Informed Consent Form

February 23, 2021, Hualien Tzu Chi Hospital Research Ethics Committee Meeting Revised Version

You are invited to participate in this study. This form provides you with relevant information about the study. The principal investigator or authorized personnel will explain the study details and answer any questions you may have. Please do not sign this consent form until your questions have been satisfactorily addressed. You are not required to decide immediately whether to participate in this study; please take the time to carefully consider before signing. Your signature is necessary for you to be involved in this research. If you choose to participate, this document will serve as a record of your consent. Even after your agreement, you can withdraw from the study at any time and for any reason.

Research Project Title

Application of diaphragmatic breathing in patients with disorders of gut-brain interaction: impact on gastrointestinal and psychological symptoms as well as autonomic nervous system

Executing agency：Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation

Funding Source：Hualien Tzu Chi Hospital

Research host：Wong,Ming-Wun	Department: Gastroenterology	Phone：(03)8561825 extension 13224
Co-host：Chen,Chien-Lin	Department: Gastroenterology	Phone：(03)8561825 extension 13224
Co-host：Yi,Chih-Hsun	Department: Gastroenterology	Phone：(03)8561825 extension 13224
Co-host：Liu,Tso-Tsai	Department: Gastroenterology	Phone：(03)8561825 extension 13224
Co-host：Lei,Wei-Yi	Department: Gastroenterology	Phone：(03)8561825 extension 13224
Co-host：Hung,Jui-Sheng	Department: Gastroenterology	Phone：(03)8561825 extension 13224
Researchers：Chen,Yan-zhu	Department：Research Department	Phone：(03)8561825 extension 13224
Researchers：Jian,Yu-xuan	Department：Research Department	Phone：(03)8561825 extension 13224

※24-Hour Plan Contact Person：Wong, Ming-Wun　**Telephone**：0982-098812

Group：☐**Healthy subjects** ☐**Laryngopharyngeal reflux disease subject** ☐**Functional dyspepsia subject** ☐**Irritable bowel syndrome subject**

Research Subject's Name：

A. Research Purpose：

The purpose of this study is to investigate the autonomic nervous system responses through standardized autonomic nervous system detection. We aim to explore the effects of diaphragmatic breathing on the autonomic nervous system in both healthy subjects and patients with Disorders of Gut–Brain

Interaction (DGBI). Additionally, we seek to confirm that the introduction of diaphragmatic breathing can improve symptoms in patients with Disorders of Gut–Brain Interaction (DGBI). This study aims to provide a basis for future reference in the treatment of Disorders of Gut–Brain Interaction (DGBI) patients.

B. Inclusion and Exclusion Criteria for the Study：

Inclusion Criteria for Participants：

Inclusion criteria for healthy subjects：

1. Aged between 18 and 70 years old, clear consciousness, and willing to sign the informed consent form for the study.
2. Without any gastrointestinal symptoms or the use of gastrointestinal medications.

Inclusion criteria for Laryngopharyngeal reflux disease subject：

1. Aged between 18 and 70 years old, clear consciousness, and willing to sign the informed consent form for the study.
2. The definition of Laryngopharyngeal Reflux (LPR) is characterized by the presence of symptoms lasting for more than three months, including hoarseness, a sensation of a lump in the throat, chronic cough, and frequent throat clearing. These symptoms occur at least once a week. Diagnosis is confirmed through a standardized LPR assessment questionnaire (Reflux Symptom Index - RSI), which consists of nine reflux-related symptoms. Each symptom is rated on a severity scale from 0 (asymptomatic) to 5 (most severe). If the total score exceeds 13 points, the patient meets the criteria for Laryngopharyngeal Reflux.

Inclusion criteria for Functional dyspepsia subject：

1. Aged between 18 and 70 years old, clear consciousness, and willing to sign the informed consent form for the study.
2. Those who meet the FD definition Functional dyspepsia is characterized by chronic (occurring at least once a week, lasting for a minimum of three months, with the first symptoms manifesting at least six months ago) upper gastrointestinal symptoms (any of the following): postprandial bloating, a tendency to feel full easily, upper abdominal pain or a burning sensation, without symptoms of gastrointestinal bleeding or significant weight loss, and with no abnormalities found upon upper gastrointestinal endoscopic examination.

Inclusion criteria for Irritable bowel syndrome subject：

1. Aged between 18 and 70 years old, clear consciousness, and willing to sign the informed consent form for the study.
2. Those who meet the definition of IBS. Irritable bowel syndrome (IBS) is a chronic condition characterized by lower gastrointestinal symptoms occurring at least once a week and lasting for a minimum of three months. These symptoms include abdominal pain accompanied by either diarrhea

or constipation, without any signs of gastrointestinal bleeding or significant weight loss. Individuals with IBS exhibit no abnormalities upon examination through colonoscopy.

Exclusion Criteria for Participants：

1. Pregnant or lactating women.
2. Infection currently undergoing antibiotic treatment.
3. In the past two months, underwent tracheal intubation.
4. Those with myocardial hypoxia or who have recently experienced a myocardial infarction.
5. Unable to collaborate.

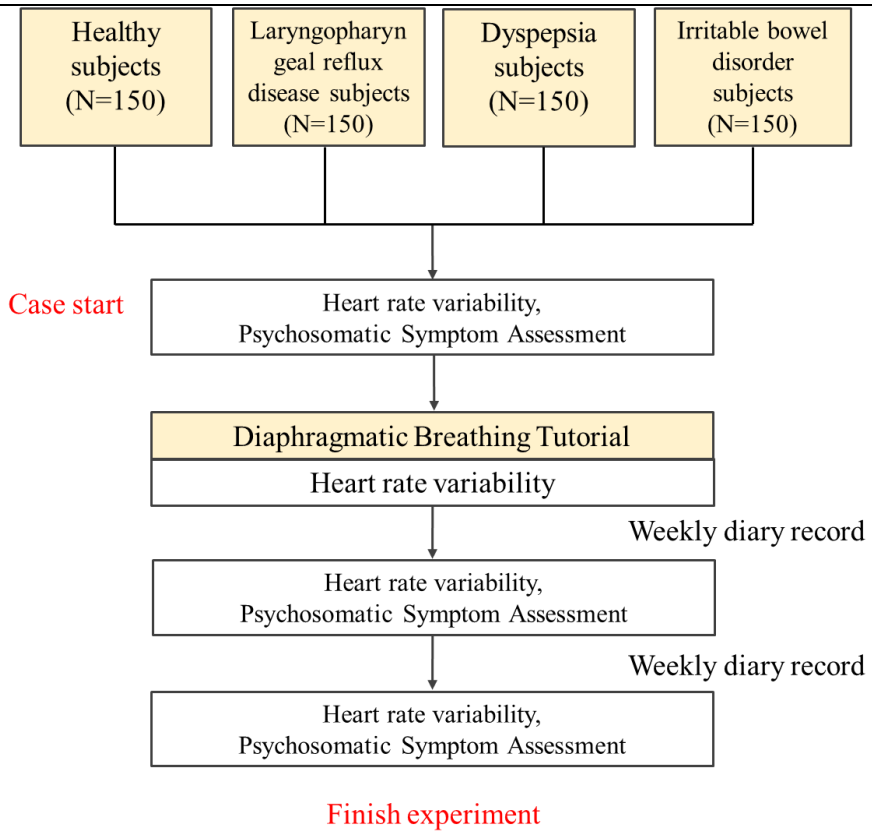
C. Research Procedures and Required Cooperation from Participants：

Research Steps

Participants who meet the inclusion criteria of this study will undergo an initial assessment, including a single Heart Rate Variability (HRV) measurement and a questionnaire on physical and mental symptoms after enrollment. Subsequently, they will participate in a two-week trial, during which they will receive one session of Diaphragmatic Breathing Training guided by the researchers. After the guided training, participants will undergo another HRV measurement. In the first week, they will practice the instructed content twice daily for 5 minutes each time and record a weekly Diaphragmatic Breathing Diary. Following the first week, participants will undergo another HRV measurement and questionnaire assessment. In the second week, they will continue the self-practice with two sessions of instructed content daily, 5 minutes each, and maintain a Diaphragmatic Breathing Diary. After the second week, participants will undergo a final HRV measurement and questionnaire assessment, completing the trial.

Researchers will instruct participants in diaphragmatic breathing training, which takes approximately 15 minutes. Heart rate variability (HRV) assessment will also take about 15 minutes. The questionnaire completion is expected to last around 20 minutes. The non-invasive instrument used for Heart rate variability (HRV) measurement is the "LEADTEK" portable electrocardiogram recorder (Ministry of Health and Welfare Medical Equipment No. 006972). During the test, participants will need to insert their national health insurance card to retrieve personal information (only extracting ID number, gender, and age). If participants have any questions or concerns during the abdominal breathing training process, they can contact the research team.

Research Flowchart



D. Expected Benefits of the Study：

The study anticipates that diaphragmatic breathing can alter the autonomic nervous system response and improve symptoms in patients with Disorders of Gut–Brain Interaction (DGBI).

E. Rights of Research Subjects：

1. **Research Participation Grant：**

   This study aims to compensate you for the transportation and time expenses incurred during your participation. Upon signing the consent form, you will receive a subsidy of 500 NTD. Additionally, upon completion of the experiment, you will receive another subsidy of 500 NTD. In total, you will be compensated with 1,000 NTD.

2. **Participating in this study incurs no cost to you.**
3. In the research process, any significant findings that may be related to your health or illness and could affect your continued participation in the study will be promptly communicated to you.
4. The present study has been reviewed and approved by the Research Ethics Committee at Hualien Tzu Chi Hospital. The review process includes an assessment of research interests and risks, the protection of the rights and interests of research subjects, and the safeguarding of personal data. If you have any concerns or suspicions about your rights as a research participant or believe that you may have suffered harm as a result of participating in the study, you are welcome to contact the Research Ethics Committee at Hualien Tzu Chi Hospital for consultation and assistance. Phone number: 03-8561825, extension 12124.
5. If you have any questions or concerns now or during the research period, please feel free to contact Dr. Wong, Ming-Wun, a gastroenterologist, at any time. (24-hour contact number: 0982-098812).
6. **Two copies of this consent form are provided, and the principal investigator or authorized personnel have handed you one signed copy. They have fully explained the nature and purpose of this research to you, and have answered any relevant questions you may have about the study.**

   ※The research subject has thoroughly understood the research project and has duly received a copy of the informed consent form for signature.

Signature of the Research Subject：_____

Date：_____/_____/_____(YYYY/MM/DD)

F. Personal Data Protection：

We will treat any records containing identifiable information about you and your personal privacy data as confidential and will not disclose them. Researchers will use a research code to represent your identity, and this code will not display your name, national ID number, address, or other identifiable information. The software and hardware storing the data will implement information security measures and will be securely stored in a controlled research environment. If research results are published, your identity will still be kept confidential.

You also understand that by signing the consent form, you agree that your personal information and research data may be directly accessed by monitors, auditors, research ethics committees, and regulatory authorities to ensure compliance with relevant laws and regulations during the research process. The aforementioned personnel pledge not to violate the confidentiality of your identity. In addition to the authorized entities mentioned above, we will diligently safeguard your privacy.

G. Withdrawal of Research Consent：

You are free to decide whether to participate in this study; you can also withdraw your consent and exit the study at any time during the research process, without providing any reasons. In any of these situations, it will not cause any discomfort or affect your legitimate rights and interests. The principal investigator may also suspend or terminate the progress of this study if necessary.

H. Foreseeable Risks and Remedial Measures：

(1) Autonomic Nervous System Stress Test：Basically quite safe, electrode patches are for single use only, repeated use may cause skin allergies or other adverse reactions. If any discomfort occurs, medical personnel will promptly provide appropriate treatment based on the symptoms that arise

(2) If the questionnaire duration becomes excessively lengthy and causes discomfort to the participants, they may inform the research coordinator or other research personnel at any time. If a participant chooses to withdraw from this study, we will respect their decision.

I. Compensation for Damages (Remedies in the Event of Harm)：

(1) If adverse reactions or damages occur as a result of participating in this study, the institution is willing to provide necessary assistance. Apart from the aforementioned assistance, this study does not offer any other form of compensation. If you are unwilling to accept such risks, please do not participate in this research.

(2) Signing this consent form will not cause you to lose any legal rights you may have.

J. Storage Duration and Utilization Planning for Human Specimens or Personal Data (hereinafter referred to as Research Materials)：

The research materials you provided will be stored at the Hualien Tzu Chi Hospital Digestive System Function Testing Room until December 31, 2027. Upon the expiration of the storage period, they will be legally destroyed. If you have any concerns about the use of the research materials or if you wish to request the destruction of the materials, please contact us immediately (Contact Person: Dr. Wong Ming-Wun; Department: Gastroenterology; Phone: 0982-098812). You may also contact the Research Ethics Committee of Hualien Tzu Chi Hospital (Phone: 03-8561825 ext. 12124) to assist you in resolving any disputes

regarding the use of the research materials in your study.

K. Agreements on Potential Commercial Benefits and Applications Arising from this Study：

The study is not expected to result in patent rights or other commercial interests.

L. Instructions for Signing the Consent Form

(1) The consent form should be presented to the research subject by the principal investigator or authorized personnel, who shall explain the research content and address any questions from the research subject. Afterward, the principal investigator or authorized personnel should sign the form and indicate the date. Subsequently, the research subject or their representative may sign the form after due consideration.

(2) Timing of Signature by Legal Representatives/Authorized Persons/Guardians/Assistants：

＊Article 79 of the Medical Care Act/Article 12 of the Human Research Act/Article 5 of the Good Clinical Practice for Drugs/Article 6 of the Guidelines for the Collection of Human Specimens for Research/Article 13 and Article 15 of the Civil Code：

1. Subjects who lack legal capacity (individuals under the age of seven or individuals under guardianship) shall be represented by their legal representatives; for those under guardianship, their guardian shall serve as their legal representative.
2. For subjects with restricted legal capacity (individuals aged seven or above who are not yet adults, or those with mental disorders or other cognitive impairments to the extent that their capacity for expressing intent, understanding the effects of expressing intent, or recognizing the effects of expressing intent is significantly impaired, and who have been subject to court-assisted declaration), consent must be obtained from the individual, their legal representative, or their assistant.
3. Even if the subjects are not lacking or have restricted legal capacity, if they are in a state of confusion or have mental and intellectual impairments that prevent effective communication and judgment, a person with the right to consent shall act on their behalf. Persons with the right to consent include spouses and cohabiting relatives.
4. When the research subject is a fetus, consent must be obtained from the mother.
5. For the provision of cadaver specimens, consent must be obtained from the nearest relatives or the individual's written consent obtained during their lifetime.

(3) Witness Signature Timing：

＊Article 21/Civil Code Article 3 of the Good Clinical Practice Guidelines for Drugs:

1. When the subject, legal representative, or person with consenting authority is unable to read, a witness should be present to participate in all discussions related to the subject's informed consent. The witness should read the subject's informed consent form and any other written materials provided to the subject, witnessing that the principal investigator or designated personnel has accurately explained its contents to the subject, legal representative, or person with consenting authority, and ensured their full understanding of all information.
2. The subject, legal representative, or person with consenting authority should personally sign and date the informed consent form. However, a thumbprint may be used as a substitute for a signature.
3. After completing the oral explanation and ensuring that the consent of the subject, legal representative, or person with consenting authority is entirely voluntary, the witness should sign and date the informed consent form.
4. Personnel involved in the research may not act as witnesses.
5. If a thumbprint, cross, or other symbol is used instead of a signature, with the signatures of two persons to certify on the document, it shall have the same legal effect as a signature.

(4) Instructions on the Signing Order for Authorized Persons：

＊ Article 12 of the Human Research Act: The research subjects shall be limited to adult individuals with decision-making capacity, excluding fetuses or corpses. However, in cases where the research proves beneficial to specific population groups or cannot be replaced by other research subjects, this limitation does not apply. When the research subjects are adults specified in the preceding paragraph, consent shall be obtained in the following order from their relevant persons.：

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

In accordance with the written consent given by the related party in the preceding clause, such written consent may be executed by one person; in the event of inconsistent expressions from related parties, the order shall be determined according to the sequence specified in the preceding clause. Among individuals with the same sequence in the preceding clause, priority shall be given to those with closer blood relations; for individuals with the same blood relation level, priority shall be given to those living together as family members, and in the absence of cohabiting family members, priority shall be given to the elder.

M. Signature

(1) The principal investigator, co-principal investigators, or researchers authorized by them have elaborated extensively on the nature and objectives of the research methods employed in this research project, as well as the potential risks and benefits that may arise.

Interpreter Consent Form (Please check)：☐Research moderator ☐Co-host ☐Researchers

Signature：_____

Date：_____/_____/_____(YYYY/MM/DD)

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

Signature：_____ **Telephone：**_____

Date：_____/_____/_____(YYYY/MM/DD)

＊ When the subject of the case meets the requirements outlined in the 【Instructions for Signing the Consent Form】, Section (2), this field must be signed.

(3) Legal Representative/ Person with Consent Authority/ Guardian/ Supportive Person

Signature：_____ **Telephone：**_____

Date：_____/_____/_____(YYYY/MM/DD)

Relationship with the research subject (please select): Spouse, Father, Mother, Son, Daughter, Other：_____

＊ When the subject of the case meets the criteria specified in 【Instructions for Signing the Consent Form】 Section (3), the signature in this field must be completed.

(4) Witness

Witness 1 Signature：_____ **Telephone：**_____

Date：_____/_____/_____(YYYY/MM/DD)

Witness 2 Signature：_____ **Telephone：**_____

Date：_____/_____/_____(YYYY/MM/DD)