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ORIGINAL ARTICLE

THE SYNERGISTIC EFFECT OF WARM SALT FOOTBATH AND FOOT-ANKLE EXERCISES IN INDIVIDUALS WITH TYPE 2 DIABETES MELLITUS: A STUDY PROTOCOL FOR MULTICENTER RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Individuals with type 2 diabetes mellitus (T2DM) experience issues with their sleep quality and elevated level of the neutrophil-lymphocyte ratio (NLR). Warm salt footbaths and foot-ankle exercises play a significant role in addressing inflammation and improving sleep quality. Nevertheless, no studies have examined the synergistic effects of warm salt footbaths and foot-ankle exercises. This study aims to investigate the synergistic effects of warm footbath water and foot-ankle exercises on sleep quality and NLR. A randomized controlled trial with a total of 108 individuals with T2DM randomly assigned to one four groups: a warm salt footbath, a foot-ankle exercises, a combination of both interventions, or a control group. The interventions administered over a period of 4 weeks (three times per week). Evaluations were performed by blinded evaluators at baseline, as well as after 2 and 4 weeks of interventions. Chi-squared test, one-way analysis of variance, and generalized estimating equations were employed for data analysis. The results of this trial were expected to elucidate the synergistic effects of warm salt water footbath and foot-ankle exercises on sleep quality and NLR. Furthermore, the combination of warm salt water footbaths and foot-ankle exercises is more effective either intervention alone or conventional treatment.

Keywords: *Foot-ankle exercises; synergistic effect; type 2 diabetes; warm salt footbath*

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a group of chronic metabolic disorders distinguished by abnormal insulin sensitivity and escalated blood glucose levels (American Diabetes Association, 2019; Buse et al., 2020). This condition can lead to increased inflammation (Halim & Halim, 2019; Rias, Gordon, et al., 2020; Rias, Kurniasari, et al., 2020) as well as sleep disturbances (Nanayakkara et al., 2020; von Schantz et al., 2021). Annually, it is estimated that four million deaths result from diabetes-related complications, which equates to one death every eight seconds (Internatonal Diabetes Federation, 2017). In Indonesia, the number of individuals with T2DM is projected to grow from 10.7 million in 2019 to 16.6 million by 2045 (Saeedi et al., 2019). To mitigate the increasing prevalence and reduce both macrovascular and microvascular complications associated with T2DM, it is essential to understand and investigate individuals characteristics related to good exercise behaviors and relaxation techniques that may help prevent the development complications(Anusruti et al., 2020; Vaghasloo et al., 2020; Zhang et al., 2020).

Low levels of sleep quality have been identified as a risk factor for vascular complication associated with T2DM. While T2DM is a leading cause of mortality on its own, it exacerbates health problems when integrated with sleep disturbances. Increased neutrophil-to-lymphocyte ratio (NLR) levels in individuals with T2DM may result from the differential effects of hyperglycemia on neutrophils and lymphocytes, potentially contributing to the elevated levels of pro-inflammatory cytokines associated with insulin resistance (Mertoglu & Gunay, 2017). Currently, the physiological mechanisms underlying the interaction between sleep quality indicators and the inflammatory pathway remains unclear. Additionally, previous study has revealed that poor sleep quality and a higher number of wakeful events during the night might induce a slight increase of sympathetic activity via the hypothalamus-pituitary–adrenergic system, which has been shown to enhance leukocytosis and the inflammatory response (Rangaraj & Knutson, 2016).

Remarkably, the previous randomized clinical trial study has shown that the use of warm footbath water was significantly declined the pain among individuals withT2DM (Vaghasloo et al., 2020). Also, pain has been linked to poor sleep quality (Choi et al., 2021), suggesting that the warm footbath therapy may escalate the sleep quality in patients with T2DM. The causal association between pain and poor sleep quality cannot be definitively established, prior research has indicated that inflammation and oxidative stress may contribute to poor sleep quality (Choi et al., 2021). Therapeutic exercises targeting the foot and ankle have proven beneficial for individuals with T2DM and were recommended for the first time in the most recent guidelines from the International Working Group on the Diabetic Foot (Silva et al., 2021). Moreover, it has been shown that foot–ankle exercises help reduce markers of vascular inflammation markers (Loader et al., 2018), but physical activity levels among in patients with T2DM remain relatively low in Indonesia (Rias, Gordon, et al., 2020). Foot-ankle exercise have also been associated with improved sleep quality in patients with T2DM (Win et al., 2020). To prevent the progression of vascular inflammation deficiencies in patients with diabetes, foot-ankle exercises have been recommended for investigation (Silva et al., 2021), but there is a lack of studies examining this approach.

As mentioned above, no study has examined the synergistic effect of warm footbaths and foot-ankle exercises on sleep quality. Therefore, in this project investigates the primary focus and novelty of this study: to assess the impact of warm footbath water and foot-ankle exercises on ameliorating NLR and improving sleep quality among Indonesians with T2DM in West Java, Indonesia. These two interventions which can address low sleep quality and elevated NLR levels. We firmly believe that the interaction of multiple therapeutic strategies (the combination of warm footbaths and foot-ankle exercises) to yield an effect greater than simply the sum of the individual effects of each intervention when used separately. Besides, the effects of warm footbaths and foot-ankle exercises have not been systematically compared, nor has the potential for a synergistic effect from combining these two therapeutic modalities been evaluated. Consequently, the feasibility of a preventive treatment program should first be explored in Indonesia among individuals with T2DM. This highlights the fact that combination of foot-ankle exercises and warm footbath water may have positive effects on reducing inflammation, which consequently increase sleep quality in individuals with T2DM.

METHOD

Study design

This trial investigation employed a 2×2 factorial design within a randomized controlled trial. The experimental design featured an equivalent control group with pre-test and post-test measures, repeatedly conducted at with 2 weeks and 4 weeks.

Participants

This study will recruit 240 eligible patients aged 21 years or older who suffer from sleep problems, encompassing difficulty falling asleep, inability to remain asleep for more than 30 minutes, waking up in the middle of the night or early morning, and who have Type 2 Diabetes Mellitus (T2DM).. Respondents were selected from six public health care centres located in 3 urban areas and 3 rural areas. The inclusion criteria for the study consisted of 108 cases with fasting plasma glucose levels greater than 126 mg/dL or 7.0 mmol/L (American Diabetes Association, 2018), with these conditions confirmed by physicians. Also, respondents must be Indonesian nationals aged between 21 and 79 years and provide signed informed consent. Exclusion criteria for this study encompassed the individuals who (1) were pregnant or had diabetic foot ulcers or wounds; (2) had a previous cancer, thrombotic autoimmune diseases, any auditory deficiencies, or other chronic and acute diseases; (3) had a disability; (4) consumed antidepressants; (5) participants did not practice the intervention procedure prior to study, or (6) participated in other clinical trials that could influence the findings of this study. Table 1 shows a trial process chart illustrating the participant recruitment process.

Table 1. Trial process chart

Items	Enrolment	Baseline	Allocation	2 Week	4 week
Inclusion criteria	x				
Exclusion criteria	x				
Informed consent	x				
Randomization	x				
Allocation			x		
Baseline		x			
Intervention		x		x	x
Follow up				x	x
Adverse events				x	x

Sample size

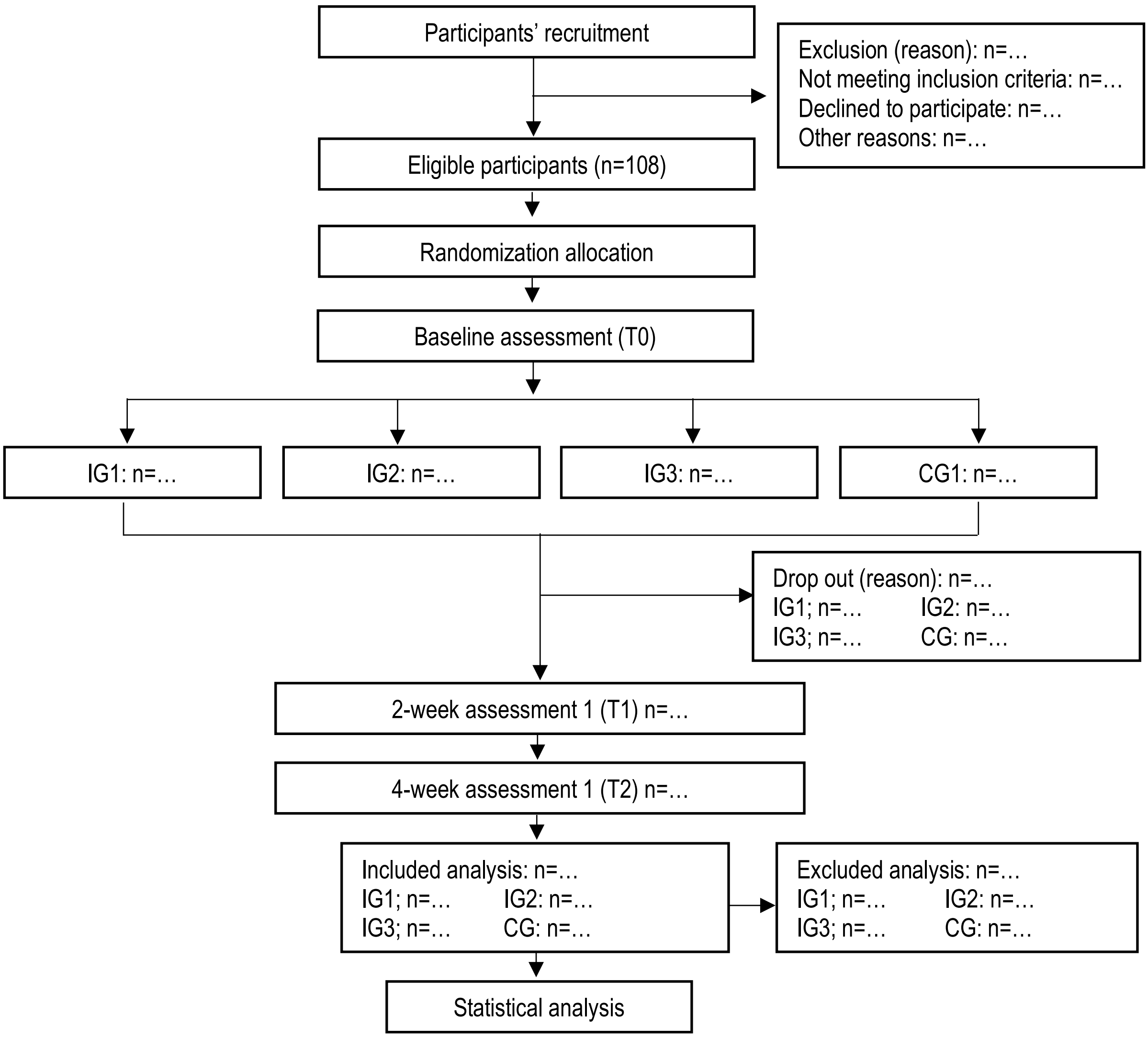
This current study utilized G-Power sample size program based on previous literature (Rias, Kurniawan, et al., 2020). We conducted a priori power analysis to project the sample size, with power (1- β) of 0.8, an α level of 0.05, and an effect size of 0.25 for four groups. This formula provided a sample size of 97 participants, with each group consisting of 24 participants. Ultimately, the present study calculated a 10% dropout rate, which escalated the sample size to 27 participants per group, resulting in a total of 108 participants.

Blinding

Given the characteristics of intervention, it is not feasible for the participants in this study to remain unaware of their group assignments. After a patient consented to participate, the research assistant communicated to a clinical nurse. The nurse then will assign patients to groups using an opaque, sealed envelope containing identifiers, in the order they entered the trial. The inherent characteristics of the therapies precluded blinding the subjects. To mitigate detection bias, each participant will be assigned a unique three-digit research code. Consequently, the researchers will not be aware of the participants' responses when entering data using the study code. Furthermore, during data analysis, the initial researcher will remain unaware of the group assignments, while the statistician will perform the analysis alongside the initial researcher. Five years after the study's conclusion, all data, both digital and hard copies, will be deleted.

Study Fidelity
Study fidelity was ensured by organizing meetings with investigators, the project leader, clinical nurses, research assistants, research fellows, and physicians. These sessions were held to examine the processes, verify the accuracy of the measurements, and align a shared understanding and implementation of the research.

Randomization and allocation
The permuted block randomization technique will generate the random allocation sequence, and a random number generator available at www.randomizer.org will facilitate the sampling process. To ensure the internal validity of the data, we will randomly and blindly assign the eligible patients to the study groups (IG1, IG2, IG3, CG), adhering to the equal percentage guideline of 1:1:1:1. A designated research assistant, who is not participating in this trial and will remain unaware of screeners and assessors until the final patient outcome assessment, will supervise the random allocation sequence. The project manager will notify the eligible members of their assigned group. The flow diagram for this trial is shown in Figure 1.



Note: CG: control group; IG1: warm salt footbath group; IG2: foot-ankle exercises group; IG3: a combination of both or control group

Figure 1 Flow diagram of participants

Treatment allocation
The trial will implement the intervention three times a week for a total of four weeks. Each session will consist of a 15-minute for a warm salt footbath followed by 30 to 45 minutes of ankle-foot exercises. The case report forms (CRFs) will contain precise documentation of the intervention, medication, and related lifestyle influence factors, such as physical activity. The first intervention session intervention was supervised by clinical nurses, who instructed to instruct the participants on how to perform the warm salt footbath and ankle-foot exercises using the video. They also provide an exercise kit containing the materials needed to perform the exercises (pail for footbath, thermometers, cotton balls, a towel, a pencil, mini elastic bands, balloons, light and

moderate resistance elastic bands, a massage ball, and finger separators). Participants were instructed to perform the exercise program at home three times a week for four consecutive weeks. Adherence to the intervention will be confirmed through telephone follow-ups and a logbook where participants will record related to the warm salt footbath and foot-ankle exercises.

Control group
Respondents in the control group were advised to continue their exercise and receive pharmacological treatment, such as insulin injections, oral medications or a combination of both. They were advised against engaging in any extra physical activities or taking other antioxidant supplements.

Warm salt footbath protocol
Participants will undergo a 4-week home-based intervention in which both feet will be immersed in a pail filled with 5 litters of warm, tolerable water (approximately 42 °C) for 15 minutes. Prior to immersion, 250 grams of powdered mineral salt will be added and dissolved in the warm water. This intervention will take place in plastic tubs with a water depth of 15 cm, carried out before bedtime (Vaghasloo et al., 2020).

Foot-ankle exercises protocol
Participants will receive a 4-week physiotherapeutic home-based foot exercise program guided by an educational video lasting 30 to 45 minutes. This video consists of an informative session and an exercise program session. The informative session provides details about autonomous footcare, vascular inflammation, appropriate footwear, and the benefits of exercising the foot and ankle. The exercise program includes six exercises categorized into three difficulty levels. The physiotherapeutic exercise program aims to strengthens both the intrinsic and extrinsic foot–ankle muscles, while increasing the range of motion in ankle joints. It features three warm-up exercises, four exercises targeting the intrinsic foot muscles and joints, and two exercises targeting to the extrinsic foot muscles and joints. Participants could adjust the difficulty level based on a perceived effort scale.
Warm salt footbath combined foot-ankle exercises. For the combined group, participants will receive a warm salt footbath along with foot-ankle exercises (at the same time)

Measurements of The Pittsburgh Sleep Quality Index (PSQI)
The PSQI a 19-item questionnaire designed to assess sleep quality and disruptions over the preceding month. The PSQI consists of seven components: subjective sleep quality, sleep latency, sleep length, habitual sleep efficiency, sleep disruptions, and usage of sleeping medication (Buysse et al., 1989). Each question is scored on a four-point Likert scale (0–3), where a score ranging from 0 (better) to 3 (worse). The scores for the seven components are summed to generate a global PSQI score. The overall rating ranges from 0 to 21, with a value of > 5 indicating poor sleep quality. The Indonesian version of the PSQI exhibited a satisfactory internal consistency (Cronbach's coefficient = 0.8) and high concurrent validity (r = 0.89) (Alim, 2015).

Measurements of clinical and biochemical measures
The data involved Body Mass Index (BMI) and Platelet-to-Lymphocyte Ratio (PLR). Research assistants assessed participants' height and weight and checked these measurements using medical records. Height and weight were examined by research assistants, who ensured accuracy by cross-referencing with the medical reports. The BMI was calculated using the formula: body weight (kg)/height^2 (m^2). Participants were categorized into two groups: obese (BMI ≥ 25 kg/m²) and non-obese (BMI < 25 kg/m^2; (Purnell, 2018). After a 12-hour fasting period, blood samples were drawn from the antecubital vein, all respondents were invited to attend each clinical examination. Neutrophil, lymphocyte counts, platelet counts and FBG were calculated using an automated haematology analyser XP-100.

Measurements of Incidence of Adverse Events
The safety of the method involving four parallel intervention groups was assessed based on the incidence of adverse events during the trial study period. Potential adverse events included fatigue, which participants self-reported and monitored by physicians weekly. Clinical nurses also maintained thorough documentation of these events. In the event of a side effect, the physician and investigators should promptly discontinue the intervention and take appropriate action.

Data collection and management
After receiving permission, a designated research assistant will collect demographic and baseline characteristic data without knowledge of the treatment assignment. The assistant will be trained to administer questionnaires consistently. The data will include demographic information such as medical history, current medications, age, duration of diabetes, body mass index, fasting plasma glucose levels, income, education, physical activity, family history, and any medications received in the past month, as well as any concurrent medications. Data will be gathered through direct patient inquiries and medical records The outcome assessors will conduct an outcome measurement following the intervention. The research assistant will oversee quality control for data collection and perform data entry tasks. The project leader will be responsible for performing the initial data cleaning, as well as identifying, coding, and converting the data into the appropriate format for data analysis. Each form must contain a date and signature from either the responsible investigator or an authorized staff member.

Ethical issue
Each participant will receive an information sheet along with a verbal briefing and explanation. All participants will provide written informed consent prior to the interview and examination of their medical records. This protocol obtained ethical approval from the Clinical Research Ethics Committee of Universitas Prima Nusantara Bukittinggi, under number 161/KEPK/UPNB/XII/2023, dated 17 December, 2023.

Statistical analysis
The statistical analyses will be conducted using SPSS version 25.0 (Chicago, IL, USA). A *p*-value of less than 0.05 will be deemed statistically significant. Descriptive statistics for continuous data will be presented as mean (standard deviation, SD), while categorical data will be reported as n (%). The Chi-squared test and one-way analysis of variance (ANOVA) will be used to compare sociodemographic and baseline results across the four groups, respectively. Generalized Estimating Equation (GEE) models, utilizing appropriate link functions and distribution assumptions, will be used to look at how outcomes change over time and between different groups. Multicollinearity will be assessed using the variance inflation factor (VIF). The models will be modified to account for potential confounding variables. Missing data resulting from loss to follow-up (n = ...) will be treated as missing completely at random, and the data will be analysed based on the intention-to-treat principle.

DISCUSSION

To the best of the authors' knowledge, this is the first RCT to examine the synergistic effects of warm footbath water and foot-ankle exercises on sleep quality and NLR among individuals with T2DM. Prior research, particularly studies on footbaths, has indicated that footbaths enhance blood flow by dilating peripheral blood vessels, alleviating sensory symptoms, stimulating tactile sensation, reducing activity in the sympathetic nervous system activity, improving the skin's ability to facilitate blood flow inf small vessels, and enhancing the medication absorption in the lower limbs (Emine & Gulbeyaz, 2022). Furthermore, a previous randomized clinical trial study has shown that the use of warm footbath water was significantly declined pain among individuals with T2DM (Vaghasloo et al., 2020). Interestingly, the physiological changes linked to warm footbath water are similar to those associated with foot exercises and a decreased sleep problems-related stress (An et al., 2019). A prior study revealed that warm footbath water effectively declined fatigue (Ozdemir & Can, 2021), which is aa key factor influencing sleep quality (Jehan et al., 2018; Yadav & Cho, 2018). By using the osmotic gradient across the skin, a hypertonic saltwater solution enhances the extraction of excess moisture and inflammation from the affected limbs. Consequently, the reduction in tissue inflammation leads to improved recovery of injured neurons and a potential decrease in fatigue (Akyuz Ozdemir & Can, 2021; vakilinia et al., 2020), which may enhance sleep quality. Moreover, footbaths have been found to regulate blood and lymph circulation, boost levels of endorphin plasma, reduce inflammation in the extremities, and promote the healing of damaged neurons by mitigating inflammation (Moradi et al., 2017; Zainiyah et al., 2019).

Performing foot-ankle exercises can enhance neurological health by assessing the degree of foot sensation (Laake-Geelen et al., 2019). Physical activity, including foot-ankle exercises, generally improves sleep quality through a variety of mechanisms. Initially, it increases the production of melatonin, a hormone that regulates the circadian rhythm (Alnawwar et al., 2023). Consequently, engaging in foot-ankle exercises can be expedite the process of falling asleep and enhance sleep quality. Furthermore, engaging in physical activity enhances one's emotional state, resulting in heightened motivation for exercise and favourable reinforcement. This implies that individuals who participate in physical activity experience a favorable emotional state and tranquillity, which that aid in regulating body temperature (Wang & Boros, 2021). This regulation is crucial for facilitating the process of falling asleep, as the rise in body temperature during physical activity leads to a subsequent decrease in body temperature within 30 to90 minutes after exercising. Consequently, this decrease in body temperature makes it easier to fall asleep (Alnawwar et al., 2023; Wang & Boros, 2021). In fact, the vascular inflammation (Demirdal & Sen, 2018; Korkmaz et al., 2015), including a high level of the neutrophil-lymphocyte ratio (NLR), has been linked to escalated severity of glycosylated haemoglobin and fasting blood glucose (Rias, Gordon, et al., 2020; Rias, Kurniawan, et al., 2020). Interestingly, the relationships between total sleep time and NLR were of moderate insignificance. Additionally, sleep quality was linked to neutrophil counts and NLR (Fang et al., 2016). Engaging in regular, moderate-intensity physical exercise can effectively regulate blood sugar levels and manage blood pressure. This approach helps minimize the risk of complications by preventing various pathophysiological mechanisms, such as reducing oxidative stress and NLR levels, which are significant factors in diabetes (Rias, Kurniawan, et al., 2020). Nonetheless, there remains lack of compelling evidence. Hence, our experiment seeks to elucidate these concerns and potentially offer a definitive response to the inquiries through the use of a randomized factorial controlled trial.

If the effectiveness of the intervention is demonstrated, the synergistic effect of warm footbath water and foot-ankle exercises has the potential to circumvent of barriers such as sleep disturbances and high levels of inflammation. In fact, sleep problems and high levels of inflammation can exacerbate complications associated with T2DM, leading to a decline in quality of life and escalated mortality rate (Ellulu & Samouda, 2022). Thus, our proposed randomized controlled trial will highlight important additional information on the effect of synergistic effects of warm footbath water and foot-ankle exercises on sleep quality and NLR among individuals with T2DM. Furthermore, this study will determine whether combined or alone of warm salt water footbath and foot-ankle exercises is more effective than conventional treatment.

The limitation of the protocol study lies in its reliance on a questionnaire rather than objective equipment to assess physical activity levels. According to the guidelines for physical activity in individuals with T2DM, subjective assessments are preferred for assessing exercise status due to their convenience and personalization. We will request that our study participants maintain an exercise diary that records the duration of their workouts. The process evaluation will incorporate this aforementioned data. At the participant level, the primary challenges will be the failure to exercise and forgetfulness. To mitigate these risks, we will instruct participants on how to complete their intervention diary and conduct video calls to evaluate and comprehend the intervention, and on how to adhere to the exercise video during the first meeting.

CONCLUSION

In conclusion, the results of this trial are expected to clarify the synergistic effects of warm salt footbaths and foot-ankle exercises on sleep quality and NLR. Furthermore, the study aims to determine whether the combination of warm salt foot baths and foot-ankle exercises is more effective than either intervention alone or the control group. If the synergistic effect of warm salt footbaths and foot-ankle exercises is proven effective, this approach could represent a low-cost intervention that is easily implemented and has significant potential for routine care.

TRIAL STATUS

Recruitment opened in February 2024 and concluded in November 2024. Data gathering is expected to conclude by December 2024 after completing the final participants. The trial closing is set for February 2025 after the completion of data analysis.

DATA AVAILABILITY

In order to maintain openness in the study, after the trial has ended, the datasets and statistical analysis will be made available upon reasonable request from the corresponding author.

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