


# Efficacy of Lingji Formula in the Treatment of Male Infertility in Obese Men: Study Protocol for a Randomized Controlled Trial

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**Background:** The incidence of male infertility is rising, with obesity being a significant-contributing factor. Studies showed that obese men often have lower sperm concentration and motility. Levocarnitine oral solution has been supported by guidelines and expert consensus in China. However, this treatment has limited efficacy and potential side effects, creating a need for new therapeutic options. Traditional Chinese Medicine (TCM) offers a multi-target approach that may improve both semen quality and obesity. Lingji formula is based on the classical TCM formula named Erjing Pill in Song Dynasty of ancient China. Lingji formula has been developed to treat male infertility in obese men by tonifying the kidney and eliminating dampness from the perspective of TCM. However, there is a lack of clinical trials on TCM interventions in male infertility of obese men.

**Methods:** This study protocol outlines a 1:1 randomized controlled trial that will enroll 78 participants diagnosed with male infertility, oligoasthenozoospermia, and obesity. Participants will be randomly assigned to a treatment group or a control group. The treatment group will receive the Lingji formula, while the control group will receive Levocarnitine oral solution for a duration of 12 weeks. The primary outcome measure is the total progressive motile sperm count at week 12. Secondary outcomes include routine semen indicators, pregnancy rate, Body Mass Index (BMI), waist-to-hip ratio, lipid-related indicators, and Traditional Chinese Medicine symptom scores, which will be assessed at baseline and at weeks 4, 8, and 12.

**Results:** The findings of this trial will fill a research gap in the use of TCM for treating male infertility in obese men and provide important clinical evidence for the application of TCM in managing obesity-related male reproductive disorders.

**Conclusion:** This study aims to provide the first clinical evidence on the efficacy and safety of the Lingji formula for treating obesity-associated male infertility. The research findings will provide significant clinical evidence for the use of TCM in regulating fertility in obese men. The study has been registered with the <http://itmctr.ccebtcn.org.cn> (ITMCTR number is ITMCTR2025001503). Registration Date: July 28, 2025.

**Keywords:** obese men, Lingji formula, protocol, male infertility, sperm

## Introduction

Infertility is defined as a couple's inability to conceive naturally after one year of regular sexual activity without contraception.<sup>1</sup> Among them, male factors account for more than half of the cases of infertility.<sup>2</sup> It is worth noting that the incidence of male infertility is still on the rise and may have a serious negative impact on social development.<sup>3</sup> So far, the causes of male infertility have not been fully clarified. A large number of studies have shown that it may be related to unhealthy lifestyle such as high-calorie foods, drinking, irregular sleep and wake schedules.<sup>4-6</sup> These factors may affect the production and maturation of sperm and eventually lead to male infertility. Epidemiological studies have widely reported the relationship between obesity and male reproductive dysfunction.<sup>7,8</sup> Multiple studies have shown that compared with men of normal weight, obese men have lower sperm concentration and motility, and a higher rate of sperm deformity.<sup>9,10</sup> From the perspective of treatment objectives, obesity-associated male infertility can be divided into weight loss treatment and fertility enhancement treatment. Weight loss strategies include dietary adjustment, increased

physical activity, and bariatric surgery.<sup>11,12</sup> Fertility improvement methods mainly involve nutritional supplementation, hormone therapy, and assisted reproductive technologies.<sup>13,14</sup> As a nutritional supplement, Levocarnitine is involved in sperm energy metabolism and plays an important role in maintaining sperm maturation and viability.<sup>15</sup> And the clinical study supports its efficacy in improving sperm viability and sperm concentration.<sup>15</sup> In Chinese guidelines and consensus, Levocarnitine is a commonly used drug for the treatment of male infertility.<sup>16,17</sup> However, some patients may experience gastrointestinal discomfort after taking Levocarnitine oral solution, which affects their compliance. Meanwhile, the efficacy of Levocarnitine oral solution in treating obesity is limited.<sup>18</sup> Therefore, the development of drugs for treating male infertility in obese patients still faces many challenges.

Traditional Chinese medicine (TCM) can leverage its multi-target regulatory advantages to exert comprehensive effects, including semen quality improvement and weight reduction. From some literature reviews, TCM can supply trace elements and vitamins, ameliorate the microcirculation of the testis, decrease the levels of serum anti-sperm antibody, and modify epigenetic markers.<sup>19,20</sup> Wang et al designed a randomized controlled trial evaluating Qixiong Formula for the treatment of idiopathic asthenozoospermia, and 66 participants were randomly assigned to either the Qixiong formula group or the Levocarnitine group.<sup>21</sup> Results indicated that after a 12-week treatment, both groups demonstrated significant improvements in semen quality compared to pre-treatment, with the Qixiong formula group exhibiting superior efficacy.<sup>21</sup> However, this clinical trial did not explicitly designate the research population as obese individuals. Some active components in Chinese herbs exhibit protective effects on the male reproductive system.<sup>22,23</sup> Furthermore, meta-analyses have provided evidence supporting TCM's efficacy in weight management for obese patients.<sup>24,25</sup> The Lingji formula is developed based on Erjing Pill, a classical prescription documented in the Song Dynasty medical compendium "Sheng Ji Zong Lu". While preserving the original composition of Erjing Pill, Lingji formula incorporates additional kidney-tonifying and dampness-eliminating Chinese herbs. Given the current lack of published clinical studies on TCM treatment for male infertility in obese men, we aim to establish a clinical trial protocol that may serve as a reference for future validation of the Lingji formula's efficacy and safety in managing this condition.

## Materials and Method

### Study Design and Settings

This study is a 1:1 randomized controlled trial with two parallel groups, conducted in accordance with the Standard Protocol Items: Recommendations for Interventional Trials 2013 guidelines ([Supplementary File 1](#)).<sup>26</sup> We will enroll 78 participants, randomly allocating 39 to each group. Following the informed consent, participants will undergo a 12-week treatment with either Lingji formula or Levocarnitine oral solution. The trial design, including the flow chart and assessment schedule, is outlined in [Figure 1](#) and [Table 1](#). The trial will comply with the Declaration of Helsinki.

### Study Participants

#### Recruitment Strategy

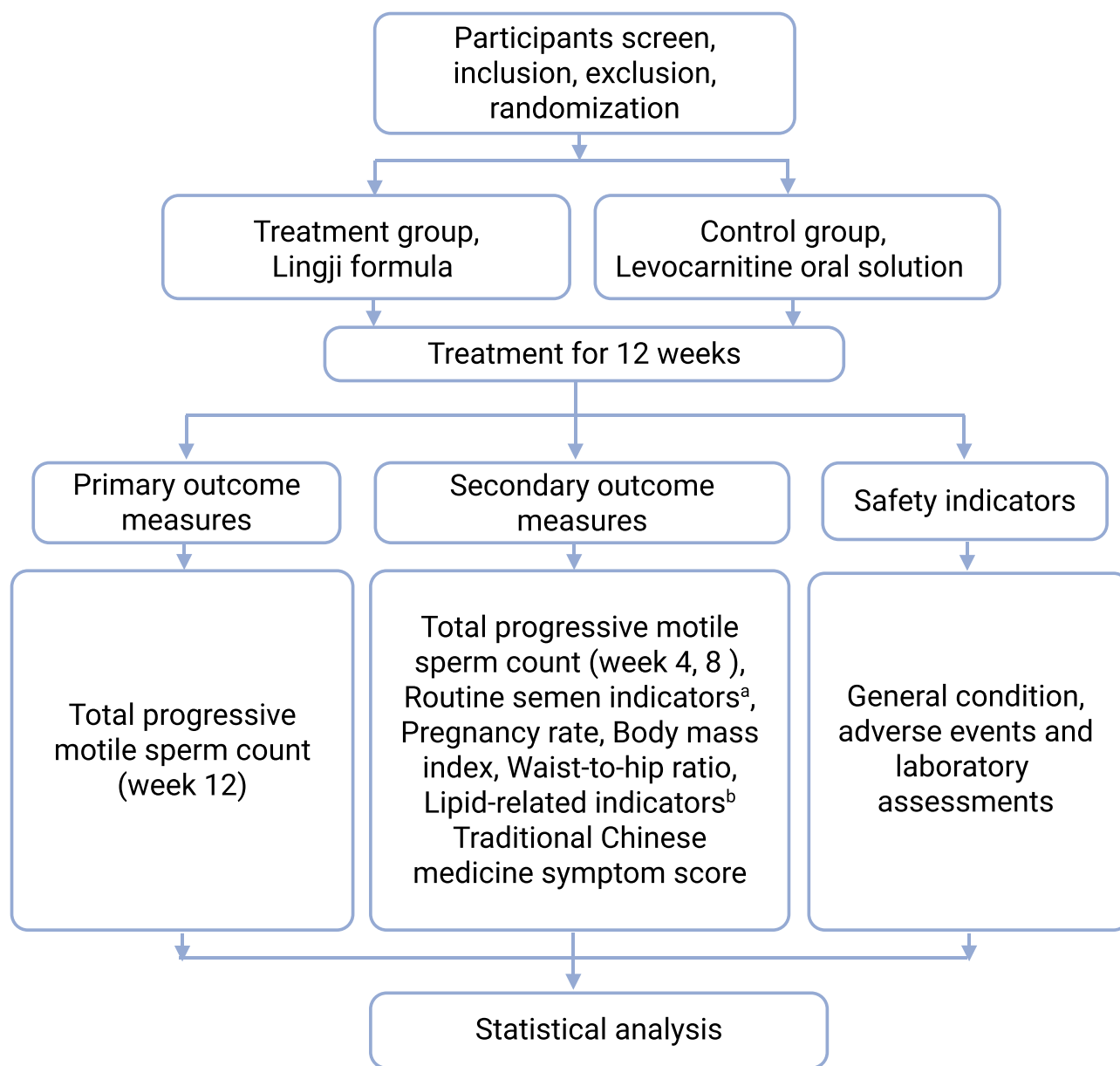
Participant screening and recruitment will be conducted over a one-year period (August 2025–August 2026) at Department of Andrology, Xiyuan Hospital, China Academy of Chinese Medical Sciences. Thoroughly trained researchers will oversee the process, ensuring all participants provide informed consent before joining. Study participation is voluntary, and participants retain the right to withdraw at any point without facing negative repercussions.

#### Diagnostic Criteria

The following diagnostic criteria are based on the guidelines.<sup>27,28</sup> The participants must simultaneously meet the diagnostic criteria for male infertility, obesity and oligoasthenozoospermia.

Diagnostic criteria for male infertility:

- a. The couple live together and have normal sexual life;
- b. The couple do not use any contraception for more than one year;
- c. The woman does not be pregnant due to male factors.



**Figure 1** Study Flowchart. <sup>a</sup>Indicates percentage of progressive motility spermatozoa, percentage of non-progressive motility spermatozoa, sperm concentration, semen volume, percentage of normal morphology spermatozoa; <sup>b</sup>Represents low-density lipoprotein, triglyceride and total cholesterol.

Diagnostic criteria for oligoasthenozoospermia: Two routine semen analyses: sperm concentration  $<15 \times 10^6/\text{mL}$  and the percentage of forward motile sperm  $<32\%$ .

Diagnostic criteria for obesity: According to body mass index (BMI),  $\text{BMI} = \text{weight}/\text{height}^2$ ,  $\text{BMI} \geq 28\text{kg}/\text{m}^2$  is defined as obesity.

### Inclusion Criteria

The study inclusion criteria are as follows:

- Meanwhile, meet the western medical diagnostic criteria of male infertility and oligoasthenozoospermia and obesity;
- Meet the TCM diagnostic criteria of kidney essence deficiency and dampness in the essence chamber;
- 22 years old  $\leq$  age  $\leq$  45 years old;
- Voluntarily sign the informed consent form.

**Table 1** The Process Chart of the Trial

Time Point	Baseline	Treatment Phase		
	Week 0	Week 4	Week 8	Week 12
<b>Enrollment</b>				
Inclusion/exclusion criteria	X			
Informed consent	X			
Physical examination	X			
Randomization and allocation	X			
Demographic characteristics	X			
<b>Intervention</b>				
Treatment group		X	X	X
Control group		X	X	X
<b>Assessment</b>				
Total progressive motile sperm count				
Routine semen indicators	X	X	X	X
Pregnancy rate	X	X	X	X
Body mass index	X	X	X	X
Waist-to-hip ratio	X	X	X	X
Lipid-related indicators	X			X
Traditional Chinese medicine symptom score	X	X	X	X
<b>Safety evaluation</b>				
General condition	X	X	X	X
Adverse events		X	X	X
Laboratory assessments*	X	X	X	X

**Notes:** "X" indicates yes. \*Laboratory assessments include routine blood tests, routine urine tests, liver function tests (alanine transaminase and aspartate aminotransferase), kidney function tests (blood urea nitrogen and creatinine) and electrocardiography.

## Exclusion Criteria

This study exclusion criteria are as follows:

- Congenital chromosomal abnormalities microdeletions of the Y chromosome or other known hereditary diseases that may cause sterility, or obstructive azoospermia resulting in infertility;
- Combined with moderate to severe varicocele cryptorchidism or chitis epididymitis, mycoplasma chlamydia and other diseases that clearly affect semen quality;
- Combined with erectile dysfunction, ejaculation abnormality and other sexual dysfunctions resulting in the inability to complete intravaginal ejaculation;
- Combined with diabetes mellitus requiring long-term medication to control the glucose;
- Combined with liver and kidney insufficiency (alanine transaminase and/or aspartate aminotransferase is more than 1.5 times of the upper limit of normal value; blood urea nitrogen and/or creatinine is more than the upper limit of normal value), serious cardiovascular, serious cerebrovascular diseases, hematopoietic system diseases, psychiatric diseases and other complications;
- History of allergy to any drugs or ingredients used in this study;
- Receipt of other relevant treatments for this disease such as aromatase inhibitors, estrogen antagonists etc. two weeks prior to treatment.

## Termination Criteria

The termination criteria are as follows:

- a. If a participant's condition deteriorates significantly during the trial, the doctor may discontinue their participation and recommend alternative treatments to ensure their safety. Such cases will be recorded as invalid.
- b. Certain comorbidities, complications, etc., occurring in the participant are not suitable to continue to undergo the trial.
- c. Poor compliance of the participant, or the use of prohibited treatments specified in the study.
- d. Serious adverse events occur.

All case record forms should be retained post-discontinuation, with efficacy and safety data analyzed using the last available results. For withdrawn participants, researchers should document: (1) withdrawal reasons, (2) final therapeutic evaluation, and (3) personalized follow-up plans based on the participant condition and preferences.

## Sample Size Consideration

In this study, the total progressive motile sperm count is used as the primary outcome measure, and a non-inferiority trial design is adopted. Based on the results of the previous pilot clinical trial, the change in the total number of forward-moving sperm after the application of Levocarnitine oral solution was  $(7.32 \pm 2.07) \times 10^6$ . It was assumed that the change in the total progressive motile sperm count after 12 weeks of treatment with Lingji formula would be the same as that of Levocarnitine oral solution. According to the guidelines and clinical considerations, we used the software (PASS 2021, NCSS LLC., Kaysville, UT, USA) to calculate the sample size and the non-inferiority margin was set at 1.464, with  $\alpha = 0.025$  (one-sided) and  $\beta = 0.2$ .  $u_{1-\alpha} = 1.96$  and  $u_{1-\beta} = 0.84$ . Considering a 1:1 randomization ratio, 32 participants in each of the two groups should be required. Taking into account a 20% dropout rate, 78 participants should be included in this trial.

## Randomization and Allocation

The study will utilize 1:1 randomized allocation between treatment and control groups. A randomization table will be created by statisticians using SAS 9.4 (SAS Institute, Cary, NC), and participants will be assigned to groups according to their serial numbers in this table. Allocation details will be sequentially numbered and secured in opaque, sealed envelopes.

## Intervention

Both of the treatment group and the control group will receive health education at the time of enrollment, including instructions from the researchers to engage in appropriate exercise, maintain a healthy lifestyle, and have regular sexual intercourse during ovulation without using contraception. In addition to the interventions of this study, participants will also be not allowed to take or apply any TCM preparations, nutritional supplements, or Western medicines that may affect sperm quality during the intervention period.

The treatment group will receive Lingji formula, which will be provided by the Department of Pharmacy, Xiyuan Hospital, China Academy of Chinese Medical Sciences. Meanwhile, the control group will receive Levocarnitine oral solution, which will be purchased from NORTHEAST PHARMACEUTICAL GROUP CO., LTD. The daily dosage of Lingji formula is a decoction containing 71g of raw medicine. Participants in the treatment group will take Lingji formula twice daily, half an hour after breakfast and dinner. Also, participants in the control group will take Levocarnitine oral solution twice daily for 10 mL each time, half an hour after breakfast and dinner. The treatment period will last 12 weeks.

## Outcome Measures

### Primary Outcome Measures

The total progressive motile sperm count (the total progressive motile sperm count = sperm concentration  $\times$  semen volume  $\times$  percentage of progressive motile sperm) in week 12 is an important indicator in semen analysis, used to

evaluate male fertility. It refers to the absolute quantity of sperm that can move forward in a semen sample, reflecting the effective motility of sperm during the fertilization process.<sup>29</sup>

### Secondary Outcome Measures

The total progressive motile sperm count at weeks 4 and 8 serve as the secondary outcome measures in this study. Semen routine indicators (include the percentage of progressive motile sperm, percentage of non-progressive motile sperm, sperm concentration, semen volume, percentage of normal morphology sperm) are used to assess the sperm quality. Lipid-related indicators such as low-density lipoprotein, triglyceride and cholesterol will be tested to evaluate the lipid profile at the baseline and week 12. Additionally, the Chinese Medicine Symptoms Score (CMSS) will be evaluated based on changes in indicators at weeks 4, 8, and 12 in comparison to baseline efficacy. In addition, pregnancy rate, BMI, and waist-to-hip ratio at weeks 4, 8 and 12 will be evaluated.

### Safety Evaluation and Adverse Events

Safety will be evaluated through general condition monitoring, laboratory tests, and adverse events. At each visit, participants will undergo physical examinations and vital sign checks. Laboratory assessments will include blood and urine tests, alanine transaminase, aspartate transaminase, blood urea nitrogen, creatinine and electrocardiograms (Table 1). Evaluators will document any adverse events throughout the study.

### Data Management and Quality Control

Two trained assistants will collect data, while statisticians remain blinded to treatment allocations until final analysis. The principal investigator will oversee trial coordination, including recruitment, interventions, and follow-up. A dedicated quality control team will include conducting biweekly reviews of study procedures, monitoring compliance with the treatment and quality assurance system, and reporting on overall trial quality. Standardized management protocols will be applied throughout the clinical and data processing stages.<sup>30</sup>

### Data Analysis

A third-party professional statistician who does not know the protocol will participate in this study. Statistical analyses will be performed using SPSS software (version 25.0, IBM, Chicago, IL, USA). The test level  $\alpha = 0.05$ , with  $P < 0.05$  representing a significant difference. Normally distributed continuous data will be presented as mean $\pm$ SD, analyzed using paired t-tests (within-group) or independent t-tests (between-group); Non-normally distributed data will be presented as median (interquartile spacing), with between-group comparisons analyzed using the Mann–Whitney *U*-test. Repeated measures will be analyzed using analysis of covariance, while categorical data will be presented as frequencies (%) and assessed by chi-square tests.

### Discussion

The mechanism of obesity-associated male fertility is still unclear, mainly because obesity is associated with many complications.<sup>31</sup> The accumulation of fat in the scrotum of obese patients may directly affect the microenvironment of spermatogenesis, leading to obstruction of spermatogenesis and a decrease in spermatogenesis.<sup>32</sup> The related mechanisms include oxidative stress, testicular heat stress, disorders in the hypothalamic–pituitary–gonadal axis, and the general inflammatory response.<sup>33</sup> Fat factors include adiponectin, resistin, chemotaxin, etc, and expression of these fat factors in the reproductive glands may also directly affect spermatogenesis and motility.<sup>34,35</sup> Due to the multiple mechanisms involved in obesity-associated male infertility, there is still no standardized recommended treatment for male infertility in obese men. Recently, the application of TCM in male reproductive health has gradually been emphasized.<sup>36–38</sup> Yang et al showed that the improvement of obesity-associated reproductive disorders by TCM involves the inhibition of oxidative stress as well as the improvement of endoplasmic reticulum stress in the testicular tissues of obese mice,<sup>39</sup> and in Dong et al's experiment, the mechanism of TCM to improve obesity-associated oligoasthenozoospermia may involve phosphoinositide 3-kinase/protein kinase B and mitogen-activated protein kinase signaling pathways.<sup>40</sup> However, there is no clinical study on the intervention of TCM in obesity-associated male infertility.

According to TCM, obesity is related to the dampness,<sup>41</sup> and male reproductive function is closely related to the kidney, which is based on the theory of “the kidney governing reproduction” proposed in “The Yellow Emperor’s Canon of Internal Medicine”.<sup>42</sup> Therefore, from the perspective of TCM, deficiency of kidney essence and dampness in the essence chamber may be the significant pathological mechanisms of the infertility in obese men. Lingji formula conforms to the principles of TCM in formula composition, and it includes both Chinese herbs for tonifying the kidney and those for eliminating the dampness. Due to ethical limitations on using a placebo of Lingji formula, we chose Levocarnitine oral solution as the control drug, which is supported by guidelines and expert consensus in China.<sup>16,17</sup> On the one hand, clinical evidence has confirmed that Levocarnitine has clinical efficacy in improving sperm motility and concentration.<sup>21,43</sup> On the other hand, Levocarnitine can promote fatty acid oxidation, improve energy metabolism, and improve disorders of glucose and lipid metabolism, which may benefit obese individuals.<sup>44,45</sup> Therefore, we also hope that this clinical trial can provide evidence for the improvement of semen quality in male infertility of obese men.

For the assessment of outcome indicators, we will refer to our previous study and chose the total progressive motile sperm count as the main efficacy indicator,<sup>46</sup> and we will also evaluated the trends of other routine semen indicators, BMI, waist-to-hip ratio, and CMSS by repeated measures analysis of covariance to further assess the semen quality and physical condition. The blood lipid profile is a recommended check-up for the infertile male population in addition to a simple evaluation of basic sperm parameters especially those of obese men.<sup>47</sup> Wu et al showed that TCM can improve the semen quality of high-fat diet-induced obese mice by reducing weight and lipid levels.<sup>48</sup> Evidence from a systematic review also showed the potential of TCM in improving lipid profiles such as low-density lipoprotein, triglyceride and cholesterol.<sup>49</sup> Therefore, we will evaluate these three biomarkers to confirm whether TCM improves blood lipid levels in obese male patients with infertility and whether there is an association between improved lipid levels and improved semen levels.

## Conclusion

Our randomized controlled trial will signify progress in the TCM for infertility in obese men. This study protocol will be the first one to explore the efficacy and safety of TCM for obesity-associated male infertility. The research findings will provide clinical evidence for the use of TCM in treating male infertility of obese patients. We also hope that this treatment strategy will benefit those male patients who troubled by the infertility as well as the obesity.

## Data Sharing Statement

The data presented in this study are available on reasonable request from the corresponding author (Jiwei Zhang).

## Ethics Approval and Consent to Participate

The study involving human participants was reviewed and approved by the Research Ethical Committee of Xiyuan Hospital, China Academy of Chinese Medical Sciences (2025XLA027-2). And the study has also been registered with the <http://itmctr.ccebtcn.org.cn> (ITMCTR number is ITMCTR2025001503). The researchers should provide explicit informed consent, which has been authorized by the ethics committee and render participants sufficient time to consider. Participants must sign the informed consent form before randomization. All participants will be permitted to withdraw their informed consent with or without providing any reasons at any time during the trial. All the participant details will be fully anonymous and confidential.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. No Artificial Intelligence tools have been used in the drafting of this manuscript.

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## Disclosure

The authors report there are no conflicts of interest in this work.

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