Clinical effect and mechanism study of Five Elements Music Therapy(FEMT) on depression disorder

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Contents

Researcher Information Form

1. Principal Investigator

Name	Education	Title	Medical practice qualifications	GCP training (Yes/No)	Project task division
Lanying Liu	Master	Chief Physician	Clinician	Yes	Research design

2. Project team members

Name	Unit	Title	Medical practice qualifications	GCP training (Yes/No)	Project task division
Zhen Wang	Shanghai Mental Health Center	Chief Physician	Clinician	Yes	Quality control
Wei Li	Shanghai Mental Health Center	Attending physician	Clinician	Yes	Research coordination
Chao Luo	Shanghai Mental Health Center	Assistant Researcher/Chief Chinese Pharmacist	Chinese Pharmacist	Yes	Sample collection
Anna	Shanghai Mental Health Center	Attending Chinese medicine Physician	Chinese Medicine Practitioner	Yes	Sample collection
Wangtao Li	Shanghai Mental Health Center	Resident physician	Chinese medicine practitioner	Yes	Intervention implementation
Liyuan Guo	Zhejiang Chinese Medical University	Graduate Student	Chinese Medicine practitioner	Yes	Intervention implementation

3. The sponsor

Sponsor Name	Address
Shanghai Mental Health Center	600 Wanping South Road, Xuhui District, Shanghai

4. Research Site

Shanghai Mental Health Center (No. 600, Wanping South Road, Xuhui District, Shanghai)

Research Project Title

Clinical effect and mechanism study of Five Elements Music Therapy(FEMT) on depression disorder

Background of the trial:

Major Depressive Disorder (MDD) is a mental illness that seriously affects public health. There are about 350 million people with depression worldwide, accounting for 4.4% of the total burden of the disease. The lifetime prevalence of depression in China is 6.8%. Therefore, exploring a comprehensive treatment approach with good clinical efficacy, few side effects and high acceptance has become a hot topic in current clinical research. In traditional Chinese medicine, depression is classified into categories such as "yu syndrome","zang Zao" and "Baihe disease", and is also named "Yu disease" according to the Diagnostic and Therapeutic criteria of Internal Medicine in traditional Chinese medicine. Its main causes are emotional injury and physical weakness. The key pathogenesis lies in the liver's failure to regulate the flow of qi, the spleen's failure to transform and transport, and the heart spirit's failure to nourish, which leads to the imbalance of qi, blood, Yin and Yang in the zang-fu organs. Therefore, the traditional Chinese medicine treatment of depression mainly focuses on soothing the liver and strengthening the spleen, and has

achieved good clinical results through intervention methods such as decoctions, acupuncture, massage and guiding.

Music therapy is a combination of music, medicine and psychology, and is based on clinical evidence-based practice [1]. It is an important non-pharmaceutical therapy and has shown remarkable efficacy in the treatment of psychological and mental disorders. Studies have shown that music therapy works by regulating the function of the cerebral cortex, altering the levels of neurotransmitters and hormones, and inducing resonance to regulate emotions. Several systematic review studies have confirmed that music therapy can effectively improve negative emotions such as anxiety and depression [3,4]. Geretsegger et al. [5] also found that music therapy plays a positive role in improving the mental state of schizophrenia patients and restoring their social functioning. Mental and psychological disorders fall under the category of affective disorders in traditional Chinese medicine. As an important part of music therapy, the Five Elements music therapy of traditional Chinese medicine is similar to the basic music theory of music therapy [6], but it has its own characteristics of traditional Chinese medicine and also plays an important role in the intervention of emotional disorders.

The Five Elements Music therapy is a traditional Chinese music therapy guided by the theory of Yin-Yang and Five elements in Chinese medicine and the idea of syndrome differentiation and treatment, which forms a specific correspondence among the five tones, five emotions and five internal organs. The five tones enter the five internal organs. The "Suwen: The Great Treatise on the Correspondence of Yin and Yang" states: "The liver is anger in the mind and horn in the sound; The heart is characterized by joy in mind and by sign in sound; The spleen is thought in mind and palace in sound; Lung, in mind worry, in sound shang; The kidney means fear in the mind and feather in pronunciation." The Ling Shu: Five Tones and Five Flavors attribute the five tones to the five elements and expound the theory of the five scales of gong, Shang, Jue, Zhi and Yu for the treatment of diseases. The gong sounds are peaceful, solemn, broad and melodious, making people feel broad-minded and dignified. They have the characteristics of earth and can enter the spleen. Shang

sounds are high and mournful, resounding and majestic, making people calm and solemn, with the characteristics of metal, can enter the lungs; The horn sound is warm and pleasant, full of vitality, belonging to wood, invigorating the body and mind and soothing the mood, it can enter the liver; The sound of the horn is warm, cheerful, lively and relaxed, making people feel cheerful and inspired. It belongs to fire in the five elements of traditional Chinese medicine and can enter the heart. The sound of the feather is mournful, melancholy and soft, which can inspire reverie and enlighten the mind. It has the nature of water and can enter the kidney. According to traditional Chinese medicine, the mechanism by which the five Elements music regulates emotional disorders mainly lies in the fact that the five tones correspond to the five internal organs and the five emotions. Through different modes of music, the Five Elements music can play a role in the transformation of qi, balance Yin and Yang, and regulate qi and blood in the body, thereby improving the overall physical and mental discomfort of patients, reducing anxiety and depression, and improving the quality of life. Previous studies have found that Chinese subjects have a higher level of physiological arousal to five-element music compared to Western music; The Gong tunes in traditional Chinese music therapy can significantly improve negative emotions, relieve depression and anxiety, and improve sleep quality compared to other tunes.

Modern studies have explored the mechanism of action of the Five Elements music therapy from the perspectives of nerves, immunity, and resonance [8, 9]. The Five Elements Music therapy mainly works by influencing the content of neurotransmitters, enhancing immune function, and regulating mood through the energy generated by the resonance of sound waves with the five internal organs. In recent years, more and more studies have confirmed that the Five Elements music therapy is an important method for regulating mood disorders. Multiple meta-analyses and systematic reviews have shown that Five-element music therapy is an effective intervention to improve negative emotions such as anxiety and depression in patients [10-13]. Current studies have found that the use of five-element music therapy for intervention yields better results. However, there is still no standard or regulated

method of five-element music therapy in China.

The scientific assumptions of this project:

Chinese five-element music therapy with the tones of gong and Zhi can significantly improve the HAMD scale score and depressive symptoms of patients with depressive disorder by regulating the function of the prefrontal lobe.

Objective of the trial:

(1) To verify the clinical efficacy of traditional Chinese medicine Five-element music therapy for depressive disorder;

(2) Using ERP technology to explore the mechanism of action of traditional Chinese medicine Five-element music therapy in the intervention of depressive disorder;

(3) Through this study, we will further promote the development of non-pharmaceutical traditional Chinese medicine treatment methods for depression, with the aim of promoting their application.

Type of **trial design:** Evaluator blind randomized controlled study

Randomization grouping method:

This study adopted an evaluator blind randomized controlled design. According to the computer-compiled random number table, the enrolled patients were randomly assigned to the experimental group and the control group at a ratio of 1:1. Healthy controls were recruited at the same time, and baseline electroencephalogram and pulse wave data were provided, and the impact of daily life events on patients' mood and neurophysiological indicators was excluded.

Subjects of study:

The subjects of this study were patients with depressive disorders who visited the outpatient department of Shanghai Mental Health Center, and all subjects signed the informed consent form; Healthy controls were recruited through advertising at the same time.

Inclusion and exclusion criteria for the patient group:

Inclusion criteria:

1) Conforming to the ICD-10 diagnostic criteria for depressive episodes;
2) Hamilton Depression Scale -17 items score ≥14;

3) No gender restrictions, age 18-60;

4) Confirmed by at least two physicians with the title of attending physician or above;

5) Have sufficient visual and auditory levels to ensure that the necessary examinations and tests for the study can be completed;

6) Sign the written informed consent form and agree to be enrolled in the trial as required by the study plan.

Exclusion criteria:

1) The presence of serious heart, liver or kidney diseases, organic brain diseases, serious cardiovascular diseases, tumors, blood history, rheumatism, malnutrition and neurodegenerative diseases; Depressive episodes secondary to other mental or physical illnesses;

2) A history of abuse of tobacco, alcohol and other psychoactive substances;

3) Comorbidities with other mental illnesses;

4) Having participated in other drug clinical trials prior to inclusion.

Inclusion criteria and exclusion criteria for the healthy control group:

Inclusion criteria:

Aged 18 to 60, should be a healthy person without mental or physical illness.

Exclusion criteria:

1) The presence of serious heart, liver or kidney diseases, organic brain diseases, serious cardiovascular diseases, tumors, blood history, rheumatism, malnutrition and neurodegenerative diseases; Depressive episodes secondary to other mental or physical illnesses;

2) A history of abuse of tobacco, alcohol and other psychoactive substances;

3) Having participated in other drug clinical trials prior to inclusion.

Subject selection steps:

（1） Obtain the subjects' informed consent for the study.

（2） We obtained the necessary information for the study, including current illness history, previous disease history, allergy history, medical records, and demographic data, and combined it with clinical symptom assessment and psychiatric interviews to confirm that the screened subjects met the inclusion

criteria.

Subject allocation method:

After the subjects were included in the study, they were randomly divided into the experimental group and the control group according to a computer-generated random number table, and the corresponding examination tests were completed.

Sample size estimation:

This study is a superiority test. Due to the current lack of efficacy parameters of traditional Chinese medicine five-element music in improving depressive symptoms, referring to previously published electroencephalogram studies [14,15], the sample size of this study is 30 people per group. Based on the 20% dropout rate of previous clinical studies, the sample size is determined to be 40 people per group.

Intervention regimens:

Experimental group:

1）The self-made music piece "Five Elements Music 1" was selected to intervene in the subjects. The song took the palace key and the signature key as the main notes. The production melody had no large jumps, and the notes maintained a natural continuity, avoiding sudden ups and downs in the melody and creating a peaceful atmosphere. Using the pentatonic scale of G major (G, A, D, E, G), the notes in the melody are distributed reasonably, especially the gong (G) and sign (D) notes as important notes on the strong beat, creating a stable and soothing auditory experience; By avoiding the use of semitones or tense notes like "fa" and "ti" in the melody, it does not create a sense of dissonance or suspense. Adjust the duration of the musical intervention according to the patient's daily life schedule, usually during the midday break and 1 hour before bedtime.

2）Before the intervention, give the patient a comprehensive explanation of the purpose, process, etc. of the intervention and wear headphones to listen to music for 30 minutes; During the intervention, have the patient slightly close their eyes, relax their body, and ensure that the surrounding environment is quiet and free of background noise. After listening to the music, rest for 5 to 10 minutes and then slowly open your eyes.

3）Play music through headphones using a mobile phone, computer, tablet, etc., at a volume of 20-60 dB, play a short sound before the experiment starts, and ask the patient if they feel comfortable with the volume. It is best for the patient to feel pleasant and comfortable. Try to minimize interference from external factors during the intervention.

4）The daily completion status needs to be checked in the pre-established wechat group to ensure the daily completion status. Doctors will notify patients in the wechat group if necessary.

5）The duration of the music intervention is directly related to the patient's own sleep state. Generally, music is played during the midday break and 1 hour before bedtime, twice a day, for 4 weeks, a total of 28 days.

6）In the course of the traditional Chinese medicine Five Elements music intervention, antidepressant drug treatment (fluoxetine hydrochloride) was combined. Other antipsychotic drugs, antidepressants and mood stabilizers should not be combined during the treatment.

- Control group:

1）A self-made piece of music, "Five Elements Music 2", was selected to intervene in the subjects, with the main note adjusted to the shang key (A) and yu key (E) without changing the rhythm and timbre of "Five Elements Music 1"; Adjust the duration of the music intervention according to the patient's daily life schedule, usually during the midday break and 1 hour before bedtime.

2）Before the intervention, give the patient a comprehensive explanation of the purpose, process, etc. of the intervention and wear headphones to listen to music for 30 minutes; During the intervention, have the patient slightly close their eyes, relax their body, and ensure that the surrounding environment is quiet and free of background noise. After listening to the music, rest for 5 to 10 minutes and then slowly open your eyes.

3）Play music through headphones using a mobile phone, computer, tablet, etc., at a volume of 20-60 dB, play a short sound before the experiment starts, and ask the patient if they feel comfortable with the volume. It is best for the patient to feel

pleasant and comfortable. Try to minimize interference from external factors during the intervention.

4）The daily completion status needs to be checked in the pre-established wechat group to ensure the daily completion status. Doctors will notify patients in the wechat group if necessary.

5）The duration of the music intervention is directly related to the patient's own sleep state. Generally, music is played during the midday break and 1 hour before bedtime, twice a day, for 4 weeks, a total of 28 days.

6）After enrollment, the patients were treated with antidepressant drugs (fluoxetine hydrochloride) for 4 weeks, 28 days. No other antipsychotic drugs, antidepressants or mood stabilizers were allowed to be used during this period.

Healthy control group:

The baseline scale assessment was completed, and ERP electroencephalogram detection was conducted to dynamically observe the changes in brain waves. The eye tracker recorded the eye movement data, and the pulse diagnosis instrument recorded the pulse information of the closed pulse (radial artery pulse). No additional intervention was carried out. Possible differences were identified by comparing the electroencephalogram (EEG), eye movement data and pulse wave data of healthy individuals and those with depressive episodes.

Evaluation of clinical symptoms and side effects:

Observation indicators were scheduled at baseline, week 2, and week 4 of enrollment. The observation indicators included:

1) Demographic data: Using self-made general demographic data questionnaires, including patient name, age, gender, marital and reproductive history, history of smoking and drinking, disease duration, history of previous physical illness, family history, history of anti-anxiety drug treatment, drug category and dosage, current medication use, etc.

2) ERP electroencephalogram (EEG) tests were conducted dynamically to observe changes in brain waves at baseline and after 4 weeks;

3) Eye tracker records eye movement data for testing at baseline and 4 weeks

later;

4) The pulse diagnosis instrument records the pulse information of the guan pulse (radial artery pulse), which is tested at baseline and 4 weeks later;

5) Primary efficacy indicators: Hamilton Depression Scale (HAMD-17 scale), Hamilton Anxiety Scale (HAMA scale), Neuropsychological State Repeatability Checklist (RBANS scale), etc. were measured at baseline, week 2, and week 4;

6) Adverse reactions: Assessment of Adverse Reactions Scale (TESS).

7) Evaluation of effectiveness: The efficacy for depressive symptoms was evaluated by the difference in the rate of reduction from the HAMD-17 scale before and after the intervention. Repeated measures analysis of variance was performed between the two groups to observe the differences between the groups, the time differences and the interaction effects, and post hoc to observe the changes before and after the intervention. $P < 0.05$ suggested that traditional Chinese medicine Five-element music therapy might be effective (the difference in efficacy between the two groups was statistically significant).

Primary efficacy indicators:

HAMD-17 score reduction rate after treatment: Score reduction rate =(baseline HAMD-17 scale score - HAMD-17 scale score 4 weeks later)/ baseline HAMD-17 scale score. A HAMD-17 score reduction rate of ≥50% is considered effective.

Secondary efficacy indicators:

1）Other symptomatological indicators: HAMA for improvement in anxiety symptoms, RBANS for improvement in cognitive function;

2）Safety indicators: Adverse reactions as assessed by TESS scale;

3）Changes in electrophysiological indicators and eye movement data: Changes in neurophysiological indicators evaluated by EEG and EM:

4）Traditional Chinese medicine syndrome differentiation: Changes in the syndrome types of the four diagnostic methods combined and alterations in the indicators of the pulse diagnosis instrument.

Research scale:

1) Hamilton Depression Scale-17 (HAMD-17) : It is one of the most commonly

used other scales in psychiatric practice for assessing depressive states. Previous studies have reported good reliability and validity of the scale. The scale uses a five-point scale to assess depressive symptoms in the subjects, with a higher total score indicating more severe depressive symptoms; A total score of more than 24 indicates severe depression; More than 17 points indicates mild or moderate depression; A score of less than 7 indicates no depressive symptoms.

2) Hamilton Anxiety Scale (HAMA) : An other-scale used to assess the severity of anxiety symptoms in neurotic and other patients. Previous studies have reported good reliability and validity of the scale. According to the assessment criteria provided by the Psychiatric Scale Collaboration Group of our country, a total score of more than 29 points indicates severe anxiety; A score above 21 indicates obvious anxiety; Over 14, there must be anxiety; Over 7 points, anxiety is likely; A score less than 7 indicates no anxiety symptoms. In previous studies, a score of 14 has been used as the cut-off point, with a higher total score indicating more severe anxiety symptoms.

3) Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) : Used to assess the cognitive function of the subjects, this scale has the advantages of short measurement time, simple operation, sensitive and effective results in clinical application, and patients with depressive episodes cooperate to complete it to a high degree. The RBANS consists of five factor scores: ① Immediate memory factor score, which reflects the subject's ability to remember for a short time after the tester provides information; ② Visual breadth factor, which reflects the subject's ability to perceive spatial relationships and correctly replicate a picture; ③ Speech function factor score, reflecting the speech response ability of the subjects; ④ Attention factor score, reflecting the subject's memory capacity and the ability to extract short-term memory banks visually and orally to express information; ⑤ Delayed memory factor score, reflecting the subject's ability to perform anterograde memory.

4) Treatment Emergent Symptom Scale (TESS) : It is the most comprehensive and extensive scale of its kind, including both common adverse symptoms and signs as well as several laboratory test results. The TESS requires an assessment of each symptom in three aspects: severity, the relationship between the symptom and the intervention, and

the measures taken.

ERP electroencephalogram test records:

The ERP data was collected in the laboratory using the curry system, with the international standard 64 conductive cap. The right mastoid M2 was used as the reference electrode, and electrode sheets were pasted above and below the left eye socket to record the vertical electroencephalogram, and electrodes were pasted at the left and right eyes to record the horizontal electroencephalogram. ERP data collection began when the resistances were both below 5KΩ. Electroencephalogram data analysis: The electroencephalogram data is filtered through a band-pass at a sampling rate of 0.1-30Hz and sampled continuously at 500Hz per channel. The data were measured in cycles of 1700 milliseconds, including a baseline period of 200ms before stimulus presentation and 1500ms of stimulus presentation. Peaks of each ERP component were calculated separately for each group.

Eye movement check:

1) Subject preparation : Ensure the subject is seated properly, adjust the height of the seat and chin rest so that the subject 's horizontal gaze is at the center of the screen or the center of the upper half of the screen. Adjust the orientation of the eye tracker through the eye tracker stand to ensure that the subject's eye to be captured is at the center of the main test machine's image.

2) Calibration : Calibrate using the eye tracker to ensure that the subject 's eyes are within the field of view of the eye tracker. This usually involves adjusting the focal length of the lens to make the image of the eye clearly visible. Ensure accurate identification of eye and corneal reflex points through automatic threshold adjustment or manual adjustment. Have the subject look at the calibration point on the screen to start the calibration process. After the calibration is done, check the calibration results and recalibrate if necessary.

3) Data recording : Once the calibration is successful, begin presenting the stimulus material and recording the data.

4) Data saving : At the end of the experiment, the data will be automatically saved to the designated folder.

Pulse record:

1）Youdaoplaceholder0 Preparation of the subject ：Ensure that the subject is in a proper position, with the arm level with the heart at approximately the same level, the wrist straight with the palm facing up, and a cloth pillow placed behind the wrist joint.

2）Device connection: The location of the pulse is determined by the Chinese medicine practitioner, and the sensor is connected.

3）Youdaoplaceholder0 Data recording ：The operator records the pulse of the subject in the calm state through software. Generally, it is advisable to record in a 1-minute experiment.

4) Data saving ：At the end of the experiment, the data will be automatically saved to the designated folder.

Study process:

The study was divided into an inclusion phase and a trial phase.

Inclusion phase:

（1） Obtain informed consent from the subjects for the study.

（2） We obtained the necessary information for the study, including current illness history, previous disease history, allergy history, medical records, and demographic data, and combined it with clinical symptom assessment and psychiatric interviews to confirm that the screened subjects met the inclusion criteria.

Trial phase:

（1） The subjects were treated according to the above-mentioned treatment and intervention plan, and the side effects were evaluated by the TESS after the intervention ended.

（2） After the intervention, clinical symptom assessment, electroencephalogram (EEG) examination, eye movement examination and pulse recording were conducted.

Measures to ensure compliance of the subjects:

After the subjects are enrolled, we will insist on regular (weekly) phone inquiries about changes in the subjects' conditions and maintain communication with the

outpatient physicians to ensure the subjects' safety during the trial and timely feedback of medical information. After the intervention, all subjects will receive a combination of Five Elements music and Western medicine to ensure the effectiveness of the treatment, and follow-up will continue through various means such as phone calls and the Internet.

Dropout criteria:

During the course of the trial, if any of the following circumstances occur, the investigator is responsible for discontinuing the participant from the trial. Subsequently, the reasons for discontinuation, the date of discontinuation, and the clinical course that led to this event are stated and evaluated on the case report form, and the participant may also decide to withdraw at their own discretion.

(1) It is determined by the investigator that the trial cannot be continued due to adverse events or abnormal laboratory test values

(2) The subject voluntarily withdraws from the trial

(3) Obvious violation of the protocol (including those deemed to have poor compliance by the researchers)

(4) Those whom other investigators consider inappropriate or difficult to continue the trial

(5) Lost to follow-up

Subjects have the right to withdraw from the trial at any time without any reason. If a subject decides to withdraw from the trial, the investigator should find out the reasons as much as possible and record them in the original data and case report form. When a subject withdraws from the trial early, he must be evaluated at the end.

Risks and their controls:

The current high-level clinical research evidence for Five-element music therapy is still insufficient, and its effectiveness for depressive episodes has not been fully confirmed, which may pose a risk of no significant improvement in patients' conditions. As a result, throughout the study, professional physicians will monitor the patient's condition regularly, follow up and control the patient's condition in a timely manner after it changes, and ensure the patient's safety by terminating the study, changing the

medication regimen, or referring the patient to the outpatient department of another professional doctor. At the end of each examination, we assess the side effects of the subjects and record them in detail.

Recording requirements for adverse events and reporting methods and handling measures for serious adverse events:

Any clinically significant laboratory test results, vital signs, electrocardiogram tests, and other test results discovered should be recorded by the investigator or assistant investigator on the "Pre-existing Diseases and Study Adverse Events" page of the case report form; For findings of clinical significance for which a specific diagnosis can be made, the diagnosis should be recorded as an adverse event; For findings that cannot be diagnosed, their clinical significance should be determined by the investigator, and findings identified as clinically significant should be recorded as adverse events.

After discovering a serious adverse event, the investigator must report it to the designated person within 24 hours by means approved by the PI. After reporting by phone, it must be completed immediately and the serious adverse event record form for this study must be sent: death; Initiation of hospitalization or extension of hospital stay; Life-threatening situations (i.e. the risk of immediate death); Persistent or obvious disability or dysfunction; Congenital malformations or birth defects; The researcher considers the event meaningful for any reason.

During the trial, the adverse event record form was filled out truthfully, recording the time of occurrence, severity, duration, effective measures taken, and outcome of the adverse event.

In the event of serious adverse events, necessary measures must be taken immediately to protect the safety of the subjects. All adverse events should be followed up, with detailed records of the handling process and results until they are properly resolved or the condition stabilizes, and if the test results are abnormal, they should be followed up until they return to normal. Follow-up visits can be made in various forms, such as hospitalization, outpatient visits, home visits, phone calls, and correspondence, depending on the severity of adverse reactions.

Any serious adverse events that occur during the trial must be immediately

reported to the medical ethics committee of the institution or the primary research institution and the sponsor institution, and the "Serious Adverse Event Report Form" must be filled out. Inform the ICF of the phone number and contact person of the unit listed in the ICF. Follow-up of unrelieved adverse events: All adverse events should be followed up until they are properly resolved or the condition stabilizes.

Statistical analysis plan:

Descriptive analysis and general statistics of the data were performed using SPSS 23.0 statistical software. Descriptive analysis was conducted for each efficacy indicator at each follow-up time point. Measurement data were expressed as mean ± standard deviation. Paired t-tests were performed between the measured values at each time point and the baseline values, and P values were calculated. Count data were expressed as percentages (%), and chi-square tests were performed between the measurement results at each time point and the baseline results to calculate the P value. Including comparability analysis, validity analysis, safety analysis, compliance analysis, etc.

Study data management:

In this study, data was entered using EpiData 3.1 and double-entry verification was implemented.

1) EpiData database construction: The data administrator builds the database based on the research protocol and research medical records.

2) Data entry: The clinical investigator or the data entry officer (clinical coordinator) appointed by the investigator enters the data from the study medical records into EpiData in a timely and accurate manner. EpiData is not an original record, and its content is derived from the medical record and the study visit manual.

3) Data locking and export: Data is locked by the data manager after each subject completes the trial and is reviewed by the monitor without error. During the trial, the locked data will be exported in real time as needed for interim analysis. After all the trial data of all subjects were locked, the data administrator exported them to the

designated database for final statistical analysis by the statisticians.

Quality control and quality assurance of the trial:

Investigators should perform their respective duties and strictly follow the clinical trial protocol and use standard operating procedures to ensure the implementation of the quality control and quality assurance system in the clinical trial. All observations and findings in the clinical trial should be verified, and quality control must be carried out at every stage of data processing to ensure that the data is complete, accurate, true and reliable. Appoint managers to conduct a systematic review of clinical trial-related activities and documentation to evaluate whether the trial was conducted in accordance with the trial protocol, standard operating procedures, and relevant regulatory requirements, and whether the trial data was recorded in a timely, true, accurate, and complete manner.

Trial expected progress:

Annual	Annual plan and annual goals for the project (dividing work nodes by quarter, requiring clear key, must-achieve node goals)
2025 Annual	Quarter 1: Complete review writing, ethics registration Quarter 2: Complete clinical trial registration, and pre-trials. Quarter 3: Collect 30 patients who met the inclusion criteria for randomization and intervention follow-up. 15 healthy individuals who met the inclusion criteria were collected. Quarter 4:30 patients who met the inclusion criteria were collected for randomization and intervention follow-up. 15 healthy individuals who met the inclusion criteria were collected Node goals: Complete the enrollment, intervention, and evaluation of 60 study subjects, and complete the evaluation of 30 healthy study subjects
2026 Annual	Quarter 1: Data summary, cleaning, conducting data analysis, writing and submitting articles, writing research summary reports, completing project defense and conclusion. Node objective: Complete data organization, project defense and project conclusion.

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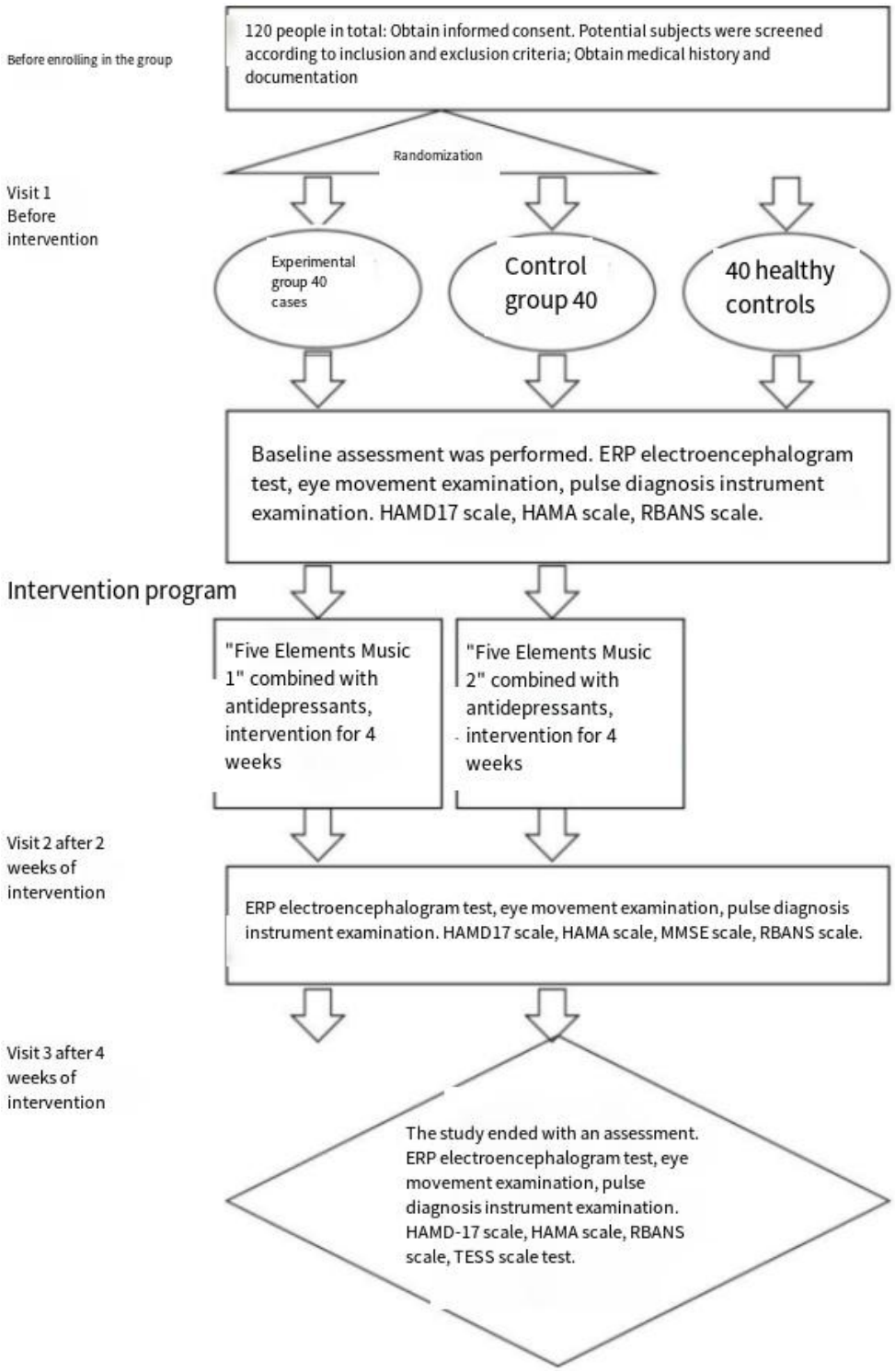
1. Study flowchart



2. Research Schedule

Research schedule

Stages	Screening period	Introduction period	Treatment period	
Visits	V1	V2	V3	V4
Visit time	W1	W1	W2	W4
Sign informed consent form	X			
Medical history collection	X			
Randomization	X			
Demographic data	X			
Inclusion and exclusion criteria	X			
Scale testing		X	X	X
Electroencephalogram		X	X	X
Eye movement examination		X	X	X
Pulse diagnosis instrument		X	X	X