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STUDY PROTOCOL

# Electroacupuncture Prevent and Treat Perioperative Cognitive Impairment in Elderly Patients Undergoing Hip Surgery: A Protocol for a Randomized Controlled Trial

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**Background:** Electroacupuncture is effective in treating perioperative neurocognitive disorder (PND) and has good application prospects in the prevention and treatment of PND. However, the mechanism of electroacupuncture treatment for PND is comparatively unexplored.

**Methods/Design:** This is a single-center clinical, prospective randomized controlled clinical trial protocol. 180 patients will be randomly divided into the treatment group and the control group in a ratio of 1:1. Both groups of subjects received routine care, while the treatment group will receive electroacupuncture treatment twice a day for 10 days. Acupoints will include Baihui (DU20), Shangxing (DU23), Yintang (EX-HN3), Meichong (BL3), Fengchi (GB20), Cuanzhu (BL2), Laogong (PC8), Hegu (LI4), and Zusanli (ST36). The primary outcome measure is the Mini-mental State Examination (MMSE). And the secondary outcome measures are the Confusion Assessment Method (CAM), Visual Analog Scale (VAS), Pittsburgh Sleep Quality Index (PSQI), Generalized Anxiety Disorder (GAD-7), Patient Health Questionnaire-9 (PHQ-9), and interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), neuron-specific enolase (NSE), superoxide dismutase (SOD), central nervous system-specific protein (s100-β) in serum. The outcome measures will be evaluated at baseline, during treatment and 1 week after treatment. What's more, the incidence of non-delirium complications and mortality within 30 days will also be measured.

**Discussion:** Results of this trial are expected to clarify the value of electroacupuncture performed on perioperative cognitive impairment in elderly patients undergoing hip surgery.

**Ethics:** This trial has been approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (No.2024–037).

**Trial Registration:** International Traditional Medicine Clinical Trial Registry, ITMCTR2024000298 (http://itmctr.ccebtcm.org.cn/), registered on 25 August, 2024. The trial will comply with the Declaration of Helsinki.

**Keywords:** protocol, electroacupuncture, perioperative cognitive impairment, elderly patients



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## Introduction

Perioperative Neurocognitive Disorder (PND) is a recognized public health issue[1] including Preoperative Neurocognitive Disorder, Postoperative Delirium, Delayed Neurocognitive Recover and Postoperative Neurocognitive Disorder. Although cognitive impairment occurs after various types of surgeries, it is most common after cardiac surgery using cardiopulmonary bypass, orthopedic, and vascular procedures.[2] One research has indicated that orthopedic operations are associated with an increased risk of cognitive decline three months after surgery, which appears not to improve over the course of a 6-year follow-up, with implications for reduced daily functioning.[3] Therefore, the cognitive function status of orthopedic surgery patients cannot be ignored. Advanced age is widely recognized as a high-risk factor in the development of PND. One research has found that approximately a quarter of elderly patients undergoing major surgery suffer from cognitive impairment, with 50% of patients experiencing permanent functional impairment.[3] According to the research, the incidence of postoperative delirium rises to 12.0%–23.8% in patients 60 years of age and beyond,[4] and it can reach 41% in senior patients 65 years of age and older who have hip fractures.[5] An increasing number of studies indicate that elderly patients with hip fractures have more comorbidities and underlying diseases, coupled with the effects of fracture trauma, surgery, anesthesia, etc., cognitive dysfunction increases significantly during the perioperative period.[6] The prevention of perioperative neurocognitive problems and the provision of early diagnosis and care have become critical tasks in today's aging society.[7]

The destruction induced by peripheral inflammation and subsequent neuroinflammation are widely accepted factors in the pathogenesis of PND. Peripheral inflammatory cytokines increase the permeability of the blood–brain barrier by disrupting the tight connections between endothelial cells, causing peripheral inflammatory cytokines to penetrate the blood–brain barrier and trigger neuroinflammation, ultimately leading to changes in brain structure and function, leading to the occurrence of PND.[8] Animal studies have found that surgery and anesthesia can raise HMGB1 levels in both the periphery and hippocampus, accompanied by the development of cognitive impairment,[9] indicating that changes in peripheral inflammatory signals can have a negative impact on central nervous system function, leading to cognitive decline.

PND can be prevented and treated with both drug and non-drug therapies. Among them, non-pharmacological therapy is the first-line measure for treating diagnosed PND, such as preoperative cognitive rehabilitation, comprehensive geriatric assessment, implementation of fast track surgery, improvement of sleep (including providing a quiet and dim sleeping environment, reducing interference from night care activities, using night goggles and earplugs, etc)., and avoiding prolonged liquid fasting, deep anesthesia, decreased brain oxygen saturation, as well as intraoperative hypothermia. Drug therapy mainly focuses on symptomatic treatment, including the use of dexmedetomidine to improve sleep, the use of nonsteroidal anti-inflammatory drugs and acetaminophen for pain relief, the use of haloperidol and second-generation antipsychotics to treat patients with severe agitation or mental disorders, and the avoidance of benzodiazepines and anticholinergic drugs.[10] Antipsychotic medications, however, have been linked to adverse effects such as delirium and decreased patient survival, according to studies.[11] There is currently little study on PND treatment in modern medicine, and the findings are inconsistent. In addition, drug therapy has a lot of side effects, and non-drug therapy also has certain limitations. Therefore, it is urgent to find effective prevention and treatment methods with minimal adverse reactions.

Acupuncture is the most representative non-pharmacological therapy in traditional Chinese medicine, with advantages such as wide applicability and no side effects. Electroacupuncture is the combination of acupuncture and electrical stimulation effects to enhance the therapeutic effect of conventional acupuncture.[12] According to an earlier research, electroacupuncture primarily reduces neuronal death and inhibits inflammatory responses to alleviate neurocognitive impairment.[13] Clinical studies have found that electroacupuncture can improve patients' pain, neurocognitive function, and mental state.[14] It has found that electroacupuncture can improve PND induced by factors such as cerebral ischemia-reperfusion and sevoflurane in elderly rats,[15,16] reduce the synthesis of early postoperative inflammatory mediators in elderly rats, inhibit neuronal cell apoptosis in hippocampal tissue, and slow down the occurrence of PND in rats.[13]

Therefore, this study conducted a single center, prospective, and block randomized controlled design to provide evidence-based support for electroacupuncture in the prevention and treatment of PND. The aim is to elucidate the clinical efficacy of electroacupuncture intervention in PND, investigate potential mechanisms of action, and uncover its regulatory effect on inflammatory factor levels. Our goal is to identify sensitive biomarkers that could be utilized for early identification and prediction of perioperative cognitive function prognosis.

# Methods/Design

## Study Design

This single-center clinical trial will be conducted at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine. This trial has been approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (No.2024–037) and has been registered in clinical trials. The government approval number is ITMCTR2024000298. The trial design is summarized in Figure 1.

## Participant Recruitment

This trial is conducted from March 2024 to May 2026. Patients will be recruited from the trauma orthopedic ward. Participants and their families will be informed about the character, objective, and potential risks of the trial. Before enrollment, participants will voluntarily sign a consent form.

## Inclusion Criteria

1. American Society of Anesthesiologists (ASA) grades I–III.
2. Age ≥ 65 years old and ≤ 95 years old, gender not limited.
3. Hip fracture patients: 1) Femoral neck fracture, elective joint replacement, or internal fixation surgery under general anesthesia; 2) Femoral intertrochanteric fracture, scheduled for intramedullary nail fixation surgery under general anesthesia.
4. Understand and agree to participate in this study and sign the informed consent form.

## Exclusion Criteria

1. Severe heart, liver, and kidney dysfunction.
2. Having a history of traumatic brain injury, mental illness, drug abuse, or alcoholism.

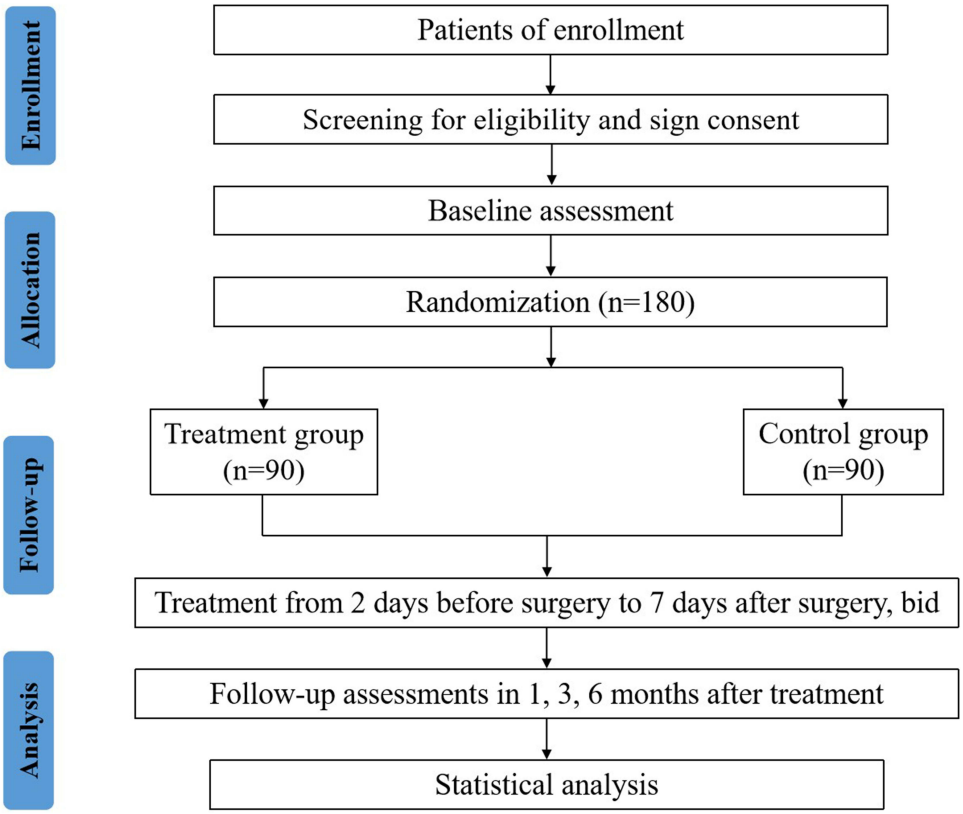


**Figure 1** Flow chart of the study process.


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3. Equipped with pacemakers or other electrical stimulation devices.
4. With language barriers or uncorrected hearing impairments that prevented them from comprehending or responding to the standardized assessment scales (eg, failure to complete ≥ 80% of questionnaire items due to communication limitations).

## Drop-Out Criteria

1. Unable to tolerate electroacupuncture treatment or unable to cooperate with scale evaluation, laboratory tests, etc.
2. Those who experienced serious adverse reactions and complications during the research period.
3. During the research period, if the patients' condition worsens, it is not advisable to continue participating in the study.

## Randomization and Blinding

This study is a block randomization, parallel-group controlled design with a block size of 6. A randomization table will be generated using SPSS 26.0 software, and participants who completed the informed consent form will be randomly assigned to the treatment group and the control group in a 1:1 ratio. The randomization plan will be assigned by the trial researcher, and the patient grouping information will be placed in a sealed, opaque envelope which is sequentially numbered. The envelope will be kept by a dedicated person and randomly assigned after the patients have been screened and have signed the informed consent. Group assignment results will be concealed from the outcome assessors, supervising doctors, data analysts.

## Interventions

### Anesthesia Plan

All surgeries will be performed using iliac fascial nerve block and laryngeal mask anesthesia. After patients entering the operating room, peripheral and internal jugular vein access will be opened, and 8–10 mL/kg of Ringer's solution acetate will be administered. The ECG, invasive arterial blood pressure, $SpO_2$, $PETCO_2$, respiratory function monitoring, and BIS value monitoring will be connected.

### Anesthesia Induction

The anesthesiologist will administer intravenous injection of 0.3 mg/kg cyclosporine, 5 μg/kg sufentanil, 0.6 mg/kg rocuronium bromide, and inhalation of pure oxygen through a face mask. Artificial assisted breathing will be performed. After muscle relaxation, a laryngeal mask will be inserted to start mechanical ventilation. We will ensure that patients maintain the tidal volume of 8–10mL/kg, the respiratory rate of 10–12 breaths per minute, and an oxygen flow rate of 2L/min during the operation. The affected limb will undergo iliac fascial nerve block: 30mL of 0.25% ropivacaine.

### Anesthesia Maintenance

Intraoperative infusion of rocuronium bromide 0.3mg/(kg·h), target controlled infusion (TCI) of propofol 4–8 mg/(kg·h), and remifentanil 0.2–0.5 μg/(kg·min) will be administered to maintain muscle relaxation. We will adjust the plasma concentration of propofol or remifentanil to maintain BIS between 40 and 60. Blood pressure and heart rate will be maintained within ± 20% of baseline during surgery. When blood pressure and heart rate above baseline by more than 20%, sufentanil 0.1 μg/kg and vasoactive drugs will be used as needed. Muscle relaxants will be stopped and the concentration of propofol and remifentanil will be reduced 10 minutes before the end of the surgery.

## The Treatment Group

We will provide routine orthopedic perioperative care to patients and administer electroacupuncture treatment. The prescription for acupoints will include Baihui (DU20), Shangxing (DU23), Yintang (EX-HN3), Meichong (BL3), Fengchi (GB20), Cuanzhu (BL2), Laogong (PC8), Hegu (LI4), and Zusanli (ST36). The names and locations of acupoints will be in accordance with the national standard of the People's Republic of China (GB/T 12346–2021). The patients will be in a supine position and used 0.25mm × 40mm disposable sterile acupuncture and moxibustion needles (Andy, Guizhou Andy Pharmaceutical Co., Ltd). Among them, DU20 and DU23 will be horizontally inserted to

a depth of 0.5–0.8 cun, EX-HN3 and BL3 will be horizontally inserted to a depth of 0.3–0.5 cun, GB20 will be stabbed 0.8–1.2 inches towards the nose tip, BL2 will be stabbed 0.3–0.5 inches towards the inner edge of the eye socket, PC8 will be stabbed straightly 0.3–0.5 inches, LI4 will be stabbed straightly 0.5–1 inches, and ST36 will be stabbed straightly 1–2 inches. We will use a low-frequency pulse electroacupuncture treatment device to perform acupuncture until there is a sense of qi retention. We will connect one pair of electrodes to DU20 and GB20, and the other pair to DU23 and EX-HN3. DU20 and DU23 will be connected to the negative pole, and GB20 and EX-HN3 will be connected to the positive pole. The waveform of the electrical stimulation pulse will be a sparse wave with a frequency set at 2Hz/100Hz. The current intensity is based on the patients' tolerance. After continuous stimulation for 30 minutes, the acupoint will be compressed with a disinfectant cotton ball to prevent bleeding when the needle pulled out. The treatment will be administered twice a day from 2 days before surgery to 7 days after surgery. All treatment procedures will be performed by the same acupuncture and moxibustion.

## The Control Group

This group of patients will receive routine perioperative care in orthopedics without electroacupuncture intervention.

## General Information

Before the surgery, we will record the patients' basic information, including name, gender, age, education, occupation, marital status, home living conditions (whether accompanied by family members or caregivers), dietary preferences, alcohol consumption history, smoking history, current routine medication, previous surgical history, anesthesia method, diagnosis, preoperative complications, and record blood routine, blood glucose, and liver and kidney function tests within one week before surgery; preoperative visit to patients, record electrocardiogram, heart rate, blood pressure, blood glucose and other indicators, and record ASA grading.

During surgery, we will record anesthesia drugs, dosage and duration of use, fluid and blood product dosage, bleeding and urine volume, as well as other adjuvant therapy drugs and dosage, intraoperative blood pressure, lowest hemoglobin level, hematocrit, etc.

After the surgery, we will record the patients' surgical time, anesthesia recovery time, postoperative recovery status, heart rate, blood pressure, percutaneous arterial $SpO_2$ and other vital signs indicators.

## Outcome Measurement

### Primary Outcome

The primary outcome will be assessed using the Mini-mental State Examination (MMSE). MMSE mainly includes five dimensions: computing power, attention, orientation, recall ability, and language ability, with a total score of 30 points. Defining illiteracy<17 points, elementary school<20 points, and middle school and above<24 points as cognitive impairment. MMSE will be evaluated on the baseline, the $1^{st}$, $3^{rd}$, and $7^{th}$ day after surgery.

### Secondary Outcome

1. Confusion Assessment Method (CAM): CAM is a method used to assess a patients' state of consciousness, characterized by acute onset, fluctuating conditions, and lack of concentration. When evaluating, it is necessary to observe whether the patient has acute changes in their mental state, as well as whether there are fluctuations in symptoms throughout the day, such as occasional or mild behavioral abnormalities. At the same time, it is important to pay attention to whether the patient has difficulty concentrating, such as being easily distracted or unable to keep up with the conversation. If the patients' thinking is confused or incoherent, such as the conversation topic being scattered or unrelated to the conversation content, or suddenly shifting from one topic to another without warning, evaluation is also necessary. If features 1 and 2, combined with features 3 or 4, are positive among the above features, then the patient is diagnosed with delirium, ie CAM positive.
2. Pittsburgh Sleep Quality Index (PSQI): PSQI is used to evaluate the sleep quality of the population, including seven components: sleep quality, falling asleep time, sleep duration, sleep efficiency, sleep disorders, hypnotic

drugs, and daytime dysfunction. The total score of PSQI ranges from 0 to 21 points, and the score is inversely proportional to sleep quality, meaning that a higher PSQI score indicates poorer sleep quality.

3. Visual Analog Scale (VAS): VAS is used for pain assessment, using a 10cm long moving ruler with 10 scales on one side, with "0" and "10" points on both ends. A score of 0 indicates painlessness; 1–3 points belong to mild pain; 4–7 points belong to moderate pain; 8–10 points belong to severe pain.
4. Generalized Anxiety Disorder (GAD-7): GAD-7 is, respectively, used to measure patients' anxiety states.
5. Patient Health Questionnaire-9 (PHQ-9): PHQ-9 is, respectively, used to measure patients' depression states.
6. We will collect serum Interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), neuron-specific enolase (NSE), superoxide dismutase (SOD), central nervous system-specific protein (s100-β). The evaluation time points of the secondary outcome are the same as the primary outcome.

## Safety Evaluation

Adverse events will be recorded including shock, local infection, intolerable tingling during EA, and postoperative adverse reactions.

## Quality Control

This trial will be conducted with careful reference to suggestions provided by experienced acupuncturists, orthopedics doctors, and anesthesiologists. To assure the quality of this experiment, the operator will be an acupuncture clinician with at least five years of experience. All researchers will participate in professional training to ensure a full understanding of standard operating procedures and treatment plans. At the same time, clinical trial experts will supervise the trial and hold regular meetings to ensure the quality of the trial.

## Sample Size

The calculation of sample size will be based on the PND incidence rate. According to preliminary experiments, the overall incidence of PND in the treatment group was 11.3%, while the overall incidence of PND in the control group was 32.4%. Assuming bilateral α=0.05 and a confidence level of 90%, the sample size will be calculated using the formula.

By calculation, n=81 cases can be obtained, which means that the treatment group and the blank control group each require 81 research subjects. Considering a 10% loss to follow-up and refusal to follow-up situation, the final required research subjects for the treatment group and the control group will be at least 90 each, with a total of at least 180 research subjects included.

$$n = \frac{2\overline{pq}\left(z_{\alpha} + z_{\beta}\right)^2}{\left(p_1 - p_2\right)^2}$$

## Statistical Analysis

In this study, all statistical analyses will be conducted by an independent statistician using SPSS26.0 software (IBM, Armonk, NY, USA). The measured data will be expressed as mean ± standard deviation, and the count data will be expressed by the ratio or composition ratio. For comparing measured data between the two groups, the first normal analysis will be performed. T-test will be used for the measured data conforming to normal and homogeneity of variance, and non-parametric rank sum test will be used for non-normally distributed measured data. The data will be counted by the Chi-Square test or Fisher's exact test. $P<0.05$ will be considered statistically significant.

The intention-to-treat (ITT) principle will be applied in all primary analyses. All randomized participants (N=180) will be included in the analysis, irrespective of protocol adherence, dropout, or missing follow-up data. Missing outcome values will be addressed using multiple imputation by chained equations (MICE) with imputed datasets. Baseline covariates and observed outcome measures will be incorporated into the imputation model under the missing-at-random (MAR) assumption. Sensitivity analyses will be performed to assess robustness, including complete-case analysis and last observation carried forward (LOCF) methods.

## Discussion

Current researches suggested that the pathogenesis of PND primarily involves pathological factors such as neuroinflammation, impaired synaptic function, neuronal apoptosis, oxidative stress, and abnormal accumulation of β-amyloid protein (Aβ).[17] Inflammation plays a significant role in the pathogenesis of PND, with numerous studies confirming that inflammatory factors can cause neuronal damage.[18] Inflammation can interfere with normal hippocampal neural function and cause damage to the hippocampal neurons, with their synaptic ultrastructure potentially disrupted by volatile inhaled anesthetics.[19] Reports indicated that inflammatory cytokines including IL-6 and TNF-α are elevated in the serum and hippocampal tissue of patients with PND.[20,21] Additionally, researches have found that anesthesia or surgery can significantly elevate the levels of IL-6 in mouse plasma and olfactory epithelial cells. The administration of IL-6 neutralizing antibodies can reverse the impairment of learning and memory abilities in mice,[22] further underscoring the close association between the etiology of PND and inflammation of the central nervous system.

Acupuncture is an important part of external treatment of traditional Chinese medicine. Acupoint stimulation treats systemic diseases through meridians and acupoint conduction.[23] Studies have confirmed that acupuncture has the effects of inhibiting the expression of inflammatory factors, anti-oxygen free radical damage, inhibiting apoptosis of hippocampal neurons, regulating the function of central cholinergic system, regulating synaptic function and improving stress level. It can protect the brain through multiple ways and targets, and has an important regulatory effect on cognitive function.[24] On the basis of acupuncture and moxibustion, combined with electrical stimulation, electroacupuncture is a disease treatment method that uses different waveform, frequency, intensity, time, and other parameters to adjust the balance of qi and blood and improve human function.[25] Electroacupuncture has been used for perioperative patients and has shown positive effects in relieving postoperative pain, protecting organ function stability, and promoting faster postoperative recovery. Clinical trials have shown that electroacupuncture can inhibit inflammatory reactions and neuronal apoptosis, regulate the balance of pro-inflammatory and anti-inflammatory factors, have significant neuroprotective effects, alleviate oxidative stress reactions, improve cerebral blood flow, and exert potential neuroprotective effects.[26] It can effectively prevent or reduce the occurrence of PND in elderly patients.[27,28]

Based on the above-mentioned studies, we designed this single-center, prospective, and block randomized controlled. The study will preliminarily investigate the potential mechanisms of electroacupuncture in preventing and treating PND, and seek sensitive biomarkers for early identification and prediction of perioperative cognitive function prognosis. This study will not only detect the levels of blood inflammatory factors and cognitive related indicators in patients, but also plan to conduct correlation analysis between the test results and cognitive scale results, in order to further explore the mechanism of electroacupuncture improving cognitive function in elderly patients during the perioperative period, and provide more reliable evidence-based support for electroacupuncture prevention and treatment of PND.

This study still has some limitations: 1) The limited sample representativeness due to a single-center experimental design may introduce bias. Additional influencing factors should be considered and further verified in a larger sample population. 2) The study included patients aged between 65 and 95 years, covering a broad age range with varied preoperative cognitive functions. These differences could significantly affect the research outcomes. Thus, the analysis will include stratification and subgroup studies based on age and preoperative cognitive function. 3) This study used fixed frequencies and waveforms for intervention, lacking the impact of different frequencies and waveforms on cognitive function improvement. This part can be improved in future research.

## Trial Status

Participants of the trial are currently being recruited.

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## Author Contributions

All authors have made significant contributions to the work of this experimental protocol and paper, whether in terms of concept, research design, execution, data collection, analysis, and interpretation, or in all of these fields; participate in drafting, revising or critically reviewing articles; provide final approval for the upcoming version. We have reached an agreement on the journal to which the article has been submitted, and agree to be responsible for all aspects of the research plan.

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## Disclosure

The authors declare that the research is conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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