Protocol Title:

Transcutaneous Electrical Acustimulation (TEA) for the Treatment of Non-Erosive Gastroesophageal Reflux Disease (NERD): A Multicenter, Randomized, Sham-Controlled Trial

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Sponsor: Ningbo Medical Center Lihui Hospital

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Study Phase: N/A (Device/Non-Pharmacological Intervention)

IND/IDE Number (if applicable): Not applicable

1. Protocol Title

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2. Background

Disease Burden and Unmet Clinical Needs: Non-erosive reflux disease (NERD) is one of the most predominant subtypes of GERD, accounting for approximately 50–70% of patients with GERD. Although proton pump inhibitors (PPIs) are considered first-line therapy, both real-world and randomized controlled studies have shown that up to 40–50% of NERD patients have an inadequate response to PPIs [1]. The degree of symptom burden and quality of life impairment in NERD patients is comparable to that in patients with erosive GERD. However, there is a lack of effective non-pharmacological treatment options with long-term safety for this condition.

Mechanisms and Evidence Base of Transcutaneous Electrical Acustimulation (TEA) for GERD: Transcutaneous Electrical Acustimulation (TEA) is a non-invasive neuromodulation technique that activates peripheral sensory nerves via transcutaneous electrical stimulation and regulates gastrointestinal motility and esophageal function through vagal reflexes. Animal and clinical studies have demonstrated that: TEA can enhance vagal tone (supported by heart rate variability studies) [2]; TEA improves lower esophageal sphincter (LES) pressure and reduces the frequency of reflux events [3]; TEA significantly improves subjective symptoms of GERD and NERD, including heartburn, acid regurgitation, and epigastric discomfort [4]. A series of studies led by Professor Jiande Chen's team further showed that TEA ameliorates gastrointestinal motility disorders, epigastric discomfort, and reflux symptoms [4]. Even after discontinuation of PPIs, TEA continues to provide clear symptom relief. These lines of evidence position TEA as one of the most promising non-pharmacological treatment options for NERD.

Although TEA has been supported by clinical trials in the fields of functional gastrointestinal disorders and GERD, there remains a lack of evidence from a multicenter, randomized, sham-controlled setting to validate the efficacy of TEA for NERD. This study will provide cross-institutional clinical evidence conducted under a unified standard operating procedure (SOP). The implementation of this study will fill a critical evidence gap regarding TEA treatment for NERD and lay the foundation for future guideline inclusion or larger-scale studies.

3. Study Objectives

3.1 Primary Objective

To assess the efficacy of transcutaneous electrical acupoint stimulation at Zusanli (TEA) compared with control stimulation in improving the proportion of 24-hour heartburn-free days [5] over the 4-week treatment period (Days 1–28) in patients with non-erosive reflux disease (NERD).

3.2 Secondary Objectives

The secondary objectives of this study are to:

(1) Evaluate the proportion of 24-hour heartburn-free days per week during treatment.

(2) Change from baseline in GERD-Q total score at Week 4 and Week 8

(3) Change from baseline in GERD-HRQL total score at Week 4 and Week 8

(4) Comparison of rescue medication use

(5) Persistence of efficacy after discontinuation of TEA (proportion of 24-hour heartburn-free days during the last week of the follow-up period)

(6) Patient global impression of change and treatment acceptability

(7) Assess the overall safety profile of TEA in patients with NERD.

4. Study Design Type, Principles, and Trial Procedures

4.1 Study Design Type: Randomized, Double-Blind, Multicenter, Prospective Parallel-Group Clinical Study

4.2 Sample Size Estimation

The primary endpoint is the proportion of 24-hour heartburn-free days during the 4-week treatment period. Based on prior randomized GERD trials and published TEA studies, the expected proportion of heartburn-free days is estimated at 45% in the TEA group and 25% in the Sham-TEA group (absolute difference 20%).

With a two-sided α of 0.05 and 80% power, 86 subjects per group are required. Allowing for an anticipated dropout rate of approximately 15%, 102 subjects per group will be enrolled, yielding a total sample size of 204 subjects.

4.3 Randomization and Blinding

Subjects will be randomized in a 1:1 ratio to TEA or Sham-TEA, stratified by study center. Randomization sequences will be generated by an independent statistician using permuted block randomization with a fixed block size of four.

Due to differences in stimulation location, treatment administrators will be aware of group assignment. Subjects, outcome assessors, and data analysts will remain blinded. Treatment allocation will be recorded in the eCRF using masked group labels (Group A / Group B).

4.4 The total study duration is 10 weeks, consisting of the following phases:

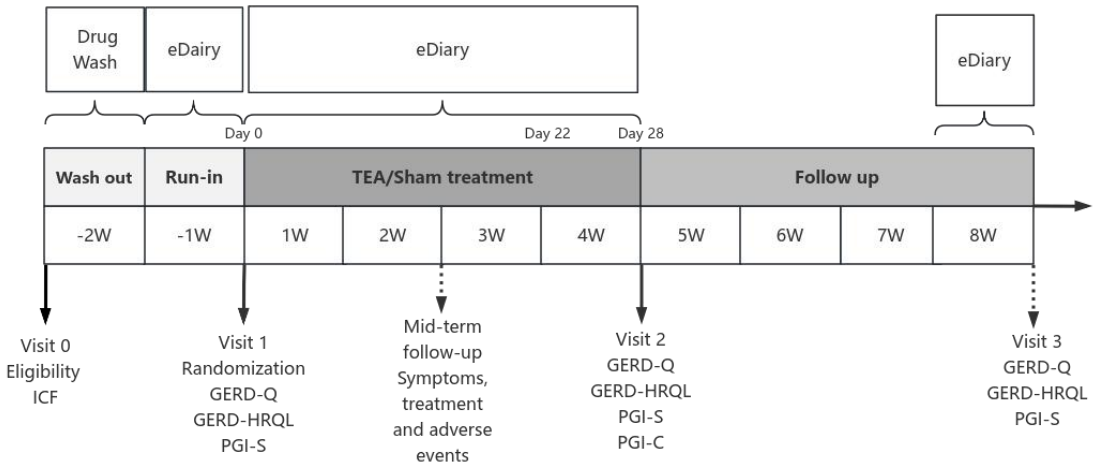
Washout period (Week -2 to Week -1): Discontinuation of relevant medications.

Baseline run-in period (Week -1 to Week 0): Completion of symptom diaries, baseline assessments, and enrollment of eligible participants.

Screening period (Week -1 to Week 0): Assessment of inclusion/exclusion criteria, discontinuation of relevant medications, establishment of electronic symptom diaries, and evaluation of baseline symptoms.

Treatment period (Week 0 to Week 4): Daily administration of TEA or Sham-TEA intervention, with continuous completion of symptom diaries.

Follow-up period (Week 4 to Week 8): Discontinuation of the intervention, with continued monitoring of symptom changes and safety outcomes.



5. Study Population

Adult patients with a confirmed diagnosis of non-erosive gastroesophageal reflux disease (NERD) who are willing to discontinue acid-suppressive therapy during the study period will be enrolled. All subjects must meet predefined inclusion and exclusion criteria to ensure scientific validity and regulatory acceptability.

5.1 Inclusion Criteria

Subjects must meet all of the following criteria:

- Age 18–75 years, irrespective of gender

- Typical heartburn symptoms ≥3 months

- Heartburn on ≥2 days during run-in diary

- Endoscopically confirmed NERD (no erosions, LA grade N/M) , within 12 months

- Willingness and ability to comply with all study procedures and to provide written informed consent.

Note: To enhance the interpretability of the primary endpoint, all enrolled subjects will be categorized based on the frequency of heartburn during the baseline run-in period (based on e-Diary) into:

Subgroup A: heartburn ≥4 days/week

Subgroup B: heartburn 2–3 days/week

This categorization will be used for stratified randomization and prespecified subgroup analyses to explore potential differences in treatment effects of TEA across populations with varying symptom frequencies.

5.2 Exclusion Criteria

Subjects will be excluded if any of the following apply:

- Familiar with acupuncture points and their functions.

- Any esophageal structural or mucosal disease (e.g., Barrett's esophagus, erosive esophagitis LA A–D, eosinophilic esophagitis, esophageal stricture, varices, malignancy, or prior chemical/thermal/radiation injury).

- Presence of gastric or duodenal ulcers.

- History of or suspected diagnosis of functional heartburn or dyspepsia by the Rome IV criteria

- Systemic diseases affecting gastrointestinal motility (e.g., systemic sclerosis, dermatomyositis, systemic lupus erythematosus, amyloidosis), uncontrolled diabetes mellitus (fasting glucose ≥11.1 mmol/L or or glycated hemoglobin ≥ 7.0%), severe cardiovascular disease, significant hepatic or renal dysfunction, or severe psychiatric disorders.

- Inability to discontinue prohibited medications (PPIs, P-CABs, H2RAs, prokinetics, or other GERD-directed therapies) except for protocol-defined rescue medication during.

- Implanted electronic devices (e.g., pacemaker, defibrillator) or other implants susceptible to electrical stimulation.

- Local skin disease or severe hypersensitivity at stimulation sites.

- Pregnancy, breastfeeding, or planned pregnancy during the study period.

- Participation in other interventional clinical trials within the past 3 months.

5.3 Criteria for Exclusion from Analysis

Treatment compliance: Major protocol deviation (device usage <60% or >120%).

Outcome evaluation: Missing primary efficacy data; use of prohibited concomitant therapy affecting efficacy assessment; post-hoc determination of key eligibility violations at enrollment.

5.4 Study Withdrawal Criteria

- Adherence rate < 50%.

- Serious adverse event or intolerable toxicity.

- Use of prohibited medications during the study.

- Participant withdrawal of informed consent.

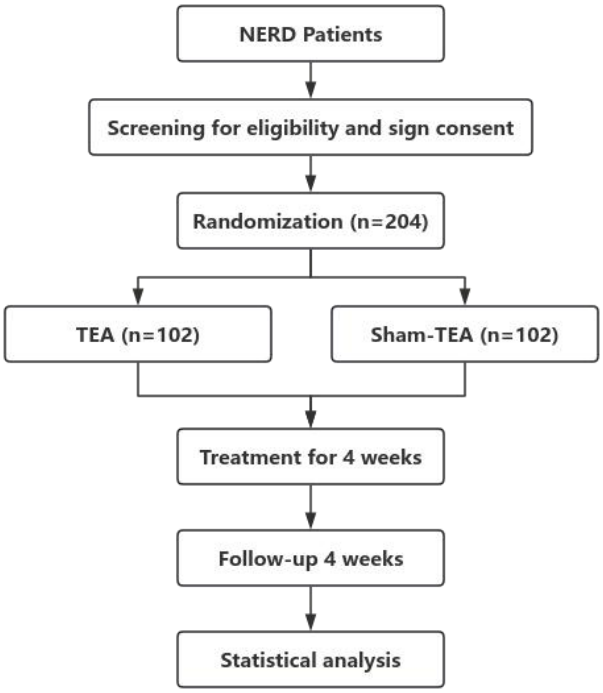
- Symptom worsening where the investigator deems continued participation detrimental to the participant.

6. Stimulation location and parameters and Study Flowchart

TEA Group: electrical stimulation will be applied unilaterally at the ST36 (Zusanli) acupoints. ST36 lies on the anterolateral aspect of the leg, about one finger breadth lateral to the anterior crest of the tibia and just below the tibial tuberosity, adjacent to branches of the peroneal and tibial nerves. TEA electrodes location: unilateral, one electrode will be placed at the ST36 and the other 3-5cm vertically down from the ST36, Figure 2.

Sham-TEA Group: electrodes placement: unilateral, one electrode will be placed at olecranon and the other 3-5cm vertically down from olecranon, Figure 3.

Parameters: Both the TEA and sham-TEA groups use the same stimulation parameters: 25 Hz, width of 0.5 ms, 2 s on, 3 s off, the current amplitude will range from 1 to 9.5 mA and will be gradually adjusted to the maximum level tolerated by the participant. TEA or sham-TEA will be performed for 1 hour, twice daily, once in the morning and once in the evening, within a flexible time window from 6:00AM to 9:00PM, for a total duration of 4 weeks.



7. Observational/Assessment Items

(1) Daily diary recording: Week -1 to Week 4, and Week 8

(2) GERD-Q / GERD-HRQL / PGI-S: Week 0, Week 4, Week 8

(3) PGI-C: Week 4

(4) Rescue medication use: Week 0 to Week 4

(5) Persistence of efficacy after discontinuation of TEA: Week 8

(6) Patient global impression of change and treatment acceptability: Week 8

(7) Treatment safety: Week 0 to Week 8

8. Efficacy Evaluation Criteria

8.1 Primary Outcome Measures
8.1.1 Proportion of 24-Hour Heartburn-Free Days During the 4-Week Treatment Period

Description Heartburn is defined as a sensation of warmth, burning, or acid-burning discomfort in the substernal or epigastric region. Heartburn severity is assessed using a 0-3 scale: 0=none; 1=mild (noticed but does not affect activities); 2=moderate (interferes with daily activities); 3=severe (significantly affects daily life or sleep). A heartburn-free day is defined as a day meeting both of the following criteria: heartburn score = 0 on that day, and no use of rescue antacids on that day. The

proportion of heartburn-free days is calculated as (number of heartburn-free days) / (number of valid observation days) during the 4-week treatment period.

[Time Frame: Day 1 to Day 28 (the 4-week treatment period)]

8.1.2 Proportion of 24-Hour Heartburn-Free Days During the 4-Week Treatment Period

Description Heartburn is defined as a sensation of warmth, burning, or acid-burning discomfort in the substernal or epigastric region. Heartburn severity is assessed using a 0-3 scale: 0=none; 1=mild (noticed but does not affect activities); 2=moderate (interferes with daily activities); 3=severe (significantly affects daily life or sleep). A heartburn-free day is defined as a day meeting both of the following criteria: heartburn score = 0 on that day, and no use of rescue antacids on that day. The proportion of heartburn-free days is calculated as (number of heartburn-free days) / (number of valid observation days) during the 4-week treatment period.

[Time Frame: Day 1 to Day 28 (the 4-week treatment period)]

8.2 Secondary Outcome Measures:

8.2.1 Weekly Proportion of 24-Hour Heartburn-Free Days During Treatment

The proportion of heartburn-free days (heartburn score = 0 and no rescue antacid use) calculated separately for each week of the 4-week treatment period.

[Time Frame: Week 1, Week 2, Week 3, and Week 4 of the treatment period]

8.2.2. Change from Baseline in GERD-Q Total Score

Description GERD-Q (Gastroesophageal Reflux Disease Questionnaire) is a 6-item patient-reported outcome measure assessing reflux symptoms and their impact. Total score ranges from 0 to 18, with higher scores indicating more severe symptoms.

[Time Frame: Baseline (Week 0), Week 4 (end of treatment), and Week 8 (end of follow-up)]

8.2.3. Change from Baseline in GERD-HRQL Total Score

GERD-HRQL (Gastroesophageal Reflux Disease-Health Related Quality of Life) is a validated instrument measuring GERD-specific quality of life. Total score ranges from 0 to 50, with higher scores indicating worse quality of life.

[Time Frame: Baseline (Week 0), Week 4 (end of treatment), and Week 8 (end of follow-up)]

8.2.4. Rescue Medication Use

The proportion of participants requiring rescue antacids during the treatment period, measured as the number of days with rescue medication use and the total amount of rescue medication consumed.

[Time Frame: During the 4-week treatment period (Week 0 to Week 4)]

8.2.5. Persistence of Efficacy After TEA Discontinuation

The proportion of 24-hour heartburn-free days during the last week of the follow-up period, after TEA treatment has been discontinued. Heartburn-free day defined as heartburn score = 0 and no rescue antacid use on that day.

[Time Frame: Last week of follow-up period (Week 8)]

8.2.6. Patient Global Impression of Change and Treatment Acceptability

The PGI-C (Patient Global Impression of Change) assesses the participant's perceived change in symptoms on a 7-point scale ranging from 1 to 7, with higher scores indicating greater improvement (better outcome). Treatment acceptability is measured by participant-reported willingness to continue TEA or recommend it to others.

[Time Frame: Week 4 (PGI-C) and Week 8 (treatment acceptability)]

8.2.7. Overall Safety Profile of TEA

Description Incidence, severity, and relationship of adverse events (AEs) to the intervention. Expected AEs include local skin reactions (itching, redness, rash, swelling), electrical stimulation-related discomfort (tingling, muscle twitching, dizziness, nausea), and device-related issues.

[Time Frame: From Week 0 to Week 8 (entire study period)]

8.3 Safety Evaluation:

During the treatment and follow-up periods, adverse events will be collected systematically, including assessments at each visit and spontaneous reports by participants. All adverse events will be evaluated by the study investigators for severity, seriousness, and their relationship to the intervention. Serious adverse events will be reported promptly in accordance with the requirements of the ethics committee of each study site and applicable regulations.

9. Adverse Event Monitoring

9.1 Definition： Adverse event (AE) is defined as any untoward medical occurrence that occurs in a participant following the administration of study intervention (including transcutaneous electrical acustimulation/sham stimulation). The event does not necessarily have a causal relationship with the treatment regimen.

9.2 Expected Adverse Events：Based on the intervention characteristics of TEA (transcutaneous electrical acustimulation), anticipated adverse events in this study include, but are not limited to:

- Local skin reactions: Itching, redness, rash, tingling, burning sensation, mild swelling, or skin breakdown at the electrode placement site.

- Electrical stimulation-related discomfort: Intolerable tingling sensation, involuntary muscle twitching, dizziness, nausea, etc., during or after treatment.

- Device-related issues: Minor problems caused by device malfunction or improper operation.

9.3 Common Adverse Events Potentially Unrelated to Study Intervention：such as common cold, headache, diarrhea, etc., occurring during the study period should also be recorded as AEs.

9.4 Severity Grading

The severity of AEs will be graded by the study physician based on clinical judgment:

- Mild: Mild symptoms that do not affect daily activities.

- Moderate: Symptoms that affect daily activities and may require intervention.

- Severe: Symptoms that significantly affect daily life or require active medical intervention.

9.5 Management and Documentation of AEs

All AEs must be documented in the Case Report Form (CRF). The study physician shall provide appropriate medical management based on the nature and severity of the AE. Follow-up of AEs should continue until symptom resolution, stabilization, or the end of the study.

9.6 Immediate Management and Reporting of Serious Adverse Events (SAEs)

Immediate Management: Once an SAE occurs, priority should be given to ensuring participant safety and providing necessary medical management. If necessary, study intervention should be suspended or discontinued for the affected participant.

Reporting Procedure: SAEs should be reported to the principal investigator as soon as the study site becomes aware of the event. SAE reporting shall be completed in accordance with ethics committee and regulatory requirements. The reporting timeline for SAEs is within 24 hours.

Follow-up and Outcome Determination of SAEs：All SAEs must be followed up until the outcome of the event is clarified. Outcomes include recovery, improvement, no recovery, sequelae, or death. Follow-up information shall be updated promptly in the CRF.

10. Study Quality Control and Quality Assurance

To ensure the scientific validity of this study, the reliability of the data, and the regulatory acceptability of the results, the following quality control and quality assurance measures have been established:

All study sites must strictly adhere to the approved study protocol, standardized operating procedures (SOPs), and electronic Case Report Form (eCRF) completion guidelines to ensure consistency and comparability of procedures across sites.

Systematic Investigator Training： Prior to study initiation, all participating investigators and clinical research coordinators (CRCs) must attend a unified investigator meeting to gain a comprehensive understanding of the study protocol, SOPs, and GCP principles. Regular cross-site coordination meetings will be held during the study to address issues encountered during implementation and to reinforce protocol adherence.

Enhancement of Participant Compliance Management： Participant treatment compliance will be monitored in real time via stimulation completion data automatically recorded in the daily electronic symptom diary (eDiary). Study personnel will periodically review compliance data and provide reminders and guidance to participants with inadequate compliance. Diary completion rate will serve as an important indicator of protocol adherence.

Implementation of Full-Process Quality Monitoring： The study coordinating center will designate clinical research associates (CRAs) to conduct regular remote monitoring at each study site. Monitoring focuses will include: the informed consent process, adherence to the protocol and SOPs, consistency between source data and CRF records, documentation and reporting of adverse events, and completeness of study documents. Issues identified during monitoring will be documented in reports, and study sites will be required to implement corrective actions within a specified timeframe.

Independent Quality Control of Core Data： Primary endpoint data (24-hour heartburn-free status recorded in the eDiary) are entered directly by participants into the electronic system, which incorporates logic checks and time-stamping functions to minimize bias that might be introduced by research personnel involvement. The data management team will perform independent quality checks and logical validation of key variables prior to database lock.

11.Statistical Analysis

11.1 Primary Analysis Plan

Statistical analyses will primarily follow the intention-to-treat (ITT) principle, including all randomized participants who received at least one treatment session and provided at least one post-baseline assessment. Per-protocol (PP) analysis will be

conducted as a sensitivity analysis, including participants who completed at least 80% of the planned treatment and had no major protocol deviations.

Baseline characteristics will be summarized using descriptive statistics. Continuous variables will be compared between groups using t-tests or non-parametric tests, and categorical variables will be compared using chi-square tests.

The primary outcome variable will be compared between groups using the chi-square test, and further analyzed using logistic regression models adjusting for study site and baseline symptom measures. Secondary outcome variables will be analyzed using appropriate statistical methods according to their data types, among which repeated continuous measures will be analyzed using mixed-effects models.

In the ITT analysis, missing data for the primary outcome will be handled according to a conservative imputation principle, i.e., missing diary days will be considered as non-heartburn-free days (non-responder imputation). Mixed-effects models will be used to handle missing data for continuous outcomes. All statistical tests will be two-sided, with a significance level set at 0.05. Results of secondary outcome analyses will be interpreted as exploratory and will not be adjusted for multiple comparisons.

11.2 Subgroup Analysis Plan

To enhance the interpretability and clinical generalizability of the efficacy results, the following pre-specified subgroup analyses will be conducted, focusing on the potential modifying effect of heartburn frequency on the response to TEA intervention:

Heartburn frequency stratification (based on e-Diary records during the baseline run-in period):

- Subgroup A: Heartburn frequency ≥ 4 days/week

- Subgroup B: Heartburn frequency 2–3 days/week

The treatment effect on the primary endpoint (proportion of 24-hour heartburn-free days during the treatment period, Days 1–28) and secondary endpoints (GERD-Q score, PGI-S, etc.) will be evaluated separately within each subgroup.

Statistical methods: Logistic regression models or linear mixed-effects models will be used to compare the primary and key secondary endpoints between subgroups. An interaction term "group × heartburn frequency subgroup" will be included to test the heterogeneity of treatment effect across subgroups (P_{interaction}). If the interaction term is significant (P_{interaction} < 0.10), stratified effect sizes and confidence intervals will be reported.

Interpretation principles: All subgroup analyses are pre-specified exploratory analyses. The results will be used to support hypothesis exploration and mechanistic inference,

and will not serve as evidence for primary conclusions. Adjustments for multiple testing (e.g., Bonferroni or False Discovery Rate control) will be considered as appropriate.

12. Ethics of the Clinical Study

This clinical study will be conducted in accordance with the relevant provisions of the World Medical Association Declaration of Helsinki. The study protocol will be approved by the Ethics Committee prior to study initiation. Before enrolling each participant, the investigator is responsible for providing a complete and comprehensive explanation of the purpose, procedures, and potential risks of the study to the participant or their legal representative. Written informed consent must be obtained. Participants should be informed of their right to withdraw from the study at any time. The informed consent forms shall be retained as clinical study documentation for future reference.

The privacy and data confidentiality of study participants will be protected throughout the study. Paper documents will be stored in locked filing cabinets, and electronic documents will be password-protected with access restricted to authorized research personnel only. To ensure that the study is conducted as required, government regulatory authorities or Ethics Committee members may, when necessary, access participant information at the study site for study-related purposes; however, they shall undertake not to disclose participant information to other parties. Although the study results may be published, participant identities will not be disclosed in such publications.

13. Study Period:

① Total Duration: 4/1/2026 – 3/31/2028

② Patient Recruitment Intervention Period:4/1/2026 – 12/31/2027

③ Data Management Statistical Analysis: 1/1/2028 – 1/31/2028

④ Study Report Writing: 2/1/2028 – 3/31/2028

14. References

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