Informed Consent Form

蓋本委員會戳章
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Revised Version of the Research Ethics Committee Meeting on November 28, 2023

You are invited to participate in this study. This form provides you with relevant information about the research. The principal investigator or authorized personnel will explain the study to you and answer any questions you may have. Please do not sign this consent form until all your questions have been satisfactorily answered.

You do not have to decide immediately whether to participate. Please take the time you need to carefully consider your decision before signing. You must sign the consent form before participating in this study.

If you agree to take part, this document will serve as a record of your consent. Even after giving your consent, you are free to withdraw from the study at any time without providing any reason.

Project Title：

Esophageal visceral hypersensitivity and hypervigilance in disorders of gut-brain interaction: the roles of cognitive-behavioral therapy

Implementing Institution：Buddhist Tzu Chi Medical Foundation Hualien Tzu Chi Hospital Department of Gastroenterology

Funding Source: Hualien Tzu Chi Hospital

Principal Investigator: Dr. Wei-Yi Lei	Department/Title: Department of Gastroenterology /Attending Physician
Co-Principal Investigator: Dr. Chien-Lin Chen	Department/Title: Department of Gastroenterology /Director
Co-Principal Investigator: Dr. Ming-Wen Weng	Department/Title: Department of Gastroenterology /Attending Physician
Co-Principal Investigator: Dr. Chih-Hsun Yi	Department/Title: Department of Gastroenterology /Attending Physician
Co-Principal Investigator: Dr. Tso-Tsai Liu	Department/Title: Digestive Function Testing Department / Director
Co-Principal Investigator: Dr. Rui-Sheng Hong	Department/Title: Department of Gastroenterology /Attending Physician
Co-Principal Investigator: Dr. Chun-Wei Wang	Department/Title: Attending Physician, Department of Gastroenterology, Kaohsiung Medical University Hospital
Co-Principal Investigator: Dr. Shu-Wei Liang	Department/Title: Attending Physician, Department of Gastroenterology, Chung Shan Medical University Hospital

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Co-Principal Investigator: Dr. Ming-Tsung Hsieh	Department/Title: Attending Physician, Department of Gastroenterology, National Cheng Kung University Hospital
Co-Principal Investigator: Professor Yi-Mei Lin	Department/Title: Professor, Department of Psychology, Kaohsiung Medical University
Co-Principal Investigator: Dietitian Hui-Min Lin	Department/Title: Clinical Nutrition Division, Department of Nutrition / Dietitian
Researcher: Psychotherapist Pei-Yun Lin	Department/Title: Psychotherapist, Yuli Hospital
Researcher: Counseling Psychologist Ssu-Ting Hsu	Department/Title: Counseling Psychologist, Secret Garden Counseling Center
Researcher: Dietitian Chen-Ying Su	Department/Title: Clinical Nutrition Division, Department of Nutrition / Dietitian
※ **24-Hour Project Contact**：Wei-Yi Lei	**Phone**： 0970-339629
Name of Research Participant:	**Date of Birth:**_____Year_____Month_____Day

1.Purpose of the Study：

This trial is a multi-center clinical study conducted in Taiwan, aiming to recruit a total of 120 participants (including 40 from our hospital, 40 from Kaohsiung Medical University Hospital, and 40 from E-Da Hospital). The study is expected to last for two years, with an end date of December 31, 2025. Participants will be recruited from the outpatient clinic of the Department of Gastroenterology and must present with esophageal symptoms related to disorders of gut-brain interaction (DGBI) affecting the esophagus. The purpose of this study is to investigate the effects of cognitive behavioral therapy (CBT) on esophageal disorders of gut-brain interaction.

2.Main Inclusion and Exclusion Criteria of the Study：

Inclusion Criteria (Eligibility for Participation in the Study)：

(1) Aged between 18 and 75 years, conscious, and willing to sign the informed consent form.

(2) Participants with chronic esophageal symptoms associated with esophagogastric dysmotility disorders (such as heartburn, acid reflux, sensation of a foreign body in the throat, difficulty swallowing, and chest pain or discomfort).

Exclusion Criteria (If you have any of the following conditions, you will not be able to participate in this study)：

(1) Esophageal stricture, or a history of esophageal, gastrointestinal, or throat surgery.

(2) Structural esophageal diseases (such as diverticula, esophageal rings, etc.), infectious esophagitis, erosive esophagitis, or eosinophilic esophagitis.
(3) Non-erosive reflux disease or significant esophageal motility disorders.
(4) A history or current diagnosis of malignancy in the esophagus, gastrointestinal tract, or other organs.
(5) Major endocrine or rheumatological/immune diseases that could affect gastrointestinal motility.
(6) Continuous use of medications that may impact esophageal motility (such as anticholinergics, opioids, nitrates, calcium channel blockers, etc.) in the past month.
(7) Use of or current treatment with antidepressants, selective serotonin reuptake inhibitors (SSRIs), or other psychiatric medications within the past three months.
(8) Pregnant or breastfeeding women.
(9) Individuals with mental health disorders or those unable to cooperate.
(10) Known allergy to tricyclic antidepressants.
(11) Known allergy to selective serotonin reuptake inhibitors (SSRI).
(12) Known allergy to any component of proton-pump inhibitors (PPI).

3.Study Procedures and Participant Responsibilities：

Study Procedures

Before receiving treatment, all participants will undergo a questionnaire assessment and heart rate variability (HRV) measurement. The questionnaires include: 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), and assessments related to sleep and psychological well-being, including the Pittsburgh Sleep Quality Index (PSQI), the Taiwanese Depression Questionnaire (TDQ), the State-Trait Anxiety Inventory (STAI), the Illness Cognition Questionnaire (ICQ), and quality of life questionnaires (SF-12, and the Northwestern Esophageal Quality of Life scale, NEQOL). Completing the questionnaires will take approximately 20 to 30 minutes.

Heart rate variability will be measured using a non-invasive device — the “Biofeedback System” by Thought Technology (Department of Health medical device license No. 011374).

Participants will then be randomly assigned in a single-blind manner via computer-generated randomization to either a 6-week course of cognitive behavioral therapy (CBT) guided by a psychologist or a 6-week lifestyle management program (sham control). Each session will be held once a week for approximately one hour.

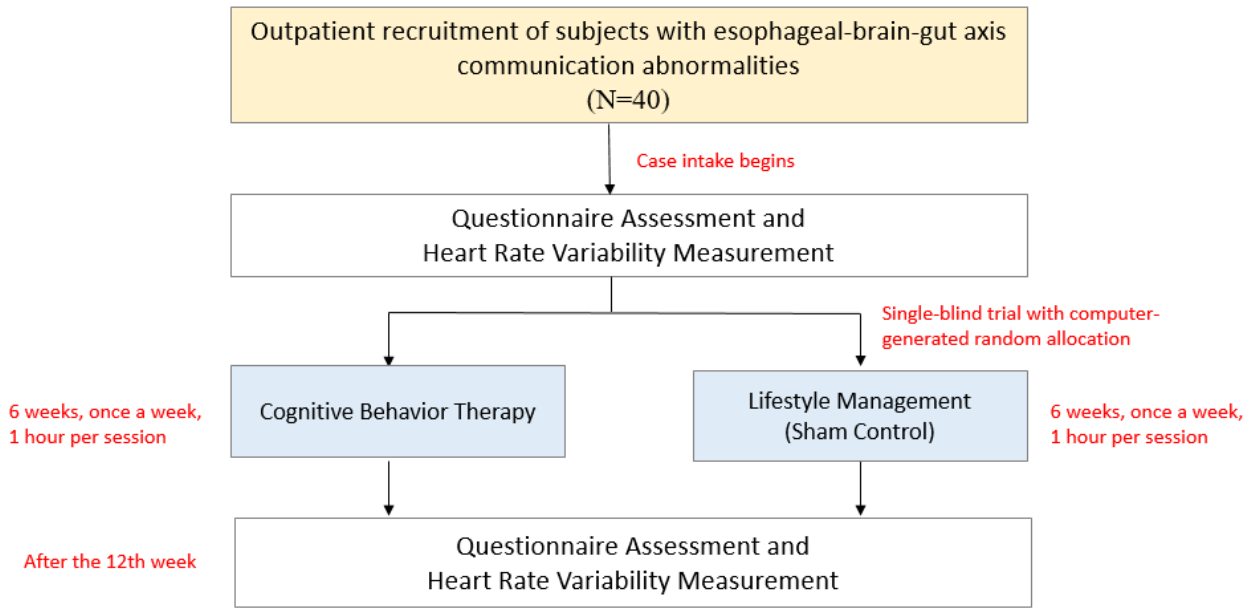
At week 12 from the beginning of participation, a follow-up questionnaire assessment and HRV measurement will be conducted. This will also take approximately 20 to 30 minutes, after which the study will be completed.

In this study, we will use non-invasive physiological signal sensors connected to a biofeedback system to

measure participants' physiological signals, including electrocardiogram (ECG) and respiration. Prior to the measurement, ECG electrodes will be applied to the participant's chest to perform a two-lead ECG, which will then be analyzed to derive heart rate variability (HRV) indices. Simultaneously, a non-invasive respiratory sensor will be used to measure the breathing rate in breaths per minute.

Apart from a very small number of participants who may experience mild skin irritation or discomfort due to the ECG electrodes, the risk of side effects is less than one percent.

Study Flowchart：



4. Expected Benefits of the Study：

This study expects that cognitive behavioral therapy (CBT) will improve symptoms and reduce the impact caused by those symptoms.

5.Rights of the Research Participants：

(1) Compensation for Participation:

You will receive a stipend as compensation for the time spent participating in this study. A total of NT$1,000 will be provided after you sign the consent form and complete the first round of questionnaire assessments.

(2) No Cost to Participants:

There will be no charges or expenses incurred by you for participating in this study.

(3) Disclosure of Relevant Health Information:

Any major findings during the study that may affect your health, disease status, or decision to continue participation will be promptly disclosed to you.

(4) Ethical Review and Approval:
This study has been reviewed and approved by the Research Ethics Committee of Hualien Tzu Chi Hospital. The review includes assessments of potential benefits and risks, protection of participants' rights, and personal data confidentiality. If you have any concerns about your rights as a participant or suspect harm as a result of participating in this study, you may contact the Research Ethics Committee at Hualien Tzu Chi Hospital for consultation. Phone number: 03-8561825 ext. 12124.

(5) Medical Contact:
If you have any questions or concerns during the study period, please feel free to contact Dr. Yu-I Lei from the Department of Gastroenterology. He is available 24 hours a day at: 0970-339629.

(6) This consent form is provided in duplicate. One signed copy has been given to you by the principal investigator or an authorized representative. The nature and purpose of the study have been fully explained to you, and all your questions regarding the study have been answered.

I confirm that I have received a copy of the consent form

Signature:_____ Date:_____Year_____Month_____Day

6.Protection of Personal Data：

We will treat all records that can identify you and your personal information as confidential and will not disclose them publicly. Your identity will be represented by a research code, which will not include identifiable information such as your name, national identification number, or address. All data will be stored using secure information systems and hardware, and kept in a restricted-access research facility. If the results of the study are published, your identity will remain confidential.

By signing this consent form, you also agree that your personal and research data may be accessed by monitors, auditors, the Research Ethics Committee, and regulatory authorities, solely for the purpose of ensuring that the study is conducted in compliance with relevant laws and regulations. These individuals are bound to maintain confidentiality and not disclose your identity. Except for the legally authorized entities mentioned above, we will take every precaution to protect your privacy.

7. Withdrawal of Consent from the Study:

You are free to decide whether or not to participate in this study. You may also withdraw your consent and discontinue participation at any time during the study without providing any reason. Doing so will not result in any unpleasant consequences or affect your legal rights or entitlements in any way.

The principal investigator or the sponsoring institution may also terminate your participation or discontinue the study if deemed necessary.

8. Foreseeable Risks and Remedial Measures：

(1) A very small number of participants may experience mid allergic reactions or discomfort from the ECG electrodes, with the likelihood of such side effects being less than one percent. If any symptoms occur, medical staff will provide appropriate treatment immediately based on the condition.

(2) If the time required for completing questionnaires, participating in cognitive behavioral therapy, or engaging in lifestyle management causes any physical or mental discomfort, participants are encouraged to inform the principal investigator or other research personnel at any time. If a participant wishes to withdraw from the study, their decision will be fully respected.

9. Compensation for Injury (Remedial Measures in Case of Harm)：

(1) If any adverse reactions or harm occur as a result of participating in this study, our hospital is willing to provide necessary assistance.

(2) Aside from the aforementioned assistance, no other forms of compensation will be provided. If you do not wish to accept this level of risk, you should not participate in this study.

(3) Signing this consent form does not mean you waive any legal rights to which you are entitled.

10. Retention Period and Use of Human Specimens or Personal Data (hereafter referred to as "Research Materials")：

The research materials you provide will be stored in the Functional Gastrointestinal Testing Room at Hualien Tzu Chi Hospital until December 31, 2028. After the retention period expires, the materials will be destroyed in accordance with legal requirements.

If you have any concerns regarding the use of your research materials, or if you wish to request their destruction, please contact us immediately (Contact: Dr. Yu-I Lei; Department: Gastroenterology; Phone:

0970-339629).

You may also contact the Research Ethics Committee of Hualien Tzu Chi Hospital (Phone: 03-8561825 ext. 12124) for assistance in resolving any disputes related to the use of research materials in this study.

11.Potential Commercial Interests and Agreements Related to This Study:

This study is not expected to generate any patents or other commercial interests.

12.Agreement Signing Instructions：

(1) **The consent form should be explained to the research participant by the principal investigator or their authorized personnel, who should also address any questions the participant may have regarding the study. Afterward, the investigator or authorized personnel should sign and date the form. The research participant or their representative should then be given time to consider the information before signing the form.**

(2) **Timing for the signature of the legal representative/individual with consent authority/guardian/ assistant：**

* Article 79 of the Medical Care Act / Article 12 of the Human Research Act / Article 5 of the Good Clinical Practice Guidelines for Drug Trials / Article 6 of the Guidelines for Collection of Human Biological Samples for Research / Articles 13 and 15 of the Civil Code：

(1) If the participant is a person with no legal capacity (a minor under seven years of age or a person declared under guardianship), the legal representative shall act on their behalf; for a person declared under guardianship, the guardian shall serve as their legal representative.

(2) If the participant is a person with limited legal capacity (a minor over seven years of age or a person with mental disorders or other cognitive impairments, such that their ability to express or recognize the effect of their expression is significantly impaired, and they have been declared under court-appointed assistance), consent must be obtained from both the individual and their legal representative or assistant.

(3) If the participant is neither a person with no legal capacity nor a person with limited legal capacity, but due to confusion of consciousness or mental and intellectual impairments, they are unable to communicate effectively or make judgments, consent may be given by someone with the authority to do so. The individuals with consent authority include their spouse or cohabiting family members.

(4) When the research subject is a fetus, consent must be obtained from the mother.

(5) The provision of cadaveric specimens should be based on written consent from the participant's closest family member or the individual prior to their death.

(3) **The timing for the witness signature:**

*Good Clinical Practice (GCP) Guidelines, Article 21 / Civil Code, Article 3：

(1) If the participant, legal representative, or person with consent authority is unable to read, a witness must be present to participate in all discussions regarding the participant's consent form. The witness should read the consent form and any other written materials provided to the participant, to witness that the study investigator or their designated personnel has thoroughly explained the contents to the participant, legal representative, or person with consent authority, and ensure that they fully understand all the information.

(2) The participant, legal representative, or person with consent authority must still sign the consent form

personally and include the date. However, a thumbprint may be used in place of a signature.
(3) After the oral explanation has been completed and the witness is certain that the participant, legal representative, or person with consent authority has given their consent freely and voluntarily, the witness must sign the consent form and include the date.
(4) Research personnel cannot serve as a witness.
(5) If a thumbprint, cross, or other symbol is used instead of a signature, the document must be signed by two individuals as witnesses, and this will have the same legal effect as a signature.

(4) Explanation of the signing order for parties with consent rights：

* Article 12 of the Human Research Act: Research subjects are limited to adults with decision-making capacity, excluding fetuses or corpses. However, if the research is clearly beneficial to a specific population group or cannot be replaced by other subjects, this limitation does not apply. When the research subject is an adult under the exceptions mentioned above, consent must be obtained from their relatives in the following order:

1. Spouse.
2. Adult children.
3. Parents.
4. Siblings.
5. Grandparents.

The written consent obtained from the relatives as specified above can be provided by one person. If the relatives' opinions are inconsistent, the order should follow the above sequence. Among individuals in the same sequence, priority is given to the closest relatives by degree of kinship. If the degree of kinship is the same, priority is given to cohabiting relatives, and if there are no cohabiting relatives, priority is given to the eldest.

13.Signature：

(1) The principal investigator, co-investigator(s), or authorized research personnel have thoroughly explained the nature and purpose of the research methods described above in this study, as well as the potential risks and benefits involved.

Person Providing the Explanation of the Consent Form (please check one)：

☐ **Principal Investigator** ☐ **Co-Investigator** ☐ **Research Personnel**

Signature:_____

Date:_____**Year**_____**Month**_____**Day**

(2) **The research participant has thoroughly understood the aforementioned research methods and the potential risks and benefits. Any questions regarding this study have been fully explained by the principal investigator, co-investigator, or research personnel. I voluntarily agree to participate as a subject in this research study.**

Participant's Signature：_____ Contact Number：_____

Date:_____Year_____Month_____Day

*** When the subject of the study meets the criteria outlined in item 2 of the [Consent Form Signing Explanation], this section must be completed with the appropriate signatures.**

(1) Legal Representative / Authorized Consenter / Guardian / Assistant

Signature：_____ Contact Number：_____

Date:_____Year_____Month_____Day

Relationship to the Participant (please circle one):

Spouse, Father, Mother, Son, Daughter, Other：_____

*** When the subject of the study meets the criteria outlined in item 3 of the [Consent Form Signing xplanation], this section must be completed with the appropriate signatures.**

(2) Witness

Witness 1 Signature: _____

Date: _____ Year_____ Month_____ Day

Contact Number：_____

Witness 2 Signature: _____

Date: _____ Year_____ Month_____ Day

Contact Number：_____