Study Protocol

Effects of a Supported Internet-Based Self-Help Mindfulness Intervention for Emotional Distress on Reflux Symptoms in Patients With Gastroesophageal Reflux Disease: A Multicenter Randomized Controlled Trial

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Abstract

Background: Gastroesophageal reflux disease (GERD) is a common chronic gastrointestinal disorder characterized primarily by heartburn, regurgitation, retrosternal discomfort, and throat-related symptoms. In some patients, GERD may lead to complications such as reflux esophagitis, esophageal stricture, and Barrett esophagus. Previous studies have shown that GERD is not only associated with acid reflux, esophageal mucosal sensitivity, and esophageal motility dysfunction, but is also closely related to anxiety, depression, perceived stress, sleep disturbance, and reduced quality of life. Emotional distress may amplify reflux symptom perception through mechanisms involving the hypothalamic-pituitary-adrenal axis, the autonomic nervous system, visceral hypersensitivity, and symptom catastrophizing. Current treatments mainly include proton pump inhibitors, lifestyle modification, and endoscopic or surgical treatment when clinically indicated; however, these approaches do not directly address psychological distress, maladaptive symptom-related responses, or long-term quality of life. Mindfulness Intervention for Emotional Distress (MIED), which integrates mindfulness training with transdiagnostic emotion-focused intervention principles, may provide a safe, low-cost, and scalable adjunctive approach for patients with GERD.

Objective: This multicenter, randomized, waitlist-controlled trial aims to evaluate the efficacy, safety, acceptability, and potential mechanisms of an internet-based MIED program in patients with GERD. The primary research question is whether MIED plus usual care, compared with waitlist control plus usual care, improves reflux-related quality of life and emotional distress. The study will further examine whether changes in emotional distress, distress tolerance, cognitive flexibility, experiential avoidance, excessive emotional behaviors, and engaging in life mediate intervention effects.

Methods: This protocol was developed in accordance with the SPIRIT reporting guidelines for clinical trial protocols. Approximately 500 eligible patients with GERD will be recruited from 10 to 15 clinical centers, with an expected final sample of approximately 400 participants after attrition. After baseline assessment, participants will be randomly assigned in a 1:1 ratio to the MIED group or the waitlist control group. The MIED group will receive a 49-day online self-guided MIED course in addition to treatment as usual. The waitlist control group will continue to receive treatment as usual and routine health management during the 49-day observation period, and may voluntarily receive the same course after completion of the 2-year follow-up. Assessments will be conducted at baseline, week 3, week 5, week 8, and at 3-, 6-, 12-, and 24-month follow-up. The primary outcome is the change in the Gastroesophageal Reflux Disease-Health Related Quality of Life questionnaire (GERD-HRQL) total score from baseline to week 8. Key secondary outcomes include GerdQ, RSI, OASIS, ODSIS, PHQ-9, GAD-7, SF-8, ISI, CPSS, CD-RISC, SWLS, EQ-5D-5L, TIC-P and adverse events. Mechanistic variables include mindfulness, engaging in life, cognitive flexibility, experiential avoidance, excessive emotional behaviors, and distress tolerance.

Statistical analysis: The primary analyses will follow the intention-to-treat principle to preserve the comparability achieved through randomization and to reduce selection bias. Continuous outcomes will be analyzed using linear mixed-effects models with group, time, and group-by-time interaction as fixed effects and participant as a random effect. Study center, baseline value, and other important covariates will be included as appropriate. The primary efficacy test will focus on the group-by-time interaction and between-group difference at week 8. Missing data will be handled within the maximum likelihood framework, with multiple imputation and sensitivity analyses used to examine robustness. Mediation analyses will be conducted using longitudinal mediation models or structural equation modeling to evaluate the pathways linking MIED, psychological mechanisms, and reflux symptom improvement.

Ethics and dissemination: The study will be conducted after approval by the ethics committees of all participating centers and will be registered in a public clinical trial registry before recruitment. Written or electronic informed consent will be obtained from all participants. Findings will be disseminated through peer-reviewed journals, academic conferences, and clinical training materials.

Keywords: gastroesophageal reflux disease; GERD; mindfulness intervention; MIED; emotional distress; multicenter randomized controlled trial; brain-gut axis; protocol

1. Introduction

1.1 Background

Gastroesophageal reflux disease is a chronic condition caused by the reflux of gastric contents into the esophagus, pharynx, or oral cavity. Typical symptoms include heartburn and regurgitation, whereas atypical manifestations may include chronic cough, hoarseness, globus sensation, chest pain, and sleep disturbance(Katz, 1998; Kellerman & Kintanar, 2017). GERD often follows a recurrent and chronic course, leading not only to physical discomfort but also to impairment in daily functioning and quality of life. If symptoms remain poorly controlled, some patients may develop reflux esophagitis, esophageal stricture, or Barrett esophagus (Kellerman & Kintanar, 2017).

Epidemiological evidence indicates that GERD is highly prevalent worldwide, with considerable geographical variation. Using weekly heartburn or regurgitation as the case definition, the global prevalence of GERD symptoms has been estimated at approximately 13.3% (Eusebi et al., 2018). Previous systematic reviews have suggested that the prevalence of GERD has increased since the 1990s, particularly in North America and East Asia (El-Serag et al., 2014). GERD is also an important public health concern in China. A recent large-scale cross-sectional study of Chinese adults aged 18 to 64 years reported a weighted prevalence of 10.5%, with substantial regional differences and the highest prevalence observed in northwest China (Yang et al., 2024).

From a psychosomatic perspective, GERD cannot be explained solely by acid reflux. A growing body of evidence indicates that GERD symptoms are closely associated with anxiety, depression, stress, sleep disturbance, and reduced quality of life (He et al., 2022). Patients with GERD have an increased risk of anxiety and depression, and individuals with anxiety, depression, or chronic stress may also have a higher likelihood of developing persistent reflux symptoms. A systematic review and meta-analysis reported a bidirectional association between GERD and

psychosocial disorders: patients with GERD were more likely to experience anxiety and depressive symptoms, and individuals with psychosocial distress were more likely to develop GERD symptoms (He et al., 2022). Mendelian randomization findings further suggest a potential causal relationship between GERD and subsequent risk of anxiety disorders and depression (Zeng et al., 2023).

This mind-body interaction may occur through multiple pathways. Psychological stress can activate the hypothalamic-pituitary-adrenal axis and the autonomic nervous system, thereby affecting acid secretion, esophageal motility, gastric emptying, and visceral sensitivity (He et al., 2022). Chronic anxiety or stress may also heighten vigilance toward reflux-related bodily sensations and maintain symptom-related distress through catastrophizing, repeated checking, repeated medical consultations, and excessive avoidance of foods or activities (Hetterich & Stengel, 2020). Conversely, persistent heartburn, regurgitation, nocturnal discomfort, and fear of serious illness may exacerbate anxiety, depression, and insomnia, forming a vicious cycle of reflux symptoms, psychological distress, symptom amplification, and functional impairment. Therefore, comprehensive management of GERD should not only control acid reflux and promote lifestyle modification, but also address patients' cognitive, emotional, and behavioral responses to symptoms.

1.2 Mindfulness-Based Interventions and Gastrointestinal Disorders

In recent years, psychological and behavioral interventions have increasingly been incorporated into the management of functional and chronic gastrointestinal disorders. Mindfulness-based interventions are psychological training approaches centered on present-moment awareness, nonjudgmental acceptance, and mind-body self-regulation. They include mindfulness-based stress reduction, mindfulness-based cognitive therapy, and related approaches (Kabat-Zinn, 1982; Segal, 2002). By helping individuals observe bodily sensations, emotions, and thoughts without immediately engaging in avoidance, control, or catastrophizing, mindfulness training may improve coping with chronic symptoms (Hetterich & Stengel, 2020).

Mindfulness-based interventions have demonstrated promising effects in functional gastrointestinal disorders that are strongly influenced by psychological factors, such as irritable bowel syndrome. Randomized controlled trials have shown that 8-week mindfulness training can significantly reduce gastrointestinal symptom severity and improve emotional status and quality of life (Gaylord et al., 2011). Meta-analytic evidence in inflammatory bowel disease also suggests that mindfulness training can reduce anxiety and depression and improve quality of life (Qian & Zhang, 2024). Although evidence regarding mindfulness interventions for GERD remains limited, preliminary studies suggest that mindfulness training may improve depressive symptoms, perceived stress, and health-related quality of life in patients with GERD (Chandran et al., 2019; Oraki & Asadpour, 2021).

Nevertheless, previous studies of mindfulness interventions for GERD have several limitations. First, most studies had small sample sizes, limiting statistical power and the stability of effect estimates (Chandran et al., 2019; Oraki & Asadpour, 2021). Second, most were conducted at a single center, limiting external validity and generalizability across regions and health care settings. Third, most studies used standard mindfulness programs and rarely adapted the intervention to GERD-specific symptom characteristics and emotional-behavioral mechanisms (Chandran et al., 2019). Fourth, the feasibility, adherence, and cost-effectiveness of internet-based mindfulness interventions for

GERD have not been sufficiently examined. Fifth, few studies have simultaneously assessed mechanistic variables such as emotional distress, cognitive flexibility, distress tolerance, experiential avoidance, excessive emotional behaviors, and engaging in life.

1.3 Theoretical Basis of MIED

Mindfulness Intervention for Emotional Distress (MIED) is a structured psychological intervention program developed by integrating the core principles and techniques of Mindfulness-Based Stress Reduction (MBSR) and the Unified Protocol (UP) for the transdiagnostic treatment of emotional disorders. Transdiagnostic approaches propose that anxiety and depressive disorders share common mechanisms, including emotional avoidance, negative emotional reactivity, cognitive rigidity, and maladaptive emotion-driven behaviors (Barlow, 2011; Southward & Sauer-Zavala, 2022). Mindfulness training emphasizes open, accepting, and nonjudgmental awareness of present-moment experience, thereby reducing automatic reactions and experiential avoidance (Hayes et al., 2011; Kabat-Zinn, 1982).

MIED targets four core strategies: increasing engaging in life, adjusting distress tolerance, reducing excessive emotional behaviors, and improving cognitive flexibility. Increasing engaging in life helps individuals redirect attention toward valued and meaningful life activities. Adjusting distress tolerance helps individuals reduce immediate escape or control responses when uncomfortable experiences arise. Reducing excessive emotional behaviors targets repeated checking, repeated medical consultation, excessive avoidance, reassurance seeking, and other safety behaviors. Improving cognitive flexibility helps individuals relate to thoughts as thoughts and reduce catastrophizing, dichotomous thinking, and overgeneralization (Barlow, 2011; Hayes et al., 2011; Liu, 2024; Southward & Sauer-Zavala, 2022).

Patients with GERD often experience persistent worry due to recurrent heartburn, regurgitation, chest discomfort, or throat symptoms. Some patients may interpret transient reflux sensations as signs of serious illness, leading to frequent medical consultations, repeated examinations, excessive monitoring of diet, avoidance of social or physical activities, and reduced engaging in life. These responses may reduce anxiety in the short term but can reinforce symptom vigilance and fear over time, thereby magnifying the impact of reflux on daily life (He et al., 2022; Hetterich & Stengel, 2020). MIED is not intended to replace standard gastroenterological care; rather, it is an adjunctive intervention designed to change patients' responses to reflux symptoms, anxiety, and bodily discomfort, reduce emotional distress and symptom amplification, and ultimately improve quality of life and disease management.

1.4 Significance of the Study

This study has several important implications. First, by using a multicenter, large-sample randomized controlled design, the study will enhance statistical power and external validity and provide more robust evidence regarding the application of MIED in patients with GERD. Second, GERD will be conceptualized within a biopsychosocial framework, with attention not only to reflux symptoms but also to emotional distress, sleep, quality of life, health care resource use, and cost-effectiveness. Third, the MIED program will be adapted to GERD-specific safety considerations, including avoiding formal practice within 2 hours after meals, replacing supine body scan exercises

with seated practices, and limiting the duration of practice. Fourth, the intervention will be delivered online, which may overcome geographical barriers and improve accessibility. Previous meta-analyses have shown that internet-based mindfulness interventions have small to moderate effects on anxiety, depression, and stress, supporting their potential for digital dissemination (Sevilla-Llewellyn-Jones et al., 2018; Sommers-Spijkerman et al., 2021; Spijkerman et al., 2016). Fifth, the inclusion of long-term follow-up and mechanistic measures will help clarify the psychological pathways through which MIED may improve symptoms and quality of life in patients with GERD.

2. Objectives and Hypotheses

2.1 Primary Objective

The primary objective is to evaluate whether a 49-day internet-based MIED program plus usual care improves reflux-related quality of life at the end of treatment compared with usual care plus waitlist control.

2.2 Secondary Objectives

1) To evaluate the effects of MIED on GERD symptom severity, laryngopharyngeal reflux symptoms, anxiety, depression, insomnia, perceived stress, resilience, life satisfaction, and general health-related quality of life.
2) To evaluate adherence, acceptability, safety, and adverse events associated with internet-based MIED in patients with GERD.
3) To evaluate whether MIED reduces health care resource use and disease-related costs and improves health utility and quality-adjusted life years.
4) To explore whether emotional distress, distress tolerance, cognitive flexibility, experiential avoidance, excessive emotional behaviors, and engaging in life mediate intervention effects.
5) To explore whether baseline emotional distress, symptom severity, disease duration, body mass index, medication use, sleep quality, and center effects moderate treatment outcomes.

2.3 Hypotheses

1) H1: Compared with the waitlist control group, the MIED group will show a greater reduction in GERD-HRQL total score at week 8.
2) H2: Compared with the waitlist control group, the MIED group will show greater reductions in GERD-Q, RSI, OASIS, ODSIS, PHQ-9, GAD-7, ISI, and CPSS scores at week 8, as well as greater improvements in SF-8, CD-RISC, SWLS, and EQ-5D-5L-related indicators.
3) H3: The effects of MIED will be at least partially maintained at 3-, 6-, 12-, and 24-month follow-up.
4) H4: Reductions in emotional distress, improvements in distress tolerance and cognitive flexibility, reductions in experiential avoidance and excessive emotional behaviors, and increases in engaging in life will mediate the relationship between MIED and improvement in GERD symptoms.
5) H5: Internet-based MIED will be safe, acceptable, and feasible, and the incidence of serious adverse events will not be higher than that in the waitlist control group.

3. Study Design

3.1 Trial Design

This study is a multicenter, parallel-group, randomized, waitlist-controlled clinical trial with blinded outcome assessment. The protocol follows the SPIRIT guidelines to enhance transparency, completeness, and reproducibility(Hróbjartsson et al., 2025). Eligible patients with GERD will be randomly assigned in a 1:1 ratio to the MIED group or the waitlist control group after baseline assessment. The MIED group will receive a 49-day online self-guided MIED course in addition to treatment as usual. The waitlist control group will continue to receive treatment as usual and routine health management during the 49-day observation period, and may voluntarily receive the same course after completion of the 2-year follow-up.

Assessments will be conducted at baseline, week 3, week 5, week 8, and 3, 6, 12, and 24 months after baseline. The primary endpoint is week 8. Long-term follow-up will be used to evaluate maintenance of intervention effects, health care resource use, and cost-effectiveness.

3.2 Study Setting

The study will be conducted across 10 to 15 clinical centers in Nanjing, Beijing, and other regions. Each participating center will be responsible for recruitment, screening, informed consent, and medical safety evaluation. The coordinating center will be responsible for outcome assessment and follow-up management. The MIED self-help program will be delivered through a WeChat mini-program platform. Trained assistants from the MIED teaching system will provide reminders and answer procedural questions. The main coordinating center will oversee randomization, data management, quality control, intervention fidelity, and statistical analysis.

3.3 Trial Procedures

The study will include six stages. In the first stage, potential participants will be recruited through gastroenterology outpatient clinics, inpatient departments, health management platforms, hospital public accounts, and physician referrals. In the second stage, eligible candidates will complete informed consent, baseline measurements including GERD-Q, GERD-HRQL, RSI, and emotional distress measures, and medical safety screening. In the third stage, participants will be randomized by center to the MIED group or the waitlist control group. In the fourth stage, participants will enter the 49-day intervention or observation period; the MIED group will complete online self-help courses and home practice, whereas the waitlist control group will continue usual care and health management. In the fifth stage, postintervention assessment and long-term follow-up will be completed at week 8 and at 3, 6, 12, and 24 months. In the final stage, data will be locked, analyzed, and disseminated. The final trial report will follow the CONSORT statement to ensure transparent and complete reporting (Sally Hopewell et al., 2025; Schulz et al., 2010).

4. Participants

4.1 Inclusion Criteria

Participants must meet all of the following criteria:

1) Aged 18 to 65 years.
2) GERD-Q score of 8 or higher.

3) Willingness to maintain a relatively stable usual treatment regimen during the study unless medically indicated changes are required.
4) Ability to use a smartphone, computer, or tablet to participate in the online program and complete online questionnaires.
5) Willingness to comply with course training and follow-up assessments.
6) Ability to understand the study and provide written or electronic informed consent.

4.2 Exclusion Criteria

Participants meeting any of the following criteria will be excluded:

1) Alarm symptoms or high suspicion of serious organic disease, including but not limited to progressive dysphagia, hematemesis, melena, unexplained weight loss, anemia, recurrent vomiting, or persistent chest pain without exclusion of cardiovascular risk.
2) Current or previous severe esophageal organic disease or gastrointestinal malignancy.
3) History of anti-reflux surgery, partial gastrectomy, or other upper gastrointestinal surgery that may substantially affect reflux symptom assessment.
4) GERD-Q score greater than 15, or symptoms judged by the study physician to be extremely severe and requiring priority medical evaluation or intensified treatment.
5) Current uncontrolled severe mental disorder, such as schizophrenia, manic episode of bipolar disorder, acute severe depressive episode, or severe substance use disorder.
6) Current suicide risk, operationalized as a score greater than 1 on item 9 of the PHQ-9.
7) Previous systematic participation in MIED, mindfulness-based stress reduction, mindfulness-based cognitive therapy, or another structured mindfulness program.

4.3 Criteria for Temporary Discontinuation and Referral During the Intervention

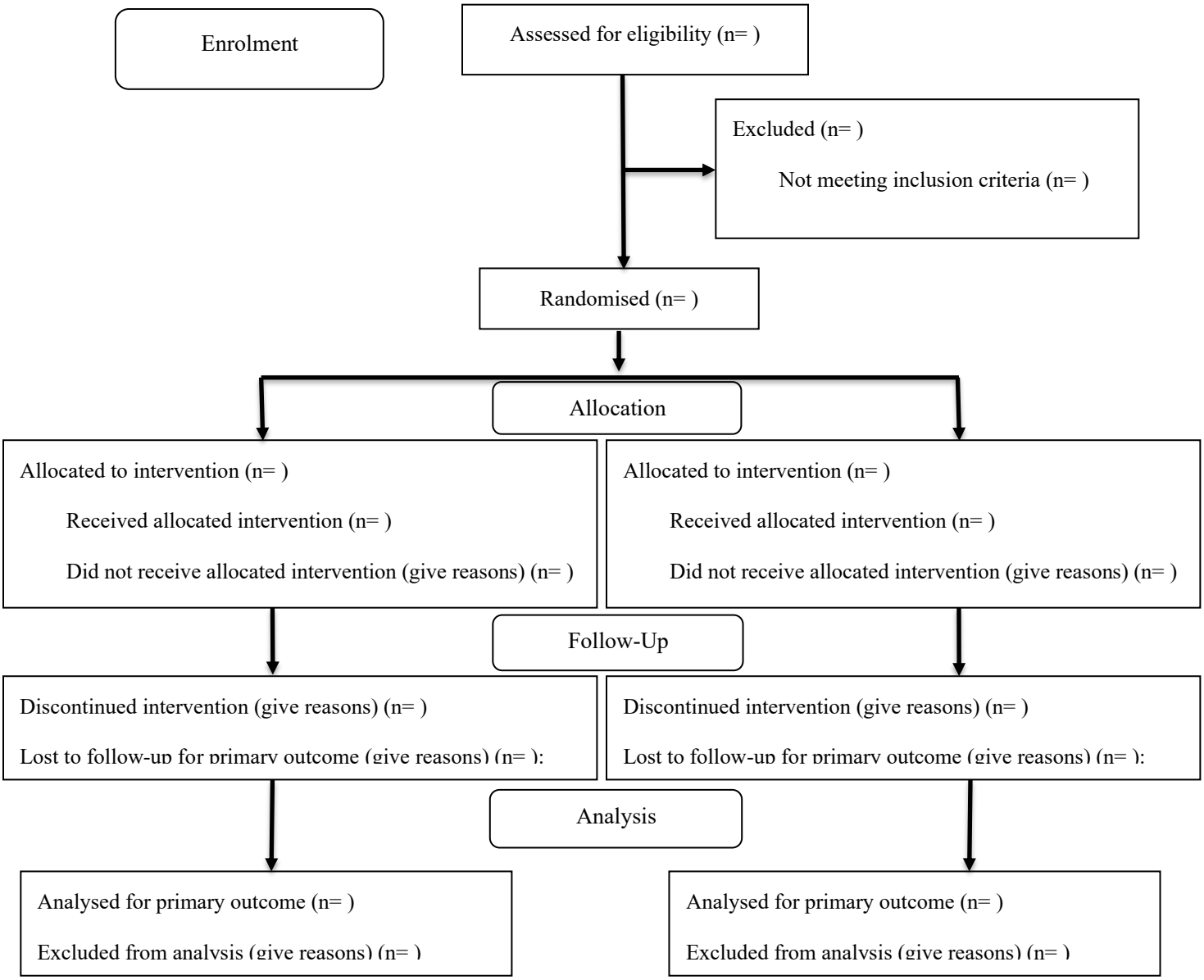
If any of the following conditions occur during the study, the intervention will be temporarily suspended and the participant will be referred to gastroenterology or another relevant specialty for further evaluation:

1) An increase in GERD-Q score of 4 points or more from baseline that persists.
2) New-onset dysphagia, odynophagia, hematemesis, melena, marked weight loss, or other alarm symptoms.
3) A psychological crisis, including suicidal ideation, self-harm behavior, or severe emotional deterioration.
4) Any condition judged by the study physician or intervention staff to pose a safety risk if participation continues.

Temporary suspension does not necessarily mean withdrawal from the study. If medical evaluation confirms that it is safe to continue, participants may resume follow-up or continue the course according to recommendations from the research team and treating clinicians.

Figure 1: CONSORT 2025 Flow Diagram(S. Hopewell et al., 2025)

Flow diagram of the progress through the phases of a randomised trial of two groups (that is, enrolment, intervention allocation, follow-up, and data analysis)



5. Randomization, Allocation Concealment, and Blinding

5.1 Randomization

After completing baseline assessment and confirming eligibility, participants will be randomly assigned in a 1:1 ratio to the MIED group or the waitlist control group. The randomization sequence will be generated by an independent statistician using computer-generated block randomization stratified by study center to reduce center-related imbalance. Randomization and allocation concealment are essential for reducing selection bias and maintaining the internal validity of clinical trials (Sally Hopewell et al., 2025; Schulz et al., 2010; Schulz & Grimes, 2002).

5.2 Allocation Concealment

Allocation will be implemented through a central randomization system or a randomization list maintained by an independent data manager. Recruitment staff and baseline assessors will not know the allocation before enrollment and baseline assessment are completed. Group allocation will be communicated to participants and intervention coordinators only after baseline assessment.

5.3 Blinding

Because of the nature of psychological and behavioral interventions, participants and intervention staff cannot be blinded. However, outcome assessors, data managers, and statistical analysts will be blinded whenever possible. Group allocation will be coded during statistical analysis, and unblinding will occur only after completion of the primary analyses. Participants will be reminded not to disclose their group allocation to outcome assessors during follow-up. In psychological intervention trials where full double-blinding is not feasible, blinded outcome assessment and blinded statistical analysis are important strategies for reducing measurement bias (Schulz et al., 2010).

6. Interventions

6.1 MIED Group

Internet-based Mindfulness Intervention for Emotional Distress (MIED) was developed from Mindfulness Intervention for Emotional Distress, an evidence-based intervention developed by Liu Xinghua and colleagues for individuals with emotional distress. Previous short-term studies have suggested that this approach may improve emotional distress and accelerate symptom improvement in emotional disorders (He et al., 2024; Ju et al., 2022; Li et al., 2024; Li et al., 2025; Wang et al., 2024).

The intervention is delivered via the internet and is grounded in the psychopathological diamond model of emotional distress proposed by Liu and colleagues (Liu, 2024). The program is supported by a MIED knowledge base, the Mindfulness Study public account, supervision and question-answer records, and official materials from Liu Xinghua and the MIED team. These resources are integrated into a WeChat self-help mini-program and the MIED Mindfulness Assistant, an artificial intelligence-supported system developed using large language models such as Tencent Hunyuan and DeepSeek R1. Together, these tools support participants' learning and practice over a continuous 49-day training period (Liu, 2024).

MIED is based on a biopsychosocial framework and uses the psychopathological diamond model as its core intervention framework. The model proposes that emotional distress is generated and maintained through four key psychological processes: insufficient engaging in life, low distress tolerance, excessive emotional behaviors, and insufficient cognitive flexibility. Correspondingly, MIED uses four intervention strategies: increasing engaging in life, adjusting distress tolerance, regulating excessive emotional behaviors, and enhancing cognitive flexibility. These strategies aim to promote improvement in emotional distress (Liu, 2024) (Figure 2).

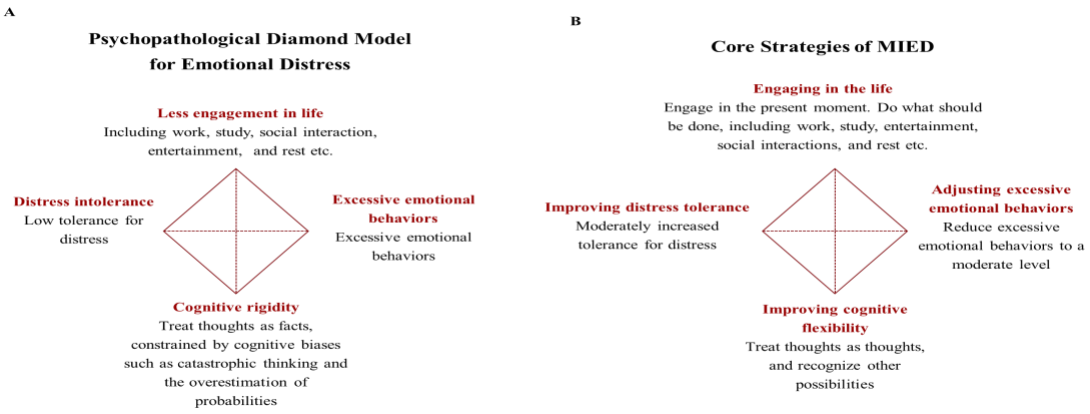


Figure 2. Psychopathological Model and Intervention Strategies of MIED (Liu, 2024)

In practice, MIED lasts 49 days, with approximately 30 minutes of learning and practice each day. Each daily session includes approximately 15 minutes of psychoeducational video and supporting text materials, followed by approximately 15 minutes of guided mindfulness audio practice. After each session, participants record their practice experiences and reflections in the mini-program using a structured check-in template. The AI-supported MIED Assistant can respond in real time to participants' questions during practice and provide necessary explanations and guidance to help participants understand and complete the exercises. The detailed 49-day check-in content is provided in Appendix 1.

MIED has substantial potential for clinical application. Its intervention period is relatively short, typically 49 days, and it may produce relatively rapid effects. The four-dimensional pathological mechanism derived from the biopsychosocial model corresponds directly to four intervention strategies, making the intervention targets clear and closely linking etiological mechanisms with operational methods. This structure may support more precise intervention and reduce risk of relapse.

6.2 GERD-Specific Safety Adaptations

To reduce reflux discomfort and practice-related risk, the MIED self-help course will be adapted for patients with GERD. Formal practice will not be conducted within 2 hours after meals. Supine body scan exercises will be replaced by seated or standing body awareness practices. Prolonged abdominal compression, deep forward bending, or positions that may trigger reflux will be avoided. The duration of each practice will be limited, and participants will be encouraged to pause practice, sit upright, drink water, or use other self-care strategies when significant reflux discomfort occurs. Participants will be clearly informed that MIED is an adjunctive intervention and does not replace gastroenterological evaluation or necessary pharmacological treatment. If alarm symptoms or marked symptom worsening occur, practice should be stopped immediately and the study physician contacted. These adaptations are based on GERD symptom management and clinical safety considerations and are consistent with the principles of adapting psychological and behavioral interventions for chronic somatic conditions (Kellerman & Kintanar, 2017) (Chan et al., 2013).

6.3 Waitlist Control Group

Participants in the waitlist control group will continue usual GERD treatment and health management during the 49-day observation period. They will not receive MIED, mindfulness training, or other structured psychological interventions during this period. Usual care may include medication, lifestyle advice, and necessary follow-up as determined by clinicians. The waitlist control group will complete assessments at the same time points as the MIED group. After the 2-year follow-up, participants in the waitlist control group who wish to receive the program will be offered the same MIED course. Waitlist control designs are commonly used in psychological intervention research and allow the incremental effects of an intervention to be evaluated against natural course and usual care while maintaining ethical acceptability (Mohr et al., 2009).

6.4 Concomitant Interventions and Restrictions

Participants in both groups may continue necessary usual medical care. Unless medically indicated, participants will be asked to maintain stable medication types and dosages during the study, and all medication changes will be recorded. Participants will be discouraged from newly participating in other structured psychotherapy, mindfulness courses, or interventions that may substantially influence study outcomes. If such changes occur, they will be recorded and addressed as covariates or in sensitivity analyses. Recording and controlling concomitant interventions are important for clinical trial protocol reporting and interpretation (Chan et al., 2013; Hróbjartsson et al., 2025).

6.5 Intervention Fidelity

This study uses a supported internet-based self-help MIED intervention delivered through a uniformly developed WeChat mini-program. All participants will complete the 49-day intervention using the same course structure, learning materials, guided audio practices, and assignment procedures. Therefore, the core intervention content and mode of delivery will be consistent across centers. The mini-program will automatically record course progress, practice completion, assignment submission, and login frequency, which will be used to assess intervention dose, adherence, and course completion.

To ensure consistency in intervention support, the study will include assistants trained within the MIED system. Assistants will not individualize or modify the core course content and will not provide additional psychotherapy. Their role will be to remind participants to complete learning tasks, answer technical questions about mini-program use, provide feedback on assignment completion, identify obvious discomfort or risk signals, and report or refer such signals according to standardized procedures. Before the study begins, all assistants will receive unified training covering the MIED framework, GERD-specific safety considerations, online support norms, risk identification, and crisis management procedures. The research team will regularly review mini-program backend data and assistant work records to evaluate implementation and the standardization of the support process. Through standardized mini-program content, unified assistant training, and backend data monitoring, this study will maximize intervention consistency and reproducibility across centers. Intervention fidelity control helps improve the internal validity and interpretability of behavioral intervention research (Bellg et al., 2004).

7. Outcomes and Measurement Instruments

7.1 Primary Outcome

The primary outcome is the change in the Gastroesophageal Reflux Disease-Health Related Quality of Life questionnaire (GERD-HRQL) total score from baseline to the end of treatment at week 8. GERD-HRQL is a disease-specific instrument designed to assess GERD symptom severity and its impact on quality of life. It covers heartburn, regurgitation, swallowing-related discomfort, satisfaction with medication use, and overall satisfaction with the current symptom state. Higher scores indicate greater reflux-related symptom burden and poorer quality of life; a decrease in score indicates improvement.

GERD-HRQL was originally developed by Velanovich and colleagues to evaluate symptom changes and health-related quality of life before and after GERD treatment. Previous studies have shown that GERD-HRQL has good face validity, content validity, construct validity, criterion validity, and responsiveness. It can distinguish patients who are satisfied from those who are dissatisfied with their current symptoms and can reflect improvement after pharmacological, endoscopic, or surgical treatment (Velanovich, 2007; Velanovich, 2023). Therefore, GERD-HRQL is suitable as the primary outcome for evaluating changes in reflux-related quality of life after MIED.

GERD-HRQL was selected as the primary outcome because the purpose of this supported internet-based self-help mindfulness intervention for emotional distress is not merely to reduce anxiety, depression, or stress. Rather, the intervention aims to improve patients' responses to reflux symptoms, bodily discomfort, and negative emotions, thereby improving reflux-related quality of life. Compared with a symptom-screening instrument alone, GERD-HRQL provides a clinically interpretable assessment of symptom severity, the impact of symptoms on daily life, and patients' subjective evaluation of treatment status (Velanovich, 2007; Velanovich, 2023).

7.2 Key Secondary Outcomes

The Gastroesophageal Reflux Disease Questionnaire (GERD-Q/GerdQ) will be used to assess the frequency and severity of GERD symptoms and will serve as a key secondary outcome for reflux symptom change. GERD-Q includes six items covering heartburn, regurgitation, epigastric pain, nausea, sleep disturbance, and use of additional medication. Jones et al. developed this tool using data from more than 300 primary care patients and reported good discriminative ability for GERD diagnosis, with a sensitivity of approximately 65% and specificity of approximately 71%, comparable to diagnosis by gastroenterologists (Jones et al., 2009). Subsequent studies have supported the acceptable reliability and validity of GERD-Q across countries and clinical samples, indicating that it can be used for GERD screening, symptom monitoring, and treatment evaluation (Jonasson et al., 2013; Zavala-Gonzales et al., 2014).

The Reflux Symptom Index (RSI) will be used to evaluate laryngopharyngeal reflux and atypical reflux-related symptoms. RSI is a 9-item patient-reported scale assessing hoarseness, throat clearing, excess throat mucus or postnasal drip, swallowing difficulty, coughing after eating or lying down, breathing difficulty or choking episodes, troublesome cough, globus sensation, and heartburn, chest pain, acid reflux, or regurgitation. Each item is scored from 0 to 5, yielding a total score from 0 to 45; higher scores indicate more severe laryngopharyngeal reflux-related symptoms. Belafsky et al. first validated the reliability and validity of RSI and showed that it is responsive to symptom changes after treatment. A score greater than 13 is commonly used as a reference threshold for abnormal laryngopharyngeal reflux symptoms (Belafsky et al., 2002). In this study, RSI will complement GERD-Q and GERD-

HRQL by evaluating whether MIED improves atypical reflux symptoms such as chronic cough, hoarseness, throat clearing, and globus sensation.

The Overall Anxiety Severity and Impairment Scale (OASIS) will be used to assess overall anxiety severity and related functional impairment. OASIS includes five items measuring anxiety frequency, anxiety intensity, avoidance, impairment in work, school, or family functioning, and impairment in social functioning. It is not limited to a specific anxiety disorder and is suitable for transdiagnostic assessment of anxiety disorders, comorbid anxiety, and subclinical anxiety symptoms. The original study by Norman et al. showed good test-retest reliability, convergent validity, and discriminant validity (Norman et al., 2011). Subsequent clinical studies further supported its internal consistency, structural validity, and clinical sensitivity (Campbell-Sills et al., 2009; Norman et al., 2011). In this study, OASIS will assess changes in anxiety-related distress among patients with GERD.

The Overall Depression Severity and Impairment Scale (ODSIS) will be used to assess overall depressive symptom severity and related functional impairment. ODSIS includes five items measuring frequency and intensity of depressed mood, loss of interest, impairment in work, school, or family functioning, and impairment in social functioning. Its structure is similar to OASIS, making it suitable for transdiagnostic emotional disorder research and brief repeated follow-up. Bentley et al. developed and validated ODSIS and reported good internal consistency, convergent validity, discriminant validity, and clinical sensitivity (Bentley et al., 2014). Validation studies in different languages and clinical samples also support its reliability and validity as a brief measure of depression severity and impairment (Ito et al., 2015; Osma et al., 2019). ODSIS will be used as a key secondary outcome for depressive emotional distress.

The Patient Health Questionnaire-9 (PHQ-9) will be used to assess depressive symptoms over the past 2 weeks. PHQ-9 consists of nine items corresponding to core diagnostic criteria for depressive disorders and has a total score ranging from 0 to 27, with higher scores indicating more severe depressive symptoms. The classic validation study by Kroenke et al. demonstrated good internal consistency and criterion validity; using a cutoff score of 10, PHQ-9 had approximately 88% sensitivity and 88% specificity for major depressive disorder (Kroenke et al., 2001). Because PHQ-9 is brief, easy to administer, and suitable for repeated measurement, it has been widely used in clinical screening, epidemiological surveys, and intervention studies. In this study, the PHQ-9 will also be used for preliminary screening of suicide or self-harm risk. Participants scoring >1 on item 9, indicating a potentially elevated risk of suicide or self-harm, will not be included in the study.

The Generalized Anxiety Disorder-7 scale (GAD-7) will be used to assess anxiety symptoms over the past 2 weeks. GAD-7 includes seven items and has a total score ranging from 0 to 21. Scores of 5, 10, and 15 are commonly used as reference thresholds for mild, moderate, and severe anxiety symptoms. The original study by Spitzer et al. reported excellent internal consistency; using a cutoff score of 10, GAD-7 had a sensitivity of approximately 89% and specificity of approximately 82% for generalized anxiety disorder (Spitzer et al., 2006). Subsequent studies have supported its structural validity, convergent validity, and screening validity in general populations, clinical samples, and different cultural contexts (Johnson et al., 2019; Löwe et al., 2008). GAD-7 will be used as an additional measure of anxiety symptom change.

The Short Form-8 Health Survey (SF-8) will be used to assess general health-related quality of life. SF-8 is a shortened version of the SF-36 Health Survey and includes eight items covering general health, physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, and mental health. It can generate physical and mental health-related indicators (Ware, 2001). Previous studies have shown that SF-8 has acceptable internal consistency, known-groups validity, and structural validity and is suitable for rapid assessment of health-related quality of life in large epidemiological studies, chronic disease research, and intervention studies (Lang et al., 2018; Roberts et al., 2008). Evidence from urban Chinese samples also supports the reliability and validity of SF-8 and its ability to reflect physical and mental health dimensions (Lang et al., 2018).

The Insomnia Severity Index (ISI) will be used to assess insomnia severity and its impact on daily functioning. ISI includes seven items assessing difficulty initiating sleep, difficulty maintaining sleep, early morning awakening, sleep satisfaction, interference of sleep problems with daily functioning, noticeability of sleep problems to others, and distress caused by sleep problems. Bastien et al. showed that ISI is a reliable and valid instrument for assessing subjective insomnia severity and is suitable as a screening and treatment outcome measure (Bastien et al., 2001). Morin et al. further showed that ISI can identify insomnia cases and is sensitive to treatment response, making it appropriate for repeated assessment in clinical intervention studies (Morin et al., 2011). Because patients with GERD often experience sleep disturbance related to nocturnal reflux, heartburn, and anxiety, ISI will be included as an important secondary outcome.

7.3 Cost-Effectiveness Outcomes

The Treatment Inventory of Costs in Patients with psychiatric disorders (TIC-P) will be used to record disease-related health care service use, medication use, health care visits, productivity loss, and social costs during the study. TIC-P is widely used in economic evaluations of mental health and psychological interventions and can record direct medical costs, direct nonmedical costs, and indirect costs from health care system and societal perspectives (Bouwmans et al., 2013). Because TIC-P is primarily a resource-use and cost measurement instrument, its value lies less in traditional psychometric internal consistency and more in the systematic recording of health care utilization, work loss, and caregiving costs.

The EuroQol Five-Dimension Five-Level Questionnaire (EQ-5D-5L) will be used to assess health status and calculate health utility values and quality-adjusted life years. EQ-5D-5L includes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with five response levels for each dimension. It was developed from the three-level EQ-5D to improve health state discrimination, enhance measurement sensitivity, and reduce ceiling effects (Herdman et al., 2011). Previous research has shown that EQ-5D-5L has good comprehensibility, face validity, and cross-disease applicability and is widely used for health utility measurement in health economic evaluations (Herdman et al., 2011). In this study, EQ-5D-5L will be used to calculate health utility and quality-adjusted life years for subsequent cost-utility analysis.

7.4 Other Outcomes and Covariates

The Chinese Perceived Stress Scale (CPSS) will be used to assess participants' subjective perception of life stress. This scale is derived from the Perceived Stress Scale developed by Cohen et al., and primarily assesses the extent to which individuals perceive life events over the past month as unpredictable, uncontrollable, and overwhelming (Cohen et al., 1983). The Chinese version of the CPSS has been applied and validated in Chinese populations, with studies demonstrating good internal consistency, structural validity, and criterion-related validity, supporting its use for assessing subjective stress levels (Leung et al., 2010; Ng, 2013). Given that stress may exacerbate GERD-related symptom experiences by influencing autonomic nervous system activity, visceral sensitivity, and symptom vigilance, the CPSS will be used in this study as an important measure of stress level and its changes.

The Connor-Davidson Resilience Scale (CD-RISC) will be used to assess the ability to cope with stress, illness, and adversity. CD-RISC was originally developed by Connor and Davidson to assess resilience, including hardiness, adaptability, sense of control, spirituality, and stress coping ability (Connor & Davidson, 2003). The original study reported good internal consistency, test-retest reliability, convergent validity, discriminant validity, and sensitivity to changes during treatment (Connor & Davidson, 2003). Subsequent cross-cultural and reliability generalization studies also support the overall reliability of different CD-RISC versions (Wojujutari et al., 2024). In this study, CD-RISC will be used to examine whether MIED enhances psychological resources for coping with chronic symptoms and stress in patients with GERD.

The Satisfaction With Life Scale (SWLS) will be used to assess cognitive evaluation of overall life satisfaction. Developed by Diener et al., SWLS includes five items rated on a 7-point scale, with higher scores indicating greater life satisfaction (Diener et al., 1985). The original validation study demonstrated a unidimensional structure, good internal consistency, and temporal stability. Subsequent reviews have further supported its reliability, structural validity, and convergent validity across populations and cultures (Diener et al., 1985; Pavot & Diener, 1993). In this study, SWLS will be used as a supplementary measure of quality of life and positive psychological functioning to determine whether MIED not only reduces symptoms and distress but also improves subjective evaluation of overall life status.

In addition to the above scales, demographic information and physical indicators will be collected. Demographic information will include age, sex, education level, marital status, and employment status. Physical indicators will include height, weight, and body mass index. These variables will be used to describe sample characteristics, examine baseline balance between groups, and serve as covariates in statistical models when necessary to control potential confounding.

7.5 Safety Outcomes

To evaluate safety, adverse events (AEs) and serious adverse events (SAEs) occurring during the study will be recorded. Events will be defined, documented, and reported according to international clinical trial standards. Descriptive analyses will include time of occurrence, severity, relationship to the intervention, management, and outcome to comprehensively evaluate the safety and acceptability of MIED (Guideline, 1994).

7.6 Mechanistic Variables

Mindfulness will be assessed using the Five Facet Mindfulness Questionnaire (FFMQ). This scale measures trait mindfulness across five dimensions: observing, describing, acting with awareness, nonjudging of inner experience, and nonreactivity to inner experience. It is one of the most widely used instruments in mindfulness research and has good reliability and validity (Baer et al., 2006). Total and subscale scores will be analyzed as exploratory continuous variables.

Engaging in life will be assessed using the Engaging in Life Scale (ELS), which measures the extent to which individuals engage in work, study, social interaction, sleep, and other life domains. It is an important instrument for assessing life engagement (Chen et al., 2026).

Distress tolerance will be assessed using the Distress Tolerance Scale (DTS). DTS measures the ability to tolerate negative emotional experiences and the way individuals regulate emotional distress (Simons & Gaher, 2005). In addition, the Discomfort Intolerance Scale (DIS) will be used to assess tolerance of unpleasant bodily sensations. DIS primarily measures the degree to which individuals can tolerate physical discomfort or negative bodily sensations and has been widely used in anxiety and emotion regulation research (Schmidt et al., 2006).

Excessive emotional behavior will be assessed using the Excessive Emotional Behavior Scale (EEBS). EEBS measures excessive emotion-driven behaviors and avoidance behaviors under negative emotional states and provides a more comprehensive assessment of this psychological process (Zhang et al., 2026). To further assess experiential avoidance, the Brief Experiential Avoidance Questionnaire (BEAQ) will also be used (Gámez et al., 2014).

Cognitive flexibility will be assessed using the Cognitive Flexibility Inventory (CFI). CFI measures the ability to adjust cognitive frames, generate alternative explanations, and use adaptive thinking strategies when facing stressful situations (Dennis & Vander Wal, 2010).

These psychological variables will be included as potential mediators in statistical analyses to examine the mechanisms through which MIED may improve anxiety, depressive symptoms, reflux symptoms, and reflux-related quality of life.

8. Schedule of Assessments

Assessment	Screening	Baseline	Week 3	Week 5	Week 8	3 months	6 months	12 months	24 months
Enrollment and allocation									
Informed consent	√								
Eligibility assessment	√								

Demographic information	√	√							
Randomization		√							
Intervention implementation									
MIED online self-help course			√	√	√				
Assistant support and course reminders			√	√	√				
Usual care			√	√	√				
Platform use data			√	√	√				
Primary outcome									
GERD-HRQL	√	√	√	√	√	√	√	√	√
Key secondary outcomes									
GERD-Q/GerdQ	√	√	√	√	√	√	√	√	√
RSI		√	√	√	√	√	√	√	√
OASIS	√	√	√	√	√	√	√	√	√
ODSIS	√	√	√	√	√	√	√	√	√
PHQ-9	√	√	√	√	√	√	√	√	√
GAD-7	√	√	√	√	√	√	√	√	√
SF-8		√			√	√	√	√	√
ISI		√	√	√	√	√	√	√	√
Cost-effectiveness outcomes									

TIC-P		√			√	√	√	√	√
EQ-5D-5L		√			√	√	√	√	√
Other outcomes and covariates									
Chinese Perceived Stress Scale (CPSS)		√	√	√	√	√	√	√	√
CD-RISC		√	√	√	√	√	√	√	√
SWLS		√	√	√	√	√	√	√	√
Height and weight		√	√	√	√	√	√	√	√
Safety outcomes									
Adverse events (AEs)		√	√	√	√	√	√	√	√
Mechanistic variables									
FFMQ	√	√	√	√	√	√	√	√	√
ELS		√	√	√	√	√	√	√	√
DTS	√	√	√	√	√	√	√	√	√
DIS	√	√	√	√	√	√	√	√	√
EEBS	√	√	√	√	√	√	√	√	√
BEAQ	√	√	√	√	√	√	√	√	√
CFI		√	√	√	√	√	√	√	√

Note: Week 8 is the primary endpoint and will be used to evaluate the change in GERD-HRQL from baseline at the end of treatment. The 3-, 6-, 12-, and 24-month follow-up assessments will be used to evaluate maintenance of effects, long-term safety, and cost-effectiveness. Week 3 and week 5 assessments are intended to capture early changes in mechanistic variables to support subsequent longitudinal mediation analyses. This schedule follows the SPIRIT recommendations for presenting enrollment, interventions, assessments, and follow-up in a clinical trial protocol(Hróbjartsson et al., 2025).

9. Sample Size Estimation

This study plans to recruit 500 patients with GERD, who will be randomized in a 1:1 ratio to the MIED group or the waitlist control group, with approximately 250 participants per group. Assuming an attrition rate of 15% to 25%, approximately 400 participants are expected to complete the study, with approximately 200 per group.

The sample size estimation is based on the between-group difference in change in GERD-HRQL from baseline to week 8. Because previous mindfulness intervention studies in GERD have had small sample sizes and unstable effect size estimates (Chandran et al., 2019; Oraki & Asadpour, 2021), this study uses a conservative small-to-moderate effect size assumption. Assuming a standardized effect size of d = 0.30 to 0.35 for the MIED group compared with the waitlist control group, a two-sided alpha of 0.05, and statistical power of 80% to 90%, approximately 175 to 235 participants per group would be required. Considering the multicenter design, long-term follow-up, mechanistic analyses, possible center-level clustering, and an expected attrition rate of 15% to 25%, the target sample size is set at 500 participants, with approximately 400 expected to complete the study.

Before study initiation, the statistical team will further verify the standard deviation of the primary outcome, the intraclass correlation coefficient, and the expected attrition rate using pilot or preliminary center data. The final sample size assumptions will be specified in the statistical analysis plan. Sample size calculations and assumptions should be prespecified before study initiation to avoid bias arising from data-driven modification (Chan et al., 2025).

10. Data Collection and Management

10.1 Data Collection

Study data will be collected using an electronic data capture system. Participants will complete online questionnaires through secure links. All data will be entered according to a unified coding system and data dictionary. Electronic data collection can improve data completeness, traceability, and quality control in multicenter studies (Chan et al., 2025).

10.2 Data Quality Control

The coordinating center will establish standard operating procedures covering participant screening, informed consent, randomization, questionnaire assessment, intervention records, adverse event reporting, and data entry. The system will include logic checks, range checks, and missing-data alerts. Research staff will regularly review data completeness and consistency and query or correct abnormal values.

10.3 Confidentiality

Each participant will be identified by a unique study number. Personally identifiable information will be stored separately from research data and will be accessible only to authorized personnel. Electronic data will be stored on encrypted servers, and paper materials will be stored in locked cabinets. Data use, storage, and sharing will comply with ethics approvals and relevant regulations.

10.4 Data Retention

Research data will be retained after study completion in accordance with the requirements of the ethics committees and participating institutions. Identifiable data will not be shared with unauthorized third parties without participant consent or ethics approval.

11. Statistical Analysis Plan

11.1 General Principles

The primary statistical analysis will follow the intention-to-treat principle, including all randomized participants regardless of whether they complete the course or all follow-up assessments. Intention-to-treat analysis helps preserve the initial balance created by randomization and reduces selection bias caused by attrition or poor adherence (Gupta, 2011). Per-protocol analyses will be conducted as supplementary analyses to evaluate intervention effects among participants with high adherence.

All statistical tests will be two-sided, with the significance level set at 0.05. For multiple secondary outcomes, appropriate adjustment or control of false-positive findings will be applied based on outcome hierarchy and analytic purpose. Statistical analyses will be conducted according to a prespecified and finalized statistical analysis plan. Prespecification helps reduce selective reporting and improves the credibility of the findings (Chan et al., 2025).

11.2 Baseline Characteristics

Baseline characteristics of the two groups will be summarized using descriptive statistics. Continuous variables will be reported as means and standard deviations or medians and interquartile ranges depending on distribution. Categorical variables will be reported as frequencies and percentages. Baseline balance between groups will be described rather than judged solely by significance testing. Important baseline imbalances will be included in sensitivity analyses or adjusted models when clinically appropriate. In randomized controlled trials, baseline significance testing is not necessary for evaluating randomization quality; reporting and clinically interpreting baseline characteristics is more important (Schulz et al., 2010).

11.3 Primary Outcome Analysis

The primary outcome is the change in GERD-HRQL total score from baseline to week 8. The primary analysis will use a linear mixed-effects model including group, time, group-by-time interaction, baseline value, and center as fixed effects, with participant included as a random intercept. Linear mixed-effects models are suitable for repeated-measures data and can include participants with partially missing follow-up data under the missing-at-random assumption, thereby improving data use (Laird & Ware, 1982; Little & Rubin, 2019). The key parameter will be the group-by-time interaction at week 8, reflecting the difference in change between the MIED and waitlist control groups.

The model will report estimated marginal means, between-group differences, 95% confidence intervals, and P values. If the outcome distribution substantially deviates from normality, robust standard errors, variable transformation, or generalized linear mixed models will be considered.

11.4 Secondary Outcome Analyses

Continuous outcomes, including GERD-Q, RSI, OASIS, ODSIS, PHQ-9, GAD-7, SF-8, ISI, CPSS, CD-RISC, SWLS, and EQ-5D-5L, will be analyzed using similar linear mixed-effects models. Categorical outcomes, such as clinically significant improvement, symptom remission, and adverse event incidence, will be analyzed using generalized linear mixed models or mixed-effects logistic regression models. Long-term effects will be evaluated using time-by-group interactions, with particular attention to between-group differences at 3, 6, 12, and 24 months.

11.5 Adherence and Dose-Response Analyses

Course viewing time, daily check-in rate, and course completion rate in the MIED group will be used as adherence indicators. Dose-response associations between intervention exposure and outcome improvement will be explored. The per-protocol population may be defined as participants who complete at least 40 sessions and complete the primary endpoint assessment. This analysis will be supplementary and will not replace the intention-to-treat analysis. In behavioral intervention research, adherence and intervention dose may influence real-world effectiveness and should therefore be prespecified and recorded (Bellg et al., 2004).

11.6 Missing Data

Linear mixed-effects models can use all available data when missingness meets the missing-at-random assumption. The proportion and reasons for missing data at each time point will be described, and baseline characteristics of completers and non-completers will be compared. If the proportion of missing data is substantial, multiple imputation will be used in sensitivity analyses. Pattern-mixture models or extreme-case analyses will be used to examine robustness under potential nonrandom missingness. Missing-data handling should be specified in the protocol and statistical analysis plan to reduce analytic selection bias (Chan et al., 2025) (Little & Rubin, 2019).

11.7 Mediation Analyses

This study will examine the mechanisms of MIED based on the theoretical model. The preliminary model proposes that MIED improves GERD symptoms and reflux-related quality of life by reducing emotional distress, increasing engaging in life, adjusting distress tolerance, reducing excessive emotional behaviors, and improving cognitive flexibility. This hypothesized pathway is grounded in the transdiagnostic intervention framework for emotional disorders, the psychological diamond model of mindfulness based intervention for emotional distress, and previous research on the relationship between GERD and psychological distress (Barlow, 2011; Hayes et al., 2011; He et al., 2022; Liu, 2024; Southward & Sauer-Zavala, 2022).

Longitudinal mediation models will be prioritized. Early changes in mechanistic variables, such as changes from baseline to week 3 or week 5, will be modeled as mediators, with changes in GERD-HRQL or GERD-Q at week 8 or follow-up as outcomes, controlling for baseline levels. Structural equation modeling or multilevel mediation models may be used to account for repeated measurements and center clustering. Indirect effects will be tested using bootstrap confidence intervals or Bayesian estimation. Longitudinal mediation models provide stronger support for temporal ordering than cross-sectional mediation models, although causal interpretation should remain cautious (MacKinnon, 2012; Preacher & Hayes, 2008).

11.8 Subgroup and Moderation Analyses

Exploratory subgroup analyses will examine whether intervention effects are moderated by baseline GERD symptom severity, baseline anxiety or depression level, disease duration, sex, age, body mass index, PPI use, insomnia severity, or study center. Subgroup analyses will be performed by adding group-by-time-by-subgroup interaction terms to mixed-effects models. Because these analyses are exploratory, findings will be interpreted cautiously and overinterpretation will be avoided (Schulz et al., 2010).

11.9 Cost-Effectiveness Analysis

Cost-effectiveness analysis will be conducted from health care system and societal perspectives. Costs will include outpatient visits, emergency visits, hospitalizations, examinations, medication use, psychological intervention implementation costs, transportation, and work loss. Health utility will be calculated from EQ-5D-5L, and quality-adjusted life years will be estimated (Herdman et al., 2011). Incremental cost-effectiveness ratios will be calculated, and uncertainty will be estimated using nonparametric bootstrapping. Cost-effectiveness acceptability curves will present the probability that MIED is cost-effective at different willingness-to-pay thresholds. Previous studies have suggested that internet-based psychological interventions may be cost-effective for anxiety and depression; this study will further examine the economic value of internet-based MIED for patients with GERD (Mitchell et al., 2021).

12. Safety Monitoring

12.1 Definition of Adverse Events

An adverse event is any unfavorable medical or psychological event occurring during the study, regardless of whether it is causally related to the intervention. Serious adverse events include death, life-threatening events, hospitalization or prolongation of hospitalization, significant disability, serious self-harm or suicidal behavior, and other events judged by the investigators to be serious. The study will define, record, and report adverse events and serious adverse events according to international Good Clinical Practice standards (Guideline, 1994).

12.2 Collection of Adverse Events

All participants will be asked about adverse events at each assessment time point. MIED research assistants will monitor for marked symptom exacerbation, psychological crisis, and practice-related discomfort during the course. Event records will include time of occurrence, duration, severity, management, possible relationship to the intervention, and outcome. Systematic recording of adverse events is an essential component of clinical trial ethics and safety evaluation (Chan et al., 2025).

12.3 Risk Management

If participants develop marked worsening of GERD symptoms, alarm symptoms, or psychological crisis, the research team will initiate safety procedures immediately, including temporary suspension of the course, notification of the study physician, referral to gastroenterology or mental health services, and recommendation of emergency care when necessary. All serious adverse events will be reported to the ethics committee and principal investigator within the required time frame.

12.4 Data and Safety Monitoring

An independent data and safety monitoring group or designated independent safety monitor will regularly review recruitment progress, adherence, attrition, adverse events, and serious adverse events. If intervention-related risks are found to increase substantially, the research team will consider protocol modification, temporary suspension of recruitment, or study termination. Independent safety monitoring in multicenter clinical trials helps protect participant rights and improve study quality (Chan et al., 2025).

13. Ethical Considerations

13.1 Ethics Approval

The study will be conducted only after approval by the ethics committee of the leading institution and the ethics committees of participating centers. Any major protocol amendment will be submitted for ethics review and implemented only after approval.

13.2 Informed Consent

All potential participants will receive information about the study purpose, procedures, potential benefits, possible risks, privacy protection, right to withdraw, and contact information before enrollment. Research staff will provide sufficient time for participants to ask questions and consider participation. Written or electronic informed consent will be obtained before enrollment.

13.3 Participant Rights

Participants may withdraw from the study at any time without providing a reason, and withdrawal will not affect their usual medical care. To ensure ethical acceptability, participants in the waitlist control group will be offered the MIED self-help program after the 2-year follow up. The research team will make every effort to minimize participant burden and risk.

13.4 Privacy Protection

Personal information and health data collected during the study will be kept strictly confidential. Publications and reports will present aggregated data only, without disclosure of identifiable information.

14. Trial Registration and Protocol Amendments

The study will be registered in a public clinical trial registry before participant recruitment begins. Registration information will include the study title, objectives, trial design, eligibility criteria, interventions, primary and secondary outcomes, sample size, recruitment status, and ethics approval information. If major protocol amendments occur during the study, the registry will be updated promptly, and the ethics committee and study staff will be informed of the content, rationale, and implementation date of the amendments.

15. Study Organization and Responsibilities

The leading institution will be responsible for overall protocol design, ethics coordination, trial registration, development of intervention materials, intervention training, data management, quality control, and statistical analysis. Participating centers will be responsible for recruitment, screening, medical evaluation, informed consent,

follow-up, and safety event reporting. The intervention team will be responsible for implementation of the MIED self-help program, feedback on home practice, and course records. The statistical team will independently generate the randomization sequence, conduct data analyses, and prepare statistical reports. The data management team will maintain the electronic data capture system, check data quality, and lock the database. Clear organizational structure and role definition are important for ensuring the quality of multicenter trials (Chan et al., 2025)

16. Quality Control

Before study initiation, unified training will be provided to ensure that all research staff understand the protocol, ethics requirements, eligibility criteria, assessment instruments, randomization procedures, and safety management processes. The coordinating center will hold regular project meetings to review recruitment progress, data quality, intervention consistency, and follow-up completion. Protocol deviations will be recorded, classified, and addressed. All centers will follow the same standard operating procedures to reduce center-related variability. Quality control in multicenter clinical trials should cover staff training, data management, intervention fidelity, retention, and safety monitoring (Bellg et al., 2004; Chan et al., 2025).

17. Dissemination Plan

After completion of the study, findings will be disseminated through peer-reviewed journals, national and international academic conferences, and clinical training materials. The research team plans to publish the main findings regardless of whether the results support the study hypotheses. The final report will follow CONSORT guidelines for randomized controlled trials, and appropriate reporting standards will be used for mediation and cost-effectiveness analyses (S. Hopewell et al., 2025). Data sharing will comply with ethics approvals, informed consent, and data management policies.

18. Discussion

GERD is a chronic disease with prominent psychosomatic interactions. Traditional treatment mainly focuses on acid suppression and mucosal protection, yet many patients continue to experience recurrent symptoms, anxiety-related worry, sleep disturbance, and reduced quality of life despite medication (He et al., 2022; Laine & Nagar, 2016). Psychological distress is not merely a consequence of GERD; it may also intensify symptom experience through stress responses, visceral hypersensitivity, catastrophizing, and avoidance behaviors (He et al., 2022; Hetterich & Stengel, 2020). Therefore, it is clinically important to develop adjunctive interventions that are safe, accessible, low-cost, and mechanistically targeted.

This study has several strengths and innovations. First, it uses a multicenter, large-sample randomized controlled design, addressing the small sample sizes, single-center designs, and limited evidence stability of previous mindfulness studies in GERD (Chandran et al., 2019; Oraki & Asadpour, 2021). Second, it applies MIED, an intervention integrating mindfulness and transdiagnostic emotion-focused principles, to patients with GERD. The intervention targets not only emotion regulation but also engaging in life, distress tolerance, excessive emotional behaviors, and cognitive flexibility (Barlow, 2011; Hayes et al., 2011; He et al., 2022; Liu, 2024; Southward & Sauer-Zavala, 2022). Third, the online delivery format may improve accessibility and scalability. Previous studies of

internet-based mindfulness interventions have shown positive effects on anxiety, depression, and stress (Sommers-Spijkerman et al., 2021; Spijkerman et al., 2016). Fourth, the inclusion of long-term follow-up and cost-effectiveness analysis will help evaluate the sustainability and health economic value of the intervention (Mitchell et al., 2021). Fifth, the inclusion of multiple mechanistic variables will help explain how a psychological intervention may influence GERD symptoms and reflux-related quality of life.

The study also has potential limitations. Because psychological and behavioral interventions cannot blind participants or intervention staff, expectancy effects may occur. Although the waitlist control design is ethically acceptable and practical, it cannot fully control for nonspecific factors such as social support, treatment attention, and group interaction (Mohr et al., 2009). The online format may also face challenges related to adherence differences, internet access, and incomplete home practice. To mitigate these issues, the study will use blinded outcome assessment, standardized intervention materials, intervention fidelity monitoring, detailed adherence records, and sensitivity analyses.

If this study demonstrates that MIED improves reflux-related quality of life, emotional distress, and long-term health outcomes in patients with GERD, it will provide new evidence for adjunctive treatment in comprehensive GERD management and will contribute to the development of mind-body and digital psychological interventions for gastrointestinal disorders.

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