Informed Consent Form

Dear_____

To investigate the recovery process of motor function after stroke, and develop a new effective treatment, now we invite you to participate in this clinical scientific research. This is a single-center randomized, double-blind controlled trial investigating the efficacy of transcutaneous auricular vagus nerve Stimulation (taVNS) in improving upper extremity motor function in stroke patients. This informed consent form will provide you the brief introduction of this study, and give the details of both the benefits and risks you may occur. If you have any questions, please contact us in anytime. Lastly, we would highly respect your personal decision whether you would like to participate in this study after fully acknowledged.

1. Introduction: Why do we invite you to participate in the study?

Recently, there has been increasing attention on the application of transcutaneous auricular vagus nerve stimulation (taVNS) in stroke. This innovative technique involves non-invasive electrical stimulation of the vagus nerve. A controlled study was conducted by Dawson et al., using a randomized, double-blind approach, which has demonstrated that vagus nerve stimulation (VNS) combined with motor function training can effectively promote the upper limb motor function in stroke patients

(2021, Lancet). Notably, the Food and Drug Administration (FDA) has approved the use of VNS combining motor rehabilitation training for ischemic stroke patients with upper extremity dysfunction in the same year. However, it is worth noting that the VNS technique requires surgical implant with side effects and contraindications. Consequently, researchers are exploring taVNS as a potential alternative intervention. Compared to VNS, taVNS offers a low-risk and user-friendly option that eliminates the surgery complications. In recent years, an increasing evidenced-based studies have highlighted the potential benefits of taVNS in stroke patients, particularly in improving upper limb function. Notably, a recent meta-analysis has demonstrated that the efficacy of taVNS in stroke patients' upper extremity rehabilitation may be comparable to that of VNS. Some studies have suggested that taVNS paired with motor training which would bring strengthening effect on motor learning (2023, Neuro). Therefore, taVNS combined with motor training has the potential to be an effective clinical therapy for post-stroke rehabilitation.

2. Do I have to participate in this study?

You can freely choose to take part in this study. If you choose not to participate, your routine treatment will remain unchanged. Patients who are already undergoing other invasive/non-invasive neuroregulatory treatments will not be included in our study. Furthermore, if you decide to participate, you will retain the right to withdraw from the study at any

time.

3. Why did this study?

The objective of this study is to investigate the potential facilitation effect of taVNS pairing with upper limb motor training for upper limb motor rehabilitation in stroke patients. Additionally, we aim to evaluate the necessity of pairing taVNS with motor training to address upper limb dysfunction in stroke. Your participation in this study will contribute valuable clinical data that will broaden our understanding of stroke rehabilitation process. The insights gained from this study will enable us to expand our knowledge of stroke rehabilitation and innovative methods to enhance the treatment outcome, ultimately increasing the chances of recovery from stroke.

4. How will the study be conducted?

If you agree to participate, we will inform the process, benefits and risks of the study. We will conduct the Fugl-Meyer assessment for Upper Extremity Test (FMA-UE), Wolf Motor Function Test (WMFT), Brunnstrom Scale, and Modified Barthel Index. Your electroencephalogram (EEG) and electromyography (EMG) will be recorded. You will receive taVNS treatment and routine rehabilitation once a day, for a total of 14 sessions. Accordingly, you will be randomized to one of the three groups, including paired taVNS group, unpaired taVNS group, and sham control group. The stimulator will be

placed on the left ear in each participant, and the stimulus intensity will be adjusted individually.

If you are assigned to the paired taVNS group, your upper extremity motor training will be paired with taVNS. While you are performing actions during the upper limb motor training, the EMG signal feature evoked by the action will trigger taVNS. The intervention will be normally performed once a day for 14 days. If you are assigned to the unpaired taVNS group, you will receive taVNS and motor training, separately. The motor training will be identical to that of the paired group. If you are assigned to the sham control group, upper limb motor training will be paired with sham stimulation. Likewise, the intervention will be conducted for 14 days, and the motor training will be identical to that of the paired group.

5. How long will I be involved in the study?

The treatment duration will span a total of 14 days, with each session lasting approximately 40-60 minutes. Pre- and post-trial evaluations will take two times to accomplish totaling around 60 minutes. These assessments will be conducted as part of the regular rehabilitation process during your hospitalization and outpatient session, and we would make an appointment with you in advance. Rest assured that these evaluations will not cause any delays in your hospitalization. Following the completion of the trial treatment and evaluation, we aim to maintain regular

communication with you and your family for a period of 30, 90 days, or even longer, to ensure ongoing monitoring of your recovery. If deemed necessary, we may request your presence at the hospital or your residence for additional assessments to evaluate the progress of the treatment. Thanks for your understanding and support.

6. Can I stop attending the research?

You can withdraw from the study at any time, and in that case, we will kindly request the reason of your decision. In the best interest of your well-being, the investigator also holds the authority to discontinue your participation in the study if deemed necessary, and you will be duly notified of such a decision.

7. What risks will I encounter in the research?

Based on the available research evidence, taVNS has not been associated with any known long-term risks, and no serious side effects or safety incidents have been reported in the available studies. Although rare, some patients have experienced mild and temporary adverse effects, such as skin irritation in the ear, tinnitus, headache, and tingling. However, these symptoms would resolve spontaneously after discontinuation of the intervention stimulus.

8. What are my possible benefits?

Your participation in this study will involve engaging in upper limb motor training led by a qualified rehabilitation therapist or physicians.

Additionally, depending on your assigned randomization group, you may also receive taVNS, as previous studies have shown its potential in supporting motor function rehabilitation. By participating in this study, the clinical data gathered from your involvement will contribute to the expansion of our understanding of motor rehabilitation in stroke and pave the way for exploring novel approaches in this field.

9. Do I have to pay for my participation in this study?

The study-related examinations, motor training and taVNS treatments will be provided to you free of charge. However, any costs associated with regular diagnosis and treatment outside of the study will be your responsibility as the patient.

10. Can I get compensation and possible compensation for participating in this study?

As a participant in this experiment, you will be eligible to receive a transportation allowance of ¥200.00 (two hundred RMB). Upon completion of the experiment, you will be compensated via a payment to your designated bank card, following the financial regulations set forth by the research center.

11. Who should I contact with if I have a question?

Your doctor will ensure timely communication with you regarding any important new information that may arise during the study, which could potentially impact your decision to continue participating. If you have

any inquiries about the study data or would like to receive the findings after the completion of the study, please feel free to ask questions at any time. For direct contact, you can reach out to Dr. Xie, the principal investigator, at +86 13903019604.

The study has been reviewed and approved by the Ethics Committee. If you have any questions concerning your rights or interests as a participant, or if you wish to report any difficulties, grievances, concerns, or provide comments and suggestions regarding the study, please contact the Ethics Committee of Pearl River Hospital, Southern Medical University at +86 020-62783254 or via email at zjyyllxs@126.com.

12. What medical information will we collect?

In order for you to participate in the study, we kindly request your permission to collect certain medical information. Please note that participation in the study is contingent upon providing this information. Rest assured that we will only collect the necessary information for the purposes of the study and adhere to strict confidentiality protocols. If you choose not to grant permission for the collection of this medical information, unfortunately, you will be unable to participate in the study.

13. Who gets access to your medical information?

Access to your medical information will be strictly limited to individuals directly involved in the clinical research, members of the ethics committee, and those responsible for supervising and ensuring

compliance with the hospital's rules and regulations regarding research activities. We prioritize the confidentiality and privacy of your medical information, and appropriate measures will be taken to safeguard it. Your information will not be shared with any unauthorized individuals or entities. Your data will be stored in a de-identified manner, and statistical analysis and publication will be conducted using extracted feature data that is not associated with personal information.

Consent to participate in the study

I have read (or had the entire consent document read to me) and all my questions have been satisfactorily answered.

The researchers have provided a clear explanation of the study's purpose, procedures, and the potential benefits and risks involved.

I agree to allow the research team to use and share my medical information and other data collected during the research.

I am participating in this study voluntarily and agree to comply with the required study procedures. I understand that I have the right to withdraw from the study at any time.

Please note: If necessary, I will receive a copy of this signed and dated consent form. I will keep this consent form in a safe place where I can easily access it, as it will serve as a reminder of our discussion today.

Subjects signed: Date: _ _ _ _ _ _ _

Contact number:

Signing of the legal agent (if applicable): Date: _ _ _ _ _ _ _

Contact number:

Investigator's signature: Date: _ _ _ _ _ _ _

Work telephone number: