

Hualien Tzu Chi Hospital  
The Application for In-Hospital Medical Technology Research Project

## 1. Basic Information

Application Number : \_\_\_\_\_

<b>Project Category (Select one)</b>	<input checked="" type="checkbox"/> Individual Research Project: The project leader is a senior staff member of the hospital. <input checked="" type="checkbox"/> Experimental Research (Up to 800,000 NTD) <input type="checkbox"/> Non-Experimental Research (Up to 400,000 NTD) <input type="checkbox"/> Holistic Care Departmental Project (Up to 800,000 NTD) (Only department heads are eligible to apply) <input type="checkbox"/> New Staff Research Project (Up to 200,000 NTD) <input type="checkbox"/> University-Hospital Collaborative Research Project (Up to 400,000 NTD) <input type="checkbox"/> Ministry of Science and Technology Transfer to Hospital Project (Up to 800,000 NTD) <input type="checkbox"/> Medical Education Research Project (Up to 400,000 NTD)					
	<b>Personnel Category (Select one)</b>	<input checked="" type="checkbox"/> Physician <input type="checkbox"/> Non-Physician				
	<b>Project Title</b>	Esophageal visceral hypersensitivity and hypervigilance in disorders of gut-brain interaction: the roles of neuromodulators and cognitive-behavioral therapy				
	<b>Name of the Project Leader</b>	Wei-Yi Lei	<b>Title/Position</b>	Attending Physician	<b>Applying Department/Division</b>	Gastroenterology Department
	<b>Project Execution Period</b>	From January 1, 2024 to December 31, 2025				
	<b>Research Nature and Classification</b>	<input type="checkbox"/> Basic Research <input checked="" type="checkbox"/> Applied Research <input type="checkbox"/> Technology Development <b>(Note: Those who select Applied Research and Technology Development must also select the category of Innovation R&amp;D.)</b>				
		Innovation R&D Classification : <input checked="" type="checkbox"/> (1) Clinical Research <input type="checkbox"/> (2) Translational Research <input type="checkbox"/> (3) Medical Engineering and Materials <input type="checkbox"/> (4) Information <input type="checkbox"/> (5) Medical Assistance Operations <input type="checkbox"/> (6) Others, please specify _____				
Holistic Care Classification : (1) Patient-Centered ( <input checked="" type="checkbox"/> Physical, <input type="checkbox"/> Psychological, <input checked="" type="checkbox"/> Environmental, <input type="checkbox"/> Spiritual) (2) Health Education ( <input type="checkbox"/> Behavior Change, <input checked="" type="checkbox"/> Health Promotion, <input checked="" type="checkbox"/> Disease Prevention, <input checked="" type="checkbox"/> Early Diagnosis, <input type="checkbox"/> Early Treatment) (3) Others, please specify _____						

Has this in-house project applied for the 2023 Ministry of Science and Technology's Special Research

Program?

No  Yes.

Has any government agency subsidy for research projects been applied for this year?

No  Yes, a total of 1 projects.

A total of 1 in-house research projects have been applied for this year as the principal investigator (jointly hosted projects are not included).

The priority of this project is 1.

Has this project applied for:

No need

Human Experiments / Human Samples (including human embryos/human embryonic stem cells)

Animal Experiments

Biosafety (including recombinant DNA experiments/genetically modified organism field trials/Level 2 or higher infectious biological materials)

【Please check the applicable items】

<b>Project Contact Person</b>	Name: Lei Wei-Yi Phone: (Office) (03) 8561825-13224 (Home) 0970-339629 E-Mail: <a href="mailto:aquarius@seed.net.tw">aquarius@seed.net.tw</a>
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## 2. Application for Subsidy Funding (The budget allocation will be included in the review and evaluation criteria, please do not inflate the figures.)

Based on the actual needs of the research project, the following items can be applied for subsidy funding:

- For individual research projects:
  - Experimental research: Maximum of 800,000 NTD
  - Non-experimental research: Maximum of 400,000 NTD
- For new personnel research projects: The total research funding is limited to 200,000 NTD.
- For collaborative research projects between schools and institutions: The total research funding is limited to 400,000 NTD.
- For holistic care department projects: The maximum funding is 800,000 NTD.
- For Ministry of Science and Technology transferred in-house projects: The maximum funding is 800,000 NTD.

Subsidy Items	Requested Amount
Administrative Expenses	1. Research Personnel Costs 480,000 NTD
	2. Experimental Animal Costs 0 NTD
	3. Consumables, Materials, Books, and Miscellaneous Expenses 160,000 NTD
Research Equipment Costs	0 NTD
Total Amount	640,000 NTD

## 3. Equipment Configuration

The names of the main instruments required for this project, their placement locations, and the signature of the responsible person consenting to their use.

Instrument Name	Installation Location (Department)	Signature and Seal of the Department Head Approving the Use of the Instrument

## 4. Personnel Involved in the Project

### (1) Principal Research Personnel

Category (Principal Investigator, Co-Principal Investigator, Collaborating Principal Investigator, Research Assistant, etc.)	Name	Current Position	Specific Job Role, Tasks, and Scope of Work in this Research Project
Principal Investigator	Lei Wei-Yi	Attending Physician, Gastroenterology	Research project planning and participant recruitment, progress monitoring, data statistical analysis, and report writing.
Co-Principal Investigator	Chen Jian- Lin	Director of Gastroenterology Department	Project progress supervision, project planning discussions, participant recruitment, and data analysis.
Co-Principal Investigator	Weng Ming- Wen	Attending Physician, Gastroenterology	Research project participant recruitment and actual case handling.
Co-Principal Investigator	Yi Zhi-Xun	Attending Physician, Gastroenterology	Research project participant recruitment and actual case handling.
Co-Principal Investigator	Liu Zuo-Cai	Director of the Digestive Function Testing Department	Research project participant recruitment and actual case handling.
Co-Principal Investigator	Hong Rui- Sheng	Attending Physician, Gastroenterology	Research project participant recruitment and actual case handling.
Co-Principal Investigator	Wang Jun- Wei	Attending Physician, Gastroenterology Department, Kaohsiung Medical University Hospital	Research project participant recruitment and actual case handling.
Co-Principal Investigator	Liang Shu- Wei	Attending Physician, Gastroenterology Department, Chung Shan Medical University Hospital	Research project participant recruitment and actual case handling.
Co-Principal Investigator	Wang Wen- Hui	Director of Gastroenterology Department, E-Da Hospital	Research project participant recruitment and actual case handling.
Co-Principal Investigator	Hsieh Ming- Tsung	Attending Physician, Gastroenterology Department, National Cheng Kung University Hospital	Research project participant recruitment and actual case handling.
Co-Principal Investigator	Lin Yi-Mei	Professor, Department of Psychology, Kaohsiung Medical University	Cognitive Behavioral Therapy coordination and data analysis.
Co-Principal Investigator	Lin Hui-Min	Dietitian, Clinical Nutrition Division, Department of Nutrition	Developing nutrition education materials and arranging the nutrition consultation process.

Research Personnel	Lin Pei-Yun	Psychotherapist, Yuli Hospital	Conducting Cognitive Behavioral Therapy.
Research Personnel	Hsu Ssu-Ting	Counseling Psychologist, Secret Garden Counseling Center	Conducting Cognitive Behavioral Therapy.
Research Personnel	Su Zhen-Ying	Dietitian, Clinical Nutrition Division, Department of Nutrition	Conducting nutrition counseling and education.
Research Assistant	Huang Chun-Hsiang	Research Assistant	Survey administration, data collection, organization and analysis, and handling administrative tasks.

※If there are insufficient fields, please copy them as needed.

**(2) Research projects that the principal investigator, co-principal investigator, and co-researchers have participated in during the past three years.**

Name	Project Name	Role and Responsibilities in the Project	Start and End Date	Funding Agency
Lei Wei-Yi	Exploring the roles and interrelationships of esophageal hypersensitivity, psychological distress, and functional gastrointestinal disorders in the pathophysiological mechanisms of esophageal symptoms in patients.	Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Exploring the pathophysiological mechanisms and treatment strategies of gastroesophageal reflux disease (GERD) through the distribution of afferent nerves, esophageal motility, and pharmacological regulation.	Principal Investigator	2022/8/1~2025/07/31	Ministry of Science and Technology (MOST)
Lei Wei-Yi	Exploring the effects of opioid analgesics on the pathophysiological mechanisms of esophageal contraction and reflux characteristics, as well as their clinical applications.	Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	The efficacy of Jingsi Herbal Concentrate on long COVID symptoms—gut-brain axis dysregulation and related physical and mental symptoms: A randomized double-blind clinical trial.	Co-Principal Investigator	2023/01/01~2023/12/31	Tzu Chi Medical Foundation
Lei Wei-Yi	Exploring the interaction between upper gastric belching, physical and mental symptoms, and esophageal acid reflux: Clinical applications for optimizing the treatment of gastroesophageal reflux disease (GERD).	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Using high-resolution pharyngeal function testing to analyze the pharyngeal swallowing physiology and dynamics in patients with ineffective esophageal motility.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Exploring the efficacy and physiological changes of anti-reflux mucosal ablation in proton pump inhibitor (PPI)-dependent gastroesophageal reflux disease (GERD).	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital

Lei Wei-Yi	Exploring the sensitivity to capsaicin, motility sensation function, and the physiological features of reflux in the esophagus: Clinical impact and treatment guidelines for esophageal dysfunction and gastroesophageal reflux disease (GERD).	Co-Principal Investigator	2023/8/1~2026/07/31	Ministry of Science and Technology (MOST)
Lei Wei-Yi	Exploring the pathophysiological mechanisms of gastroesophageal reflux disease (GERD) through esophageal reflux clearance capacity, mucosal integrity, and psychosocial characteristics, and establishing a basis for precise diagnosis and treatment.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	The application of high-resolution impedance pharyngeal function testing and the Sydney Swallowing Questionnaire in oropharyngeal dysphagia and voice disorders.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	The application of artificial intelligence in high-resolution esophageal function testing: A study on unsupervised computational models based on deep learning.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Application of supervised learning artificial intelligence in analyzing 24-hour esophageal pH-impedance monitoring: Technological efficacy and clinical applications in diagnosing gastroesophageal reflux disease (GERD).	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Exploring the clinical characteristics and the impact of gut microbiota in patients with metabolic-associated fatty liver disease under dietary and exercise regulation.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	The efficacy of Jingsi Herbal Drink on the physical and mental symptoms of functional dyspepsia: A randomized double-blind clinical trial.	Co-Principal Investigator	2022/1/1~2022/12/31	Tzu Chi Medical Foundation
Lei Wei-Yi	Exploring the pathophysiological role of esophageal mucosal afferent nerve distribution in gastroesophageal reflux disease (GERD) with concurrent esophageal motility dysfunction.	Principal Investigator	2020/8/1~2022/07/31	Ministry of Science and Technology (MOST)
Lei Wei-Yi	Exploring the pathophysiological impact of esophageal contraction, mucosal integrity, and acid sensitivity on gastroesophageal reflux disease (GERD) and the basis for treatment strategies.	Co-Principal Investigator	2020/8/1~2023/07/31	Ministry of Science and Technology (MOST)
Lei Wei-Yi	Exploring the role of esophageal microbiota in gastroesophageal reflux disease (GERD) through novel impedance parameters, clinical subtypes, and hypersensitivity.	Co-Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Exploring the interrelationship and pathogenic mechanisms of esophageal acid sensitivity, secondary esophageal contractions, and subtypes of gastroesophageal reflux disease (GERD).	Co-Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Exploring the clinical application of high-resolution impedance pharyngeal function testing in oropharyngeal dysphagia and drug response.	Co-Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital
Chen Jian-Lin	The efficacy of Jingsi Herbal Concentrate on long COVID symptoms—gut-brain axis dysregulation	Principal Investigator	2023/01/01~2023/12/31	Tzu Chi Medical Foundation

	and related physical and mental symptoms: A randomized double-blind clinical trial.			
Chen Jian-Lin	Exploring the interaction between upper gastric belching, physical and mental symptoms, and esophageal acid reflux: Clinical applications for optimizing the treatment of gastroesophageal reflux disease (GERD).	Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Chen Jian-Lin	Exploring the relationship between esophageal capsaicin sensitivity, motility sensation function, and the physiological characteristics of reflux: Clinical impacts and treatment guidelines for esophageal dysfunction and gastroesophageal reflux disease (GERD).	Principal Investigator	2023/8/1~2026/07/31	Ministry of Science and Technology (MOST)
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Chen Jian-Lin	Exploring the pathophysiological mechanisms of gastroesophageal reflux disease (GERD) through esophageal reflux clearance capacity, mucosal integrity, and psychosocial characteristics, and establishing a basis for precise diagnosis and treatment.	Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Chen Jian-Lin	Exploring the pathophysiological mechanisms and interrelationships of esophageal hypersensitivity, psychological distress, and functional gastrointestinal disorders in patients with esophageal symptoms.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Chen Jian-Lin	Exploring the efficacy and physiological changes of anti-reflux mucosal ablation in proton pump inhibitor (PPI)-dependent gastroesophageal reflux disease (GERD).	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Chen Jian-Lin	Using high-resolution pharyngeal function testing to analyze the pharyngeal swallowing physiology and dynamics in patients with ineffective esophageal motility.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Chen Jian-Lin	Exploring the pathophysiological mechanisms of laryngopharyngeal reflux: Clinical applications of artificial intelligence-assisted, precision diagnostics, and personalized treatment strategies.	Co-Principal Investigator	2022/8/1~2025/07/31	Ministry of Science and Technology (MOST)
Chen Jian-Lin	Exploring the pathophysiological mechanisms and treatment strategies of gastroesophageal reflux disease (GERD) through the distribution of afferent nerves, esophageal motility, and pharmacological regulation.	Co-Principal Investigator	2022/8/1~2025/07/31	Ministry of Science and Technology (MOST)
Chen Jian-Lin	Exploring the effects of opioid analgesics on the pathophysiological mechanisms of esophageal contraction and reflux characteristics, as well as their clinical applications.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Chen Jian-Lin	Application of supervised learning artificial intelligence in analyzing 24-hour esophageal pH-impedance monitoring: Technological efficacy and clinical applications in diagnosing gastroesophageal reflux disease (GERD).	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital

Chen Jian-Lin	The application of high-resolution impedance pharyngeal function testing and the Sydney Swallowing Questionnaire in oropharyngeal dysphagia and voice disorders.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Chen Jian-Lin	The application of artificial intelligence in high-resolution esophageal function testing: A study on unsupervised computational models based on deep learning.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Chen Jian-Lin	Exploring the clinical characteristics and the impact of gut microbiota in patients with metabolic-associated fatty liver disease under dietary and exercise regulation.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Chen Jian-Lin	Exploring the role of esophageal microbiota in gastroesophageal reflux disease (GERD) through novel impedance parameters, clinical subtypes, and hypersensitivity.	Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital
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Chen Jian-Lin	Exploring the pathophysiological role of esophageal mucosal afferent nerve distribution in gastroesophageal reflux disease (GERD) with concurrent esophageal motility dysfunction.	Co-Principal Investigator	2020/8/1~2022/07/31	Ministry of Science and Technology (MOST)
Chen Jian-Lin	Improving the diagnosis of laryngopharyngeal reflux through the proximal esophageal nighttime average baseline mucosal impedance values and establishing the indications for proton pump inhibitor therapy.	Co-Principal Investigator	2020/8/1~2022/07/31	Ministry of Science and Technology (MOST)
Chen Jian-Lin	Exploring the pathophysiological impacts of esophageal contraction, mucosal integrity, and acid sensitivity on gastroesophageal reflux disease (GERD), and establishing treatment strategies based on these factors.	Principal Investigator	2020/8/1~2023/07/31	Ministry of Science and Technology (MOST)
Weng Ming-Wen	Exploring the efficacy and physiological changes of anti-reflux mucosal ablation in proton pump inhibitor (PPI)-dependent gastroesophageal reflux disease (GERD).	Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Weng Ming-Wen	Exploring the pathophysiological mechanisms of laryngopharyngeal reflux: Clinical applications of artificial intelligence-assisted precision diagnostics and personalized treatment strategies.	Principal Investigator	2022/8/1~2025/07/31	Ministry of Science and Technology (MOST)
Weng Ming-Wen	Using supervised learning artificial intelligence to analyze 24-hour esophageal pH-impedance monitoring: Technological efficacy and clinical applications in the diagnosis of gastroesophageal reflux disease (GERD).	Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Weng Ming-Wen	The therapeutic effects of concentrated Jingsu herbal drink on physical and psychological symptoms of long COVID—gut-brain axis	Co-Principal Investigator	2023/01/01~2023/12/31	Tzu Chi Medical Foundation

	dysregulation: A randomized double-blind clinical trial.			
Weng Ming-Wen	Exploring the interplay between belching, psychological symptoms, and esophageal acid reflux: Clinical applications for optimizing the treatment of gastroesophageal reflux disease (GERD).	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Weng Ming-Wen	Exploring the pathophysiological role and interplay of esophageal hypersensitivity, psychological distress, and functional gastrointestinal disorders in patients with esophageal symptoms.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Weng Ming-Wen	Analyzing the pharyngeal swallowing physiology in patients with ineffective esophageal motility using high-resolution pharyngeal function testing.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Weng Ming-Wen	Exploring the relationship between esophageal capsaicin sensitivity, motility sensation, and physiological features of reflux: Clinical impacts and treatment guidelines for esophageal dysfunction and gastroesophageal reflux disease (GERD).	Co-Principal Investigator	2023/8/1~2026/07/31	Ministry of Science and Technology (MOST)
Weng Ming-Wen	The application of high-resolution impedance pharyngeal function testing and the Sydney Swallowing Questionnaire in the assessment of oropharyngeal swallowing difficulties and voice disorders.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Weng Ming-Wen	The application of artificial intelligence in high-resolution esophageal function testing: A study using an unsupervised deep learning-based algorithm model.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Weng Ming-Wen	Exploring the clinical characteristics and the impact of gut microbiota in patients with metabolic-associated fatty liver disease under dietary and exercise regulation.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Weng Ming-Wen	The therapeutic effects of Jing Si Herbal Drink on the psychosomatic symptoms of functional dyspepsia: A randomized double-blind clinical trial.	Co-Principal Investigator	2022/1/1~2022/12/31	Tzu Chi Medical Foundation
Weng Ming-Wen	The use of proximal esophageal nocturnal average baseline mucosal impedance values to improve the diagnosis of laryngopharyngeal reflux disease and establish indications for proton pump inhibitors.	Principal Investigator	2020/8/1~2022/07/31	Ministry of Science and Technology (MOST)
Weng Ming-Wen	The exploration of the pathophysiological impact of esophageal contraction, mucosal integrity, and acid sensitivity on gastroesophageal reflux disease, along with therapeutic strategies based on these factors.	Co-Principal Investigator	2020/8/1~2023/07/31	Ministry of Science and Technology (MOST)
Weng Ming-Wen	Exploring the role of esophageal microbiota in gastroesophageal reflux disease through novel impedance parameters, clinical classification, and hypersensitivity.	Co-Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital
Weng Ming-Wen	Exploring the relationship and pathophysiological mechanisms between esophageal acid sensitivity, secondary esophageal contraction, and subtypes of gastroesophageal reflux disease.	Co-Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital

Weng Ming-Wen	Exploring the clinical application of high-resolution impedance pharyngoesophageal function testing in the assessment of pharyngeal dysphagia and drug responses.	Co-Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital
Yi Zhi-Xun	The efficacy of Jing's Herbal Decoction Concentrate in treating long COVID symptoms—gut-brain axis dysfunction and associated physical and mental symptoms: A randomized double-blind clinical trial.	Co-Principal Investigator	2023/01/01~2023/12/31	Tzu Chi Medical Foundation
Yi Zhi-Xun	Exploring the interaction between belching, physical and mental symptoms, and esophageal acid reflux: Clinical applications for optimizing gastroesophageal reflux disease treatment.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Yi Zhi-Xun	Exploring the pathophysiological mechanisms and interactions of esophageal hypersensitivity, psychological distress, and functional gastrointestinal disorders in patients with esophageal symptoms.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Yi Zhi-Xun	Exploring the efficacy and physiological changes of anti-reflux mucosal ablation therapy in proton pump inhibitor-dependent gastroesophageal reflux disease.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Yi Zhi-Xun	Analyzing the pharyngeal swallowing physiology and dynamics in patients with ineffective esophageal motility using high-resolution pharyngoesophageal function testing.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Yi Zhi-Xun	Exploring the relationship between esophageal capsaicin sensitivity, motility sensory function, and the reflux characteristics of physical and psychological physiology: Clinical impact and treatment guidelines for esophageal dysfunction and gastroesophageal reflux disease.	Co-Principal Investigator	2023/8/1~2026/07/31	Ministry of Science and Technology (MOST)
Yi Zhi-Xun	Exploring the pathophysiological mechanisms of gastroesophageal reflux disease through esophageal clearance ability, mucosal integrity, and psychological characteristics, and establishing the basis for precise diagnosis and treatment.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Yi Zhi-Xun	Exploring the impact of opioid analgesics on the pathophysiological mechanisms of esophageal contraction and reflux characteristics, and their clinical applications.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Yi Zhi-Xun	The application of high-resolution impedance pharyngoesophageal function testing and the Sydney Swallow Questionnaire in oropharyngeal dysphagia and voice disorders.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Yi Zhi-Xun	The Application of Artificial Intelligence in High-Resolution Esophageal Function Testing: A Study on Unsupervised Computational Models Based on Deep Learning.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Yi Zhi-Xun	Artificial Intelligence Analysis of 24-Hour Esophageal pH Impedance Testing Using Supervised Learning: Technical Performance and Clinical Applications in the Diagnosis of Gastroesophageal Reflux Disease.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital

Yi Zhi-Xun	Exploring the Impact of Diet and Exercise Regulation on Clinical Features and Gut Microbiota in Patients with Metabolism-Related Fatty Liver Disease.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Yi Zhi-Xun	The Therapeutic Effect of Jinseng Herbal Drink on Psychosomatic Symptoms in Functional Dyspepsia: A Randomized Double-Blind Clinical Trial.	Co-Principal Investigator	2022/1/1~2022/12/31	Tzu Chi Medical Foundation
Yi Zhi-Xun	Exploring the Interrelationship and Pathogenic Mechanisms Between Esophageal Acid Sensitivity, Esophageal Secondary Contractions, and Subtypes of Gastroesophageal Reflux Disease.	Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital
Yi Zhi-Xun	Exploring the Role of Esophageal Microbiota in Gastroesophageal Reflux Disease: Its Impact on Novel Impedance Parameters, Clinical Classification, and Hypersensitivity.	Co-Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital
Yi Zhi-Xun	Clinical Application of High-Resolution Impedance Pharyngeal Function Testing in the Assessment of Pharyngeal Dysphagia and Drug Response.	Co-Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital
Yi Zhi-Xun	Exploring the Pathophysiological Impact of Esophageal Contractions, Mucosal Integrity, and Acid Sensitivity on Gastroesophageal Reflux Disease and the Basis for Therapeutic Strategies.	Co-Principal Investigator	2020/8/1~2023/07/31	Ministry of Science and Technology (MOST)
Liu Zuo-Cai	Exploring the Impact of Diet and Exercise Regulation on Clinical Features and Gut Microbiota in Patients with Metabolism-Related Fatty Liver Disease.	Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Liu Zuo-Cai	The Therapeutic Effect of Jinseng Herbal Extract on Long COVID Symptoms: Psychosomatic Symptoms Related to Gut-Brain Axis Dysregulation – A Randomized Double-Blind Clinical Trial.	Co-Principal Investigator	2023/01/01~2023/12/31	Tzu Chi Medical Foundation
Liu Zuo-Cai	Exploring the Interrelationship Between Belching, Psychosomatic Symptoms, and Esophageal Acid Reflux: Clinical Applications for Optimizing Gastroesophageal Reflux Disease Treatment.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Liu Zuo-Cai	Exploring the Pathophysiological Mechanisms and Interrelationship Between Esophageal Hypersensitivity, Psychological Distress, and Functional Gastrointestinal Disorders in Patients with Esophageal Symptoms.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Liu Zuo-Cai	Analyzing the Pharyngeal Physiology and Dynamics of Swallowing in Esophageal Ineffective Peristalsis Patients Using High-Resolution Pharyngeal Function Testing.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Liu Zuo-Cai	Exploring the Efficacy and Physiological Changes of Anti-Reflux Mucosal Ablation in Proton Pump Inhibitor-Dependent Gastroesophageal Reflux Disease.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Liu Zuo-Cai	Exploring Esophageal Capsaicin Sensitivity, Peristaltic Sensory Function, and Psychophysiological Reflux Characteristics: Clinical Impact and Treatment Guidelines for	Co-Principal Investigator	2023/8/1~2026/07/31	Ministry of Science and Technology (MOST)

	Esophageal Dysfunction and Gastroesophageal Reflux Disease.			
Liu Zuo-Cai	Exploring the Pathophysiological Mechanisms of Gastroesophageal Reflux Disease Through Esophageal Reflux Clearance Ability, Mucosal Integrity, and Psychosocial Traits: Establishing the Basis for Precise Diagnosis and Treatment.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Liu Zuo-Cai	Exploring the Impact of Opioid Analgesics on Esophageal Contraction and Reflux Characteristics: Pathophysiological Mechanisms and Clinical Applications.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Liu Zuo-Cai	The Application of High-Resolution Impedance Pharyngeal Function Testing and the Sydney Swallowing Questionnaire in Oropharyngeal Dysphagia and Voice Disorders.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
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Liu Zuo-Cai	Exploring the Interrelationship and Pathogenic Mechanisms Between Esophageal Acid Sensitivity, Esophageal Secondary Contractions, and Subtypes of Gastroesophageal Reflux Disease.	Co-Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital
Liu Zuo-Cai	Clinical Application of High-Resolution Impedance Pharyngeal Function Testing in the Assessment of Pharyngeal Dysphagia and Drug Response.	Co-Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital
Liu Zuo-Cai	Exploring the Pathophysiological Impact of Esophageal Contractions, Mucosal Integrity, and Acid Sensitivity on Gastroesophageal Reflux Disease and the Basis for Therapeutic Strategies.	Co-Principal Investigator	2020/8/1~2023/07/31	Ministry of Science and Technology (MOST)
Hong Rui-Sheng	Analyzing the Pharyngeal Physiology and Dynamics of Swallowing in Esophageal Ineffective Peristalsis Patients Using High-Resolution Pharyngeal Function Testing.	Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	The Application of High-Resolution Impedance Pharyngeal Function Testing and the Sydney Swallowing Questionnaire in Oropharyngeal Dysphagia and Voice Disorders.	Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital

Hong Rui-Sheng	The Therapeutic Effect of Jinseng Herbal Extract on Long COVID Symptoms: Psychosomatic Symptoms Related to Gut-Brain Axis Dysregulation – A Randomized Double-Blind Clinical Trial.	Co-Principal Investigator	2023/01/01~2023/12/31	Tzu Chi Medical Foundation
Hong Rui-Sheng	Exploring the Interrelationship Between Belching, Psychosomatic Symptoms, and Esophageal Acid Reflux: Clinical Applications for Optimizing Gastroesophageal Reflux Disease Treatment.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Exploring the Pathophysiological Mechanisms and Interrelationship Between Esophageal Hypersensitivity, Psychological Distress, and Functional Gastrointestinal Disorders in Patients with Esophageal Symptoms.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Exploring the Efficacy and Physiological Changes of Anti-Reflux Mucosal Ablation in Proton Pump Inhibitor-Dependent Gastroesophageal Reflux Disease.	Co-Principal Investigator	2023/01/01~2023/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Exploring Esophageal Capsaicin Sensitivity, Peristaltic Sensory Function, and Psychophysiological Reflux Characteristics: Clinical Impact and Treatment Guidelines for Esophageal Dysfunction and Gastroesophageal Reflux Disease.	Co-Principal Investigator	2023/8/1~2026/07/31	Ministry of Science and Technology (MOST)
Hong Rui-Sheng	Exploring the Pathophysiological Mechanisms of Gastroesophageal Reflux Disease Through Esophageal Reflux Clearance Ability, Mucosal Integrity, and Psychosocial Traits: Establishing the Basis for Precision Diagnosis and Treatment.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Exploring the Impact of Opioid Analgesics on Esophageal Contraction and Reflux Characteristics: Pathophysiological Mechanisms and Clinical Applications.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Artificial Intelligence Analysis of 24-Hour Esophageal pH-Impedance Monitoring Using Supervised Learning: Technical Performance and Clinical Applications in the Diagnosis of Gastroesophageal Reflux Disease.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	The Application of Artificial Intelligence in High-Resolution Esophageal Function Testing: A Study on Unsupervised Computational Models Based on Deep Learning.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Exploring the Impact of Diet and Exercise Regulation on Clinical Features and Gut Microbiota in Patients with Metabolism-Related Fatty Liver Disease.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	The Therapeutic Effect of Jinseng Herbal Drink on Psychosomatic Symptoms in Functional Dyspepsia: A Randomized Double-Blind Clinical Trial.	Co-Principal Investigator	2022/1/1~2022/12/31	Tzu Chi Medical Foundation
Hong Rui-Sheng	Clinical Application of High-Resolution Impedance Pharyngeal Function Testing in the Assessment of Oropharyngeal Dysphagia and Drug Response.	Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital

Hong Rui-Sheng	Exploring the Role of Esophageal Microbiota in Gastroesophageal Reflux Disease: Its Impact on Novel Impedance Parameters, Clinical Classification, and Hypersensitivity.	Co-Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital
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Liang Shu-Wei	The Application of Artificial Intelligence in High-Resolution Esophageal Function Testing: A Study on Unsupervised Computational Models Based on Deep Learning.	Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Liang Shu-Wei	Artificial Intelligence Analysis of 24-Hour Esophageal pH-Impedance Monitoring Using Supervised Learning: Technical Performance and Clinical Applications in the Diagnosis of Gastroesophageal Reflux Disease.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
Liang Shu-Wei	Exploring the Pathophysiological Mechanisms of Gastroesophageal Reflux Disease Through Esophageal Reflux Clearance Ability, Mucosal Integrity, and Psychosocial Traits: Establishing the Basis for Precision Diagnosis and Treatment.	Co-Principal Investigator	2022/1/1~2022/12/31	Hualien Tzu Chi Hospital
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Liang Shu-Wei	The Therapeutic Effect of Jinseng Herbal Drink on Psychosomatic Symptoms in Functional Dyspepsia: A Randomized Double-Blind Clinical Trial.	Co-Principal Investigator	2022/1/1~2022/12/31	Tzu Chi Medical Foundation
Liang Shu-Wei	Exploring the Role of Esophageal Microbiota in Gastroesophageal Reflux Disease: Its Impact on Novel Impedance Parameters, Clinical Classification, and Hypersensitivity.	Co-Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital
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Liang Shu-Wei	Clinical Application of High-Resolution Impedance Pharyngeal Function Testing in the Assessment of Oropharyngeal Dysphagia and Drug Response.	Co-Principal Investigator	2021/1/1~2021/12/31	Hualien Tzu Chi Hospital

※If there are insufficient fields, please copy them as needed.

## 5. Research Related to Costs

Project Name	Description	Unit Price (NTW)	Quantity	Total Price (NTW)	Remarks
1.Research Personnel Costs <i>(For related insurance premiums, please consult the Human Resources Department)</i>	<p><b>(1) Full-time Personnel (for individual project applications only):</b></p> <ul style="list-style-type: none"> <li>• Work remuneration (including year-end bonus reserve)</li> <li>• Employer contribution to labor and health insurance</li> <li>• Employer contribution to labor pension (6% of insured salary)</li> </ul> <p><b>(2) Part-time Personnel (must be enrolled students):</b></p> <ul style="list-style-type: none"> <li>• Work remuneration <ul style="list-style-type: none"> <li><input type="checkbox"/> Undergraduate student</li> <li><input type="checkbox"/> Master's student</li> <li><input type="checkbox"/> Other:</li> </ul> </li> <li>• Employer contribution to labor and health insurance</li> <li>• Employer contribution to labor pension (6% of insured salary)</li> </ul> <p><b>(3) Temporary Workers:</b></p> <ul style="list-style-type: none"> <li>• Work remuneration</li> <li>• Employer contribution to labor and health insurance</li> <li>• Employer contribution to labor pension (6% of insured salary)</li> </ul>				
1. Operational Expenses	<b>(4) Professional Assistance Fees</b>	12,000	40	480,000	
			Subtotal:	480,000	
2.Animal Experimentation Fees			Subtotal:		
3.Consumables, Equipment, Books, and Miscellaneous Expenses	Participant Stipends  Miscellaneous: Postage and Telecommunications, Printing Costs, Copy Paper, Copying	500  1,000  15,000	210  40  1	105,000  40,000  15,000	

	Fees, Binding Fees, Stationery Costs, Poster Production Fees, Computer Data Statistics Fees, Computer Data Analysis Fees, Paper Submission Fees, Paper Publication Fees, Sectioning, Embedding, and Staining Immunology Costs.				
			Subtotal:	160,000	
<b>2. Research Equipment Costs</b> (According to regulations, books, computers, and peripheral equipment are not included in the subsidy. Medium and large instruments will be applied for collectively by the research department, based on necessity, for shared use.)			Subtotal:	0	
	<b>Total</b>			<b>640,000</b>	

## 6. Project Abstract

( Please provide a summary of the key points of this project within 500 words, and create customized keywords based on the nature of the project. )

Gastroesophageal reflux disease (GERD) poses a challenging medical condition to manage, with up to 40% of patients showing refractory to standard medical intervention, which usually begins with a proton pump inhibitor (PPI). Among these cases, esophageal disorders of gut-brain interaction (DGBI), such as reflux hypersensitivity and functional heartburn, or GERD patients with concurrent occurrences of these conditions, constitute more than 90% of the patients who did not respond to twice-daily PPI treatment. Esophageal visceral hypersensitivity and hypervigilance are the two pathways that drive esophageal DGBI and symptoms. The Rome IV esophageal disorders, encompassing functional chest pain, functional heartburn, globus, functional dysphagia, and reflux hypersensitivity, are defined by present with symptoms originating from the esophagus without detectable evidence of structural, inflammatory, or motor disorders. Diagnosing esophageal DGBI necessitates testing involving endoscopy, pH-impedance monitoring, and high-resolution manometry. Neuromodulators form the basis of the pharmacological strategy for managing various esophageal DGBI and symptoms, modulating both peripheral and central hyperalgesia. Increasing evidence supports the use of brain-gut behavioral therapies, such as gut-directed hypnotherapy and cognitive behavior therapy, as effective treatments for a variety of DGBIs. However, the efficacy of neuromodulators or cognitive behavior therapy in treating esophageal DGBI and related symptoms remains largely unexplored. The primary objective of this study is to examine the efficacy of neuromodulators in managing esophageal DGBI. Additionally, we will explore various classes of neuromodulators and subtypes of esophageal DGBI to ascertain whether there are differing levels of effectiveness across these conditions. The findings from this study will contribute to a better understanding of the pathophysiology of esophageal DGBI and GERD with refractory symptoms. These clinical insights may then offer valuable guidance for future therapeutic approaches in DGBI patients who experience esophageal symptoms and do not respond to PPI treatment.

**Key words:** gastroesophageal reflux disease, disorders of gut-brain interaction, neuromodulators

## 7. Background and Objectives of the Research Project

( Please provide a detailed description of the background, objectives, significance of this research project, as well as the research status both domestically and internationally related to this project. Also, include a review of important references and literature. )

### Research Background

#### ◆ Pathophysiological Mechanisms and Importance of Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux disease (GERD) is defined as a condition where stomach contents flow back into the esophagus, resulting in symptoms or mucosal injury. Common typical symptoms include heartburn or acid reflux, while atypical symptoms may include chest tightness, a sensation of a foreign body in the throat, hoarseness, or chronic cough. Clinically, GERD is a common chronic disease. In the United States, where symptoms occur at least once a week, up to 30% of adults are affected by GERD; in East Asia, the prevalence is 5-10%, but there is a growing trend in its incidence.

There are many possible pathogenic mechanisms for GERD, including lower esophageal sphincter (LES) dysfunction or structural abnormalities, ineffective esophageal motility, esophageal mucosal integrity defects, esophageal hypersensitivity, the formation of acid pockets after meals, the composition of gastric refluxate, and delayed gastric emptying. Currently, the most common diagnostic method involves observing damage to the distal esophageal mucosa through endoscopy or confirming abnormal gastric acid exposure via a 24-hour pH monitoring test. Based on the results of endoscopy and esophageal pH monitoring, GERD patients can be classified into two categories: erosive esophagitis (EE) and non-erosive reflux disease (NERD).

Repeated gastric acid exposure to the distal esophagus not only causes mucosal damage but may also lead to severe complications such as esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma. Statistics show that in the United States, medical and non-medical losses due to GERD exceed \$930 million annually. Therefore, GERD has become an important issue both clinically and in national public health policies in recent years.

#### ◆ Disorders of gut-brain axis interaction in esophagus

Disorders of gut-brain axis interaction (DGBI) refer to gastrointestinal diseases that present with symptoms but no organic abnormalities, which were previously referred to as functional gastrointestinal disorders. In the recent Rome IV criteria , <sup>11</sup> In the esophageal context, the Rome IV criteria define five conditions: functional chest pain, reflux hypersensitivity (RH), functional heartburn (FH), globus, and functional dysphagia. Epidemiologically, the prevalence of esophageal disorders related to gut-brain axis interaction is still not well understood. Past population-based

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studies have shown that the prevalence of non-cardiac chest pain is approximately 19-33% , <sup>12,13</sup>

Further generation-based analysis of the population with psychogenic chest pain revealed that approximately 32-35% of them were diagnosed with functional chest pain.<sup>14</sup> In terms of reflux hypersensitivity, among patients with non-erosive mucosal damage in the esophagus, approximately 10-36% are diagnosed with esophageal hypersensitivity.<sup>15,16</sup> Functional heartburn has an unknown prevalence due to the limitations of current diagnostic tools and receiver operating characteristic (ROC) curves. Globus, on the other hand, is a commonly encountered disorder of gut-brain axis interaction in clinical practice. Research reports indicate that 46% of healthy adults have experienced globus at some point.<sup>17</sup> Functional dysphagia is the least common, and its prevalence remains unclear to this day.

In terms of definition, patients must have chronic esophageal symptoms lasting at least three months, with the first occurrence of symptoms being more than six months before the diagnosis of the disease. Additionally, structural, inflammatory, motility, and metabolic abnormalities in the esophagus must be excluded.<sup>1</sup> Therefore, to diagnose esophageal disorders related to gut-brain axis interaction, upper gastrointestinal endoscopy, esophageal pH-impedance testing, and high-resolution esophageal manometry are required to exclude other esophageal diseases that may cause similar symptoms. Regarding the pathophysiological mechanisms, it is currently believed that they may be related to esophageal visceral hypersensitivity and hypervigilance, but the exact mechanisms still require further research for confirmation. In terms of diagnostic criteria, according to the Rome IV criteria, the definition is as follows:<sup>11</sup>

➤ **Functional Chest Pain:**

- (1) Occurs  $\geq 1$  time per week with non-cardiac chest pain or chest tightness;
- (2) No associated heartburn or dysphagia;
- (3) Symptoms are not related to gastroesophageal reflux disease (GERD) or eosinophilic esophagitis;
- (4) No significant esophageal motility disorders.

➤ **Functional Heartburn:**

- (1) Occurs  $\geq 2$  times per week with substernal symptoms such as heartburn or chest pain;
- (2) Symptoms do not improve with antisecretory therapy;
- (3) Symptoms are not related to gastroesophageal reflux disease (GERD) or eosinophilic esophagitis;
- (4) No significant esophageal motility disorders.

➤ **Reflux Hypersensitivity (Esophageal Hypersensitivity):**

- (1) Occurs  $\geq 2$  times per week with substernal symptoms such as heartburn or chest pain;
- (2) Endoscopy is normal, and eosinophilic esophagitis must be excluded;
- (3) No significant esophageal motility disorders;

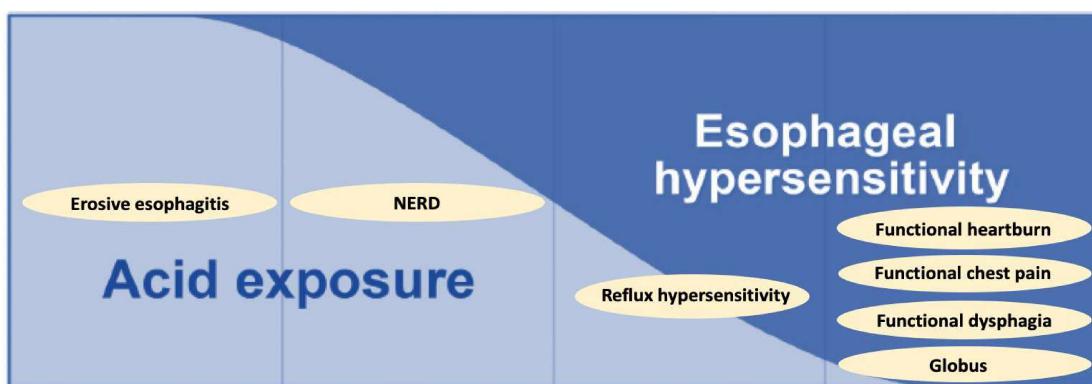
(4) Esophageal pH or pH-impedance testing shows normal acid exposure levels, but reflux is associated with symptoms.

➤ **Globus:**

- (1) Occurs  $\geq 1$  time per week with persistent or intermittent, non-painful sensation of a lump in the throat, with no organic lesions confirmed through clinical examination, laryngoscopy, or endoscopy;
- (2) Symptoms occur between meals, with no dysphagia or odynophagia, and no gastric metaplasia in the proximal esophagus (gastric inlet patch);
- (3) Symptoms are not related to gastroesophageal reflux disease (GERD) or eosinophilic esophagitis;
- (4) No significant esophageal motility disorders.

➤ **Functional Dysphagia:**

- (1) Occurs  $\geq 1$  time per week with a sensation of obstruction or abnormal feeling when solids or liquids pass through the esophagus;
- (2) Symptoms are not related to esophageal mucosal or structural abnormalities;
- (3) Symptoms are not related to gastroesophageal reflux disease (GERD) or eosinophilic esophagitis;
- (4) No significant esophageal motility disorders.



**Figure 1: Diagnostic Spectrum Classification of Gastroesophageal Reflux Disease (GERD) and Disorders of Gut-Brain Axis Interaction (DGBI).**

◆ **Physiological Tests for Diagnosing Gastroesophageal Reflux Disease (GERD) and Disorders of Gut-Brain Axis Interaction (DGBI)**

The current diagnosis of gastroesophageal reflux disease (GERD) spectrum disorders is based on endoscopic examination, esophageal pH (or pH-impedance) testing results, and the association between reflux and symptoms. Among these, esophageal pH testing, specifically the acid exposure time (AET), is the most important pathophysiological parameter used to differentiate GERD from disorders of gut-brain axis interaction (DGBI).<sup>18</sup> The measurement method involves calculating the

percentage of time during a 24-hour monitoring period in which the distal esophageal pH value is less than 4. The Lyon Consensus on the diagnosis of gastroesophageal reflux disease (GERD) states that an acid exposure time (AET) of less than 4% is considered physiological reflux, while an AET greater than 6% is considered pathological reflux. Additionally, if the total number of reflux episodes in 24 hours is less than 40, it is considered normal, while more than 80 episodes is considered abnormal.<sup>8</sup> The combination of parameters such as acid exposure time (AET), number of acid reflux episodes, number of acid reflux episodes lasting more than five minutes, and the longest reflux episode duration can be used to assess the severity of reflux.<sup>19</sup> By combining esophageal pH testing with impedance values, it is possible to detect the direction of reflux, as well as the reflux of weakly acidic, alkaline fluids, or gases.<sup>20</sup> During the detection period, patients are required to record all esophageal symptoms occurring during the esophageal pH-impedance testing. The physician will then compare these recorded symptoms with the reflux events documented by the pH-impedance monitor to calculate the association between reflux and symptoms (Symptom Association Probability, SAP, and Symptom Index, SI).<sup>21</sup>

Based on the above criteria for esophageal pH testing and endoscopic examination results, patients with esophageal reflux symptoms can be classified into erosive esophagitis, non-erosive reflux disease, esophageal hypersensitivity, and functional heartburn. Erosive esophagitis is characterized by visible mucosal damage at the distal esophagus during endoscopy; non-erosive reflux disease is identified by normal mucosa on endoscopy and pathological prolongation of the acid exposure time (AET) at the distal esophagus on esophageal pH testing; esophageal hypersensitivity presents with a normal AET, but the symptoms are associated with reflux events (refluxate may be acidic, weakly acidic, or weakly alkaline) as seen on pH-impedance testing; functional heartburn occurs when there are symptoms of gastroesophageal reflux disease, but both endoscopic examination and AET are normal. For disorders of gut-brain axis interaction, including functional chest pain, globus, and functional dysphagia, in addition to normal endoscopic and AET results, patients must not have significant esophageal motility disorders and must meet the diagnostic criteria related to esophageal symptoms, as well as the onset and duration of symptoms.

Current diagnostic tools, such as questionnaires, proton-pump inhibitor trials, and endoscopic examination, have low sensitivity and specificity for diagnosing gastroesophageal reflux disease (GERD). While esophageal pH (or pH-impedance) testing is considered the gold standard for diagnosing GERD, it can only detect and diagnose reflux events that occur during the test period. Among these, catheter-based esophageal pH testing is limited because it can only detect reflux activity during the 24-hour test period. Additionally, patients may experience discomfort from the catheter, which could lead to changes in their daily activities, thereby potentially affecting the diagnostic results to varying degrees. <sup>22-23</sup> The 96-hour wireless capsule-based esophageal pH monitoring, compared to the 24-hour esophageal pH-impedance testing, not only avoids the

discomfort caused by the catheter but also extends the monitoring period to 96 hours. Previous studies have indicated that up to one-third of patients diagnosed with functional heartburn based on 24-hour esophageal pH-impedance testing had their diagnosis corrected to non-erosive reflux disease after undergoing 96-hour wireless capsule-based esophageal pH monitoring.<sup>24</sup> However, the 24-hour esophageal pH-impedance testing can improve the probability of diagnosing or excluding gastroesophageal reflux disease (GERD) by calculating the mean nocturnal baseline impedance (MNBI). The mean nocturnal baseline impedance is derived by recording the 10-minute average impedance values during the patient's sleep at three one-hour intervals (1:00, 2:00, 3:00). Recent studies have indicated that the mean nocturnal baseline impedance is associated with mucosal integrity, acid exposure time, and reflux symptoms.<sup>25,26</sup>

## ◆The Treatment Dilemma of Refractory Gastroesophageal Reflux Disease and Esophageal Brain-Gut Axis Communication Disorders

Proton pump inhibitors (PPIs) are the primary medications used to treat gastroesophageal reflux disease. Although they are highly effective in improving typical heartburn symptoms in patients with erosive esophagitis,<sup>27-29</sup> However, their effectiveness in treating non-erosive gastroesophageal reflux disease (NERD) is less than ideal. According to statistics, up to 50% of patients treated with proton pump inhibitors (PPIs) for suspected reflux symptoms still experience persistent symptoms.<sup>1,30</sup> Studies have indicated that most gastroesophageal reflux disease (GERD) patients who are unresponsive to proton pump inhibitor (PPI) treatment have a normal acid exposure time (AET).<sup>32</sup> In patients with heartburn who remain unresponsive to high-dose proton pump inhibitor (PPI) treatment, more than 90% are diagnosed with esophageal hypersensitivity or functional heartburn.<sup>31,32</sup> In addition, patients with pathological reflux may also have concurrent esophageal brain-gut axis communication disorders. The complex pathophysiological mechanisms of gastroesophageal reflux disease (GERD) and the limited understanding of brain-gut interaction contribute to the poor treatment outcomes in such patients. Recent consensus suggests that non-reflux factors, such as altered perception or visceral hypersensitivity, may be associated with the refractory symptoms of the esophagus.<sup>33</sup>

## ◆Treatment Strategies for Refractory Gastroesophageal Reflux Disease and Esophageal Brain-Gut Axis Communication Disorders

The treatment strategies for refractory gastroesophageal reflux disease (GERD) and esophageal brain-gut axis communication disorders remain unclear. Currently, it is believed that esophageal hypervigilance, anxiety, and autonomic arousal are the primary factors influencing the severity of symptoms and the response to reflux burden. The Esophageal Hypervigilance and Anxiety Scale

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(EHAS) has been recently validated in studies as an effective tool for assessing esophageal hypersensitivity.<sup>34</sup> Therefore, it is considered a helpful tool in diagnosing esophageal brain-gut axis communication disorders. Neuromodulators are medications used clinically to treat these disorders. Previous research has shown that neuromodulators can effectively reduce symptoms in patients with irritable bowel syndrome (IBS) or functional dyspepsia by modulating visceral hypersensitivity through central and peripheral mechanisms.<sup>35,36</sup> Therefore, using neuromodulators to regulate visceral hypersensitivity and esophageal hypervigilance in esophageal brain-gut axis communication disorders is considered a feasible strategy. However, a systematic review of the literature shows that among the few available randomized controlled trials, the efficacy of neuromodulators in the various subtypes of esophageal brain-gut axis communication disorders is inconsistent.<sup>37</sup> Therefore, whether neuromodulators can be widely used in the treatment of these disorders still requires more supporting evidence.

## **Research Objectives**

The objectives of this study :

**To explore the impact of neuromodulators on disorders related to abnormal communication in the esophageal-brain-gut axis.**

Hypothesis:

- (1) Patients with disorders related to abnormal communication in the esophageal-brain-gut axis experience esophageal symptoms due to visceral hypersensitivity and heightened esophageal sensitivity, which affect their physical and mental health, sleep, and quality of life. Neuromodulators may alleviate symptoms and their associated impacts.
- (2) The effectiveness of neuromodulators may vary among patients with different subtypes of esophageal-brain-gut axis communication disorders.
- (3) The effectiveness of different neuromodulators may vary within the same subtype of esophageal-brain-gut axis communication disorders.

## 8. Research Methods, Procedures, and Execution Progress

1. Please describe in detail the research methods adopted in this project and the reasons for choosing them.
2. Potential challenges and solutions expected during the project.
3. If this is a continuous project, please also attach the progress report from the previous year or primary data.

### Research Method

#### **Participant**

This project is a multi -center study. we will recruit cases from five medical centers in Taiwan, including 210 cases from our hospital and 400 cases from other centers (120 cases each from Chengda Hospital, Kaohsiung Medical University Hospital, and E-Da Hospital, and 40 cases from Chung Shan Medical University Hospital). A total of 610 cases are expected to be recruited.

This study is expected to last for 2 years, with the study period ending on December 31, 2025. We intend to recruit participants with esophageal symptoms related to disorders of the gut-brain axis communication from the Gastroenterology outpatient clinics.

#### **Inclusion criteria for participants :**

1. Age between 18 and 75 years, with clear consciousness and willingness to sign the informed consent form.
2. Participants with chronic esophageal symptoms related to esophageal-brain-gut axis communication disorders (such as heartburn, acid reflux, sensation of a foreign body in the throat, difficulty swallowing, chest pain, and chest tightness).

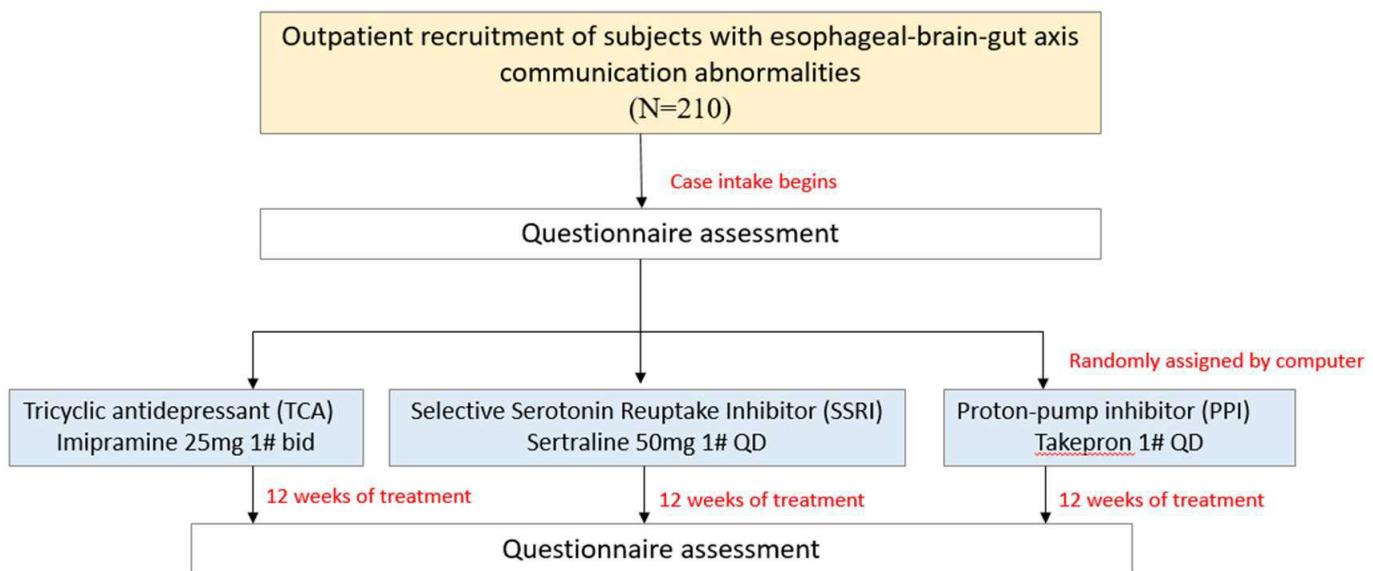
#### **Exclusion criteria for participants :**

1. Esophageal stricture, or a history of esophageal, gastrointestinal, or throat surgery.
2. Structural esophageal diseases (e.g., diverticula, esophageal rings), infectious esophagitis, erosive esophagitis, eosinophilic esophagitis.
3. Non-erosive gastroesophageal reflux disease or significant esophageal motility disorders.
4. A history or current diagnosis of esophageal, gastrointestinal, or other organ malignancies.
5. Significant endocrine or rheumatic autoimmune diseases that may affect gastrointestinal motility.
6. Continuous use of medications that may affect esophageal motility (e.g., anticholinergics, morphine-like drugs, nitrates, calcium channel blockers) within the past month.
7. Use of antidepressants, selective serotonin reuptake inhibitors, or other psychiatric medications within the past three months.
8. Pregnant or breastfeeding women.
9. Individuals with mental disorders or those unable to cooperate.

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10. Known allergy to tricyclic antidepressants.
11. Known allergy to selective serotonin reuptake inhibitors.
12. Known allergy to any component of proton pump inhibitors.

## Research Design Flowchart



## Steps to Follow

In this study, each participant will first complete a questionnaire, which includes the Gastroesophageal Reflux Disease Questionnaire (GERDQ, PROMIS GERD, DSI & GSS, RSI), the Brief Esophageal Dysphagia Questionnaire (BEDQ), the Esophageal Hypervigilance and Anxiety Scale (EHAS), the Visceral Sensitivity Index (VSI), the Sleep and Psychological Well-being Questionnaire (Pittsburgh Sleep Quality Index [PSQI], Taiwan Depression Questionnaire [TDQ], State-Trait Anxiety Inventory [STAI], Functional Dyspepsia [FD] Questionnaire, Irritable Bowel Syndrome [IBS] Questionnaire, and the Quality of Life Questionnaire [SF-12, North East Esophageal Quality of Life Scale, NEQOL]). The time to complete these questionnaires is approximately 20 to 30 minutes.

Afterwards, participants will be randomly assigned using a computer system to receive one of the following treatments for 12 weeks: a neuroregulator, the tricyclic antidepressant (TCA), or the selective serotonin reuptake inhibitor (SSRI), or a 12-week control treatment with a proton pump inhibitor (PPI). We plan to recruit 70 participants for each treatment group: TCA, SSRI, and PPI, with each participant having a 1/3 chance of being assigned to one of these groups.

The tricyclic antidepressant (TCA) will be administered as a 25 mg enteric-coated tablet of Amitriptyline (Ministry of Health and Welfare Drug Registration No. 047966), taken twice daily. The neuroregulator - selective serotonin reuptake inhibitor (SSRI) will be administered as a 50 mg

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enteric-coated tablet of Sertraline (Ministry of Health and Welfare Drug Registration No. 021780), taken once daily. The control medication - proton pump inhibitor (PPI) will be administered as a 30 mg oral dissolving tablet of Pantoprazole (Ministry of Health and Welfare Drug Registration No. 024273), taken once daily.

After the 12-week treatment period, participants will complete the questionnaire again to finalize the study.

### **Multicenter Communication and Coordination Method**

The hospital directors of the participating institutions and the principal investigator, Dr. Lei Wei-Yi, will communicate and coordinate via email and a Line group established for the project. The research data collected by each center will be managed and stored by the respective center's director. The hospital directors will assist in consolidating the research data from their institution, and the electronic data will be coded for identification. After the data is compiled, it will be sent back to the principal investigator. Additionally, the research physicians and staff at each participating center will have regular video conferences (every 2 months) to discuss and report on the progress of the study.

### **Statistical Analysis**

All data will undergo normality testing using the Kolmogorov-Smirnov test. If continuous variables follow a normal distribution, they will be expressed as means and standard deviations; if not, they will be presented as medians and interquartile ranges.

For categorical variables, the Chi-square test or Fisher's exact test will be used for analysis. Continuous variables that are normally distributed will be analyzed using the unpaired t-test, while non-normally distributed continuous variables will be analyzed using the Mann-Whitney U test.

For comparisons involving more than three groups, if the data are normally distributed, an ANOVA with post hoc tests will be conducted. If the data are non-normally distributed, the Kruskal-Wallis test will be applied. A p-value of less than 0.05 will be considered statistically significant.

Statistical analyses will be performed using SPSS 19 for Windows (SPSS, Inc., Chicago, IL, USA).

### **Clinical Significance and Originality of This Study**

The originality of this study lies in its use of visceral sensitivity, mind-body connection, esophageal hypersensitivity, anxiety questionnaires, and functional gastrointestinal questionnaires

to explore the effects of neuromodulators on diseases related to esophageal-brain-gut axis communication abnormalities. Patients with such conditions often experience more severe esophageal symptoms due to excessive visceral sensitivity and esophageal hypersensitivity. We will further compare the therapeutic effects of neuromodulators across different subtypes of esophageal-brain-gut axis communication abnormalities. Additionally, we will investigate the differences in treatment outcomes using various types of neuromodulators for these conditions.

## **9. Expected Work Items and Specific Outcomes**

- (1) Please list the expected tasks to be completed within the execution period.
- (2) Expected contributions to academic research and other applied areas.
- (3) Expected training that participants will receive.

### **1. Work items expected to be completed.**

In this study, we will explore the effects of neuromodulators on diseases related to abnormalities in the esophageal-brain-gut axis communication. We will also compare the efficacy differences between different medications and between different subtypes of esophageal-brain-gut axis communication abnormalities.

### **2. The anticipated contributions to academic research, national development, and other applications.**

- (1) The data obtained from this study will allow us to understand the role of visceral sensitivity and esophageal awareness in esophageal-brain-gut axis communication abnormalities and refractory gastroesophageal reflux disease. It will also help us establish the role of neuromodulators in esophageal-brain-gut axis communication abnormalities and their impact on the regulation of brain-gut axis communication.
- (2) Clinically, patients with esophageal-brain-gut axis communication abnormalities often experience delayed diagnoses and poor treatment outcomes. The results of this study will enable us to intervene early and accurately in such brain-gut axis communication abnormality cases, helping clinical healthcare providers develop precise and effective treatment strategies.

### **3. The expected training for the participating staff.**

In addition to receiving general research training (such as experimental design and execution, questionnaire creation and completion, result analysis and statistics, chart creation, oral presentations, writing papers, and the submission process), participants will also have the opportunity to learn more specialized research design and numerical analysis techniques.

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