acupoints. However, TENS stimulates a larger area than TEA, and the pulse width is commonly less than 0.3 ms. It has become of particular interest in treating functional GI disorders and has been shown to improve GI motility. Electrodes are placed in the affected area, and the purpose is to activate large-diameter non-noxious afferents to reduce nociceptive cell activity and sensitization. It is believed that TES such as TEA, and TENS works by modulating the Autonomic nervous syndrome. The vagus nerve and sacral plexus are part of the Parasympathetic nervous system and play a significant role in regulating interactions between the central nervous system and the GI tract, including functions of the esophagus, stomach, small bowel, and colon. It regulates motility, sensation, and secretion and maintains the

intestinal barrier. Vasodilators have been used to treat GI disorders by enhancing smooth muscle relaxation. It is hypothesized that TENS may cause an increase in blood flow and allows for the release of neuropeptides. Zhang et al found that TENS increases local blood flow in the treated area in their animal study, which contributes to its mechanism of action. TENS studies have found increased activity by neurochemicals, including acetylcholine, noradrenaline, gamma aminobutyric acid, serotonin, nitric oxide, and opioid receptors. Additionally, studies suggest a decrease in the activity of plasma vasoactive inhibitory peptide and interleukin 6. (2)

Two validated comprehensive patient-reported outcome measures have been developed to capture the symptoms and severity of gastrointestinal involvement in patients with SSc. For the purpose of this study, we will utilize the UCLA Scleroderma Clinical Trials Consortium Gastrointestinal Tract Instrument 2.0 (UCLA GIT 2.0) to assess GI involvement. The GIT 2.0 includes 34 items that capture seven scales in SSc. It assesses reflux, distention and/or bloating, diarrhea, constipation and fecal soilage, and the effect of these symptoms on social and emotional well-being. The patient-reported outcome is utilized by clinicians as part of clinical care and can facilitate the addition or up titration of medications and/or further diagnostic work-up. The total UCLA GIT 2.0 score is the average of six of the seven scales (excluding constipation), and is scored from 0.0 (better health-related quality of life) to 2.8 (worse health-related quality of life). The instrument is sensitive to change and has been translated into different languages. The instrument is available online at http://bit.ly/UCLASCTCGIT. (3)

Another clinical outcome measure is The ANMS GCSI—DD, which was developed to meet FDA recommendations for use as a Patient Reported Outcome endpoint for therapeutic trials in gastroparesis. The ANMS GCSI-DD version used in the study reported herein is paper-based, uses a 24-h recall period, and consists of five symptoms: nausea, early satiety, post-prandial fullness, upper abdominal pain, and vomiting. Nausea, early satiety, post-prandial fullness, and upper abdominal pain are rated using a 5-point verbal rating scale, and the number of vomiting episodes over the last 24 h is recorded by the patient. (4)

Given these findings, the central hypothesis of this proposal is that utilization of TEA will improve symptoms of distention/ bloating, including due to gastroparesis in participants with SSc. The objective of this study is to investigate the efficacy of TEA in alleviating symptoms and improving gastric motility in participants with scleroderma-related symptoms. The rationale for this proposal is that our work will expand treatment modalities for SSc-related GI manifestations.

Study Intervention/Investigational Device:

Study device that will be used is of a size of 76 × 44 × 31 mm in thickness, width and length (see Figure 1). As shown on Figure 1, the front of Patch-TEA device has the buttons for setting the device operations. A magnetic snap connector is located on the back of Patch-TEA device. The Patch-TEA device can be connected to the charging case and to the electrode pad.



Figure 1: Patch-TEA device

Patch-TEA device is powered using an internal rechargeable lithium polymer battery. As shown on table below, once the device is turned on, the operating mode is indicated by the LED

color. When the battery is fully charged and is in standby mode, the LED color is green; when it is in in stimulation mode, the LED color is white. The LED is flashing, when the Bluetooth is not connected and turns solid, when the Bluetooth connection with the smartphone is established. The stimulation treatment can be provided for up to 4 hours under normal operating conditions. When the device battery is discharged, the LED color changes to a flashing orange.

When Patch-TEA device is not in use, it is recommended to store it in the charging case (Figure 2). Since the charging case contains an internal battery, it can charge the stimulator, when charging is required. There is an LED on the front of the charging case. When the cover of the charging case is opened, the LED indicates the charging case status. When the charging case battery is fully charged and is ready for charging the Patch-TEA device, the LED is a solid blue. When the charging case battery is low, the Patch-TEA device cannot be charged, and the LED is a flashing yellow.



Figure 2: Inside view of the charging case with USB charging cable

To charge the charging case battery, connect it to the USB power adapter through the USB charging cable, as shown on Figure 3. Make sure to use the USB power adapter that is approved for use in the US (120 V, 60 Hz) and supports the required current/power (1A/5W). When the charging case is charging, the LED is solid yellow; and when the battery is fully charged, the LED turns solid blue.

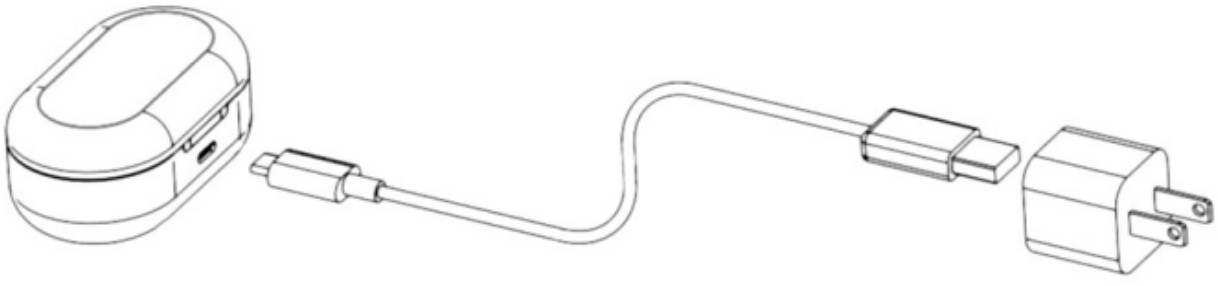


Figure 3: Charging case with USB charging cable and USB power adapter.

As shown on Figure 4, the Patch-TEA device is inserted inside the electrode pad until it snaps in the electrode pad's buckle. After removing the protective film for the bottom surface, place the electrode pad firmly on the skin. Please, make sure the skin is clean and dry before applying the electrode pad and ensure the electrode pad is well-adhered to the skin. If the skin is oily or wet, please wipe it with a dry soft cloth. If necessary, it can be disinfected by gently wiping with a cotton round dipped in sterilized alcohol.

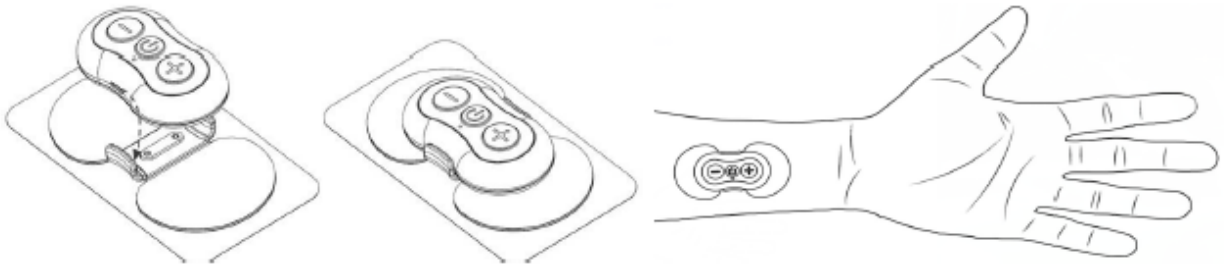


Figure 4: Electrode pad placement on the skin

As shown on Figure 5, the electrode pad is commonly placed on the following skin locations to achieve the best treatment results.

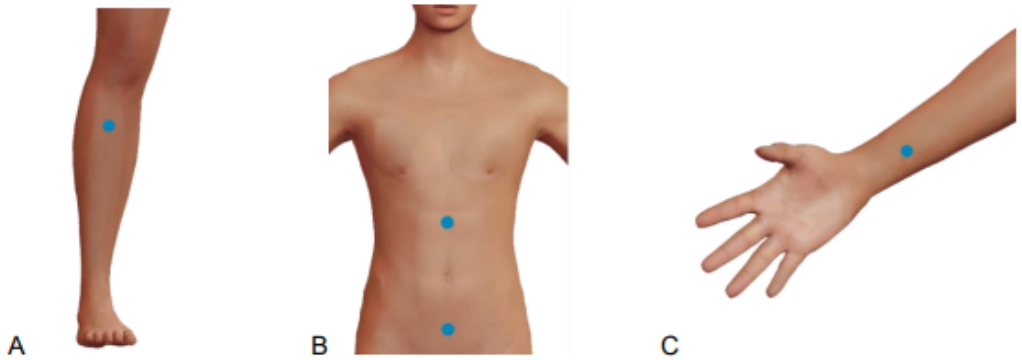


Figure 5: Skin locations for placement of the electrode pad: A) ST36 (Zusanli), B) CV4 (Guanyuan) and CV12 (Zhongwan), and C) PC6 (Neiguan)

The maximal output of the device 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 patient will be trained for the use of the device and a quick user guide will be provided to each patient.

Potential Risks and Benefits:

- ECG electrode placement on the skin: there is a possibility of allergic immune response to the ECG electrodes. The likelihood of this risk is low, approximate incidence of <1%. TEA will be delivered via the standard ECG electrodes.

- 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%.

- The risk of blood-drawing involves mild pain and a small risk of infection. Standard blood draw technique by experienced phlebotomists will be used to minimize these risks. The risk of infection likelihood is low, approximate incidence <1%.

- There is risk that surveys may elicit feelings of discomfort or cause emotional reactions.

- 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%.

The rationale behind these risks is that, overall, the risks are relatively 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 home-based TEA for participants with SSc.

Known Potential Benefits:
A potential benefit for study participants is the improvement of their distension/bloating.

Major Inclusion Criteria:

1. Classification of Systemic Sclerosis according to the 2013 American College of Rheumatology and European League against Rheumatism classification criteria.
2. Age > or = 18 years
3. English speaking.
4. Participants who report moderate to severe symptoms of distension/bloating on UCLA Scleroderma Clinical Trials Consortium Gastrointestinal Tract Instrument 2.0
5. Stable GI specific therapy including prokinetics over the last 4 weeks.

UM Scleroderma Program is directed by Dinesh Khanna (Faculty PI on this proposal). The program is a tertiary care center that manages over 1500-2000 participants on annual basis with 6-8 new consults per week. All new referrals are evaluated by one of the 4 rheumatologists with expertise in SSc (Drs Khanna, Varga, Zahn, or Mulcaire-Jones).

Major Exclusion Criteria:

1. Pregnancy, or currently lactating.
2. A history of major abdominal surgery (other than cholecystectomy, appendectomy, or deemed as non-major by the investigators)
3. Unrelated active disorder which may involve abdominal pain, such as inflammatory bowel disease, diabetes or unstable thyroid disease.
4. Known allergy to adhesive ECG electrodes.
5. Known contraindications to TEA (e.g., cardiac pacemaker, epilepsy)

Primary Objective:

Primary Objective: The primary objective of the proposed pilot clinical trial is to evaluate the acceptability of transcutaneous electrical acustimulation (TEA) as an intervention for alleviating symptoms of distension and bloating in individuals diagnosed with SSc.

Secondary Objectives:

1. To investigate the efficacy of TEA in alleviating the symptoms of distention/ bloating using the GCSI-DD.
2. To assess the effect of TEA on the gastric motility in participants with scleroderma-related gastroparesis.
3. To assess the effect of TEA on distention/ bloating on the GIT 2.0
4. To evaluate the safety and tolerability of TEA in participants with scleroderma-related GI symptoms.

Primary Endpoint

The assessment of the acceptability of TEA as measured by adherence to the treatment

regimen defined as use of the device equal or greater than 80% of the proposed applications as recorded on device.

Secondary Endpoints

1. Change in GCSI-DD scale scores from baseline at 4 weeks.
2. Change in UCLA SCTC GIT 2.0 individual symptom scores and overall score from baseline at 4 weeks.
3. The change in gastric emptying time assessed by gastric emptying scintigraphy at 4 weeks after TENS therapy compared to baseline (in those with baseline gastroparesis).
4. Adverse events related to the TEA intervention.

Study Assessments and Procedures

After enrollment, all participants will complete a gastric emptying study for both solids and liquids, unless completed in the last 6 months. All study participants with symptoms will undergo TEA treatment for 4 weeks, regardless of gastric emptying study results. Participants with an abnormal baseline gastric emptying study will repeat gastric emptying study at the end of the trial to observe any changes. Participants will be encouraged to maintain lifestyle habits e.g. diet/exercise throughout the duration of the study. The treatment will be home-based and last for a period of 4 weeks. Study participants will complete a two-week phase-in period during which they will complete daily surveys to assess baseline ANMS GCSI-DD scale. After the phase-in period they will come in for visit 1.

After the enrollment, each eligible study participant will come to the clinic at Michigan Medicine and undergo the following procedures: 1) Completion of the UCLA SCTC GIT 2.0 Questionnaire ; 2) Gastric Emptying Study (unless it was done in the last 6 months before the screening visit) 3) Blood draw for biomarkers; 4) Training on how to use the TEA device system (the electrodes, stimulator, charger), including adjusting the amplitude; and 5) The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptoms Index-Daily Diary (ANMS GCSI-DD). Then will return to the clinic after the 4-week treatment and the same procedures except the training on the use of the TEA device performed at baseline will be repeated for evaluating treatment effects. Only participants with an abnormal baseline gastric emptying study will repeat study to observe any changes.

Since home-based treatment will be required, the participant will be trained to locate the acupuncture point— ST36. During the first visit, the study team member will mark the ST36 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.

TEA administration will be recommended twice daily for 45 minutes after a major meal. This regimen is based on prior/ongoing clinical trials.

Each visit will be on a single day, lasting about 2-3 hours and up to 7 hours for those who need the gastric emptying study. During visit 1, participants will complete questionnaires, blood draw and TEA device administration training.

Participants will receive weekly calls by study coordinator and a telephone/Zoom follow visit with study physician at week 2. These visits will assess the compliance with the TEA and assess for any adverse events and confirm patient continues on their usual dietary habits.

Visit 2: completion of questionnaires, evaluation for potential side-effects. There will be 2 in person visits; the interval between the in person visit 1 and visit 2 is 4 weeks.
Participants that are of childbearing age will be asked to do a pregnancy test during visit 1 prior to gastric emptying study. If the test is positive, they will be withdrawn from the study and not undergo the procedures. If participant is of childbearing potential, the study team will recommend the use of some form of contraception during the study.

In addition to weekly follow up by study staff, adherence will also be assessed by

downloading data from the TEA device with primary endpoint being goal to meet equal to or greater than 80% applications in the 4-week period.

See **Fig.1** for detailed schematic. All participants will undergo the following:

1. UCLA SCTC GIT 2.0 Questionnaire to assess participants with symptoms of distension/bloating.
2. Gastroparesis Cardinal Symptom Index – Daily Diary (GCSI-DD)
3. Gastric emptying study for both solids and liquids (if not completed in the last 6 months before screening)
4. All participants with symptoms undergo TEA treatment 45 minutes twice daily after a major meal for 4 weeks regardless of gastric emptying study results.
5. Collect blood biomarkers at baseline and after TEA treatment.
6. Repeat gastric emptying study in participants with abnormal baseline gastric emptying study.

Schedule of Events

	Screening (+- 4 weeks)	**Week 0**	**Week 1-3**	**Week 4**	**Weeks 5-8 (Post treatment follow-up)**
Informed Consent	X				
Phase in period	X				
Eligibility (Inclusion/Exclusion) Assessment	X				
Demographics	X				
Medical History/ Chart Review	X	X		X	
UCLA SCTC GIT 2.0	X	X	X[a]	X	X[d]
PROMIS 29		X	X[a]	X	X[d]
Gastroparesis Cardinal Symptom Index – Daily Diary (GCSI-DD)	X	X	X	X	X
Gastric Emptying Study		X		X[b]	
Weekly Phone Calls by Study Team			X		
Call by Study Physician			X[c]		
Research Labs		X		X	
Pregnancy testɘ		X		X	
TEA		X	X	X	

[a] Completed at week 2
[b] If week one gastric emptying study is abnormal.
[c] Telephone visit by study physician at week 2 only.
[d] Completed weekly.

ɘ Pregnancy test is performed on Visit 1 before the TEA is applied (and gastric emptying test is performed, if needed), collected week 4 before gastric emptying study if repeat study is required

Study Overview

Screening
Eligible Patients

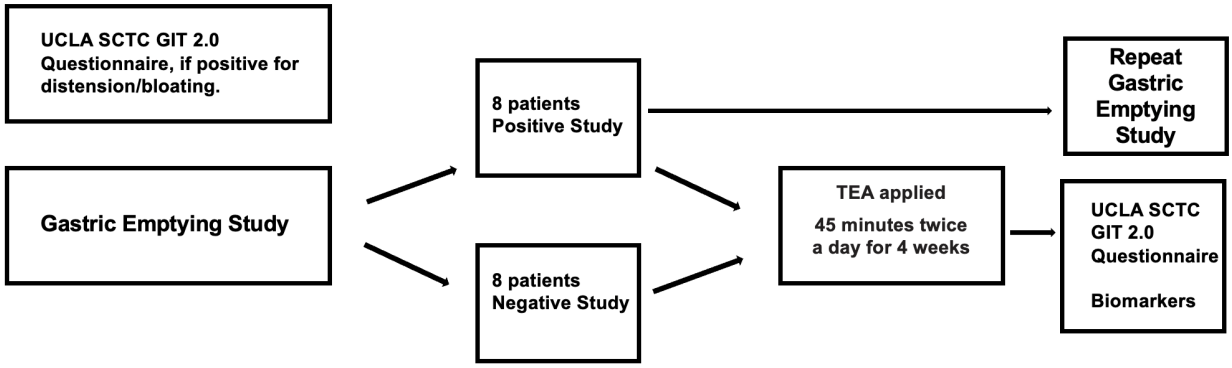


Fig.1

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