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Official Title: A multicenter randomized controlled trial on the efficacy and safety of cervical lymph vessel/node-venous anastomosis combined with donepezil versus donepezil alone in the treatment of Alzheimer's disease

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Clinical Study Protocol and Statistical Analysis Plan

Version No.: V2.2

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Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine

Investigator's Statement and Protocol Signature Page

As the principal investigator of this research project, I will follow the ethical principles of the Measures for the Ethical Review of Biomedical Research Involving Humans (National Health Commission Order No. 11 of 2016), the Measures for the Ethical Review of Life Science and Medical Research Involving Humans (Guo Wei Ke Jiao Fa [2023] No. 4), and GCP, use the protocol approved by the Ethics Committee, and conduct the research according to the requirements of this protocol so as to ensure the scientific nature of the research and protect the health and rights of the research participants.

Name: Yixin Zhang_____ Signature: _____ Date: _____2026.05.20

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I. Protocol Summary

Official Title	A multicenter randomized controlled trial on the efficacy and safety of cervical lymph vessel/node-venous anastomosis combined with donepezil versus donepezil alone in the treatment of Alzheimer's disease
NCT Number	NCT07680660
Version No. / Date	Version 2.2 / 20 May 2026
Sponsor and Participating Units	Main center: Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine; participating subcenters are listed in the appendix to the Chinese protocol.
Nature of Study	Interventional, randomized controlled, multicenter trial
Sample Size	216 participants
Study Objectives	Primary objective: to investigate the efficacy and safety of deep cervical lymph vessel/node-venous anastomosis combined with oral donepezil, compared with oral donepezil alone, in patients with Alzheimer's disease and moderate dementia. Secondary objectives: to evaluate changes in cognitive function, mental status, activities of daily living, brain structure, pathological protein deposition, and fluid biomarker levels relative to baseline, and to compare these changes between combined treatment and donepezil alone; safety will be evaluated by adverse events, clinical laboratory tests, physical examinations, and vital signs.
Study Population	Patients aged 50 to 80 years with Alzheimer's disease with dementia, MMSE score <=24, CDR-SB score 9.5-15.5, and positive beta-amyloid PET imaging.
Research Methods	This multicenter RCT includes screening, baseline collection, treatment, and post-treatment follow-up stages. Screening includes general information, history, interview and physical examination, vital signs, MMSE, CDR-SB, BADL/IADL, HAMD, Hachinski, routine laboratory tests, cardiopulmonary and auxiliary examinations, brain MRI/CTA, and Aβ-PET. After passing screening and before randomization and treatment, baseline data include MoCA, NPI, AES, glymphatic MRI research sequences, Tau-PET, AD-related pathological proteins and inflammatory factors in blood and CSF, and APOE polymorphism. Participants are randomized centrally using stratified block randomization by center and age group (50-64 and 65-80 years). Efficacy evaluators and imaging readers remain blinded. The intervention group receives deep cervical lymph vessel/node-venous anastomosis plus donepezil (5-10 mg/day); the control group receives donepezil alone. Follow-up lasts 18 months with assessments at baseline and 1 week, 1 month, 3 months, 6 months, 12 months, and 18 months after intervention.
Inclusion Criteria	1) Patient or guardian signs informed consent; 2) age 50-80 years; 3) primary diagnosis of Alzheimer's disease with dementia; 4) MMSE <=24; 5) positive beta-amyloid PET; 6) HAMD <=17; 7) Hachinski <=7; 8) no AD-related drug treatment within the past 1 month; 9) ASA class 1-3; 10) CDR-SB 9.5-15.5.
Exclusion Criteria	Contraindications to MRI, ICG angiography, PET, or lumbar puncture; severe cardiac, pulmonary, hepatic, renal, intracranial, vascular, hematologic, thyroid, infectious, psychiatric, oncologic, or other conditions specified in the full protocol; receipt of anti-Aβ monoclonal antibody treatment within the last 6 months; previous neck surgery.
Primary Outcome	Change from baseline in Clinical Dementia Rating Sum of Boxes (CDR-SB) at Month 12.
Secondary Outcomes	Changes from baseline at Month 18 in CDR-SB, MMSE, MoCA, AES, NPI, BADL, IADL, neuroimaging measures, and blood/CSF biomarkers.
Statistical Analysis Methods	Statistical analysis will be performed using R version 4.0. FAS, PPS, and SS will be defined. The primary efficacy analysis will use MMRM with change from baseline in CDR-SB at each follow-up visit as the dependent variable, baseline CDR-SB as covariate, and group, visit, age stratum, ApoE carrier status, group-by-visit interaction, and baseline-score-by-visit interaction as fixed effects. LS mean differences, 95% confidence intervals, and P values will be reported. Secondary continuous outcomes will use MMRM, ANCOVA, or appropriate methods according to endpoint and distribution. Laboratory biomarkers will be summarized descriptively, with paired t test or Wilcoxon signed-rank test for within-group comparisons and independent t test or Mann-Whitney U test for between-group comparisons as appropriate. Two-sided P<0.05 will be considered significant; multiple endpoints will not be adjusted for multiplicity and nominal P values will be reported.

II. Research Background

II、Research Background After the important deployment of actively responding to population aging was anchored at the Fifth Plenary Session of the 19th Central Committee, the report of the 20th National Congress again emphasized that its practical urgency should be attached importance to at the level of national strategy, and proposed that, by strengthening chronic disease management, attaching importance to mental health, and improving primary-level disease prevention and treatment capacity and other measures, the construction of Healthy China should be fully promoted. Affected by factors such as the large population base, increased life expectancy per capita, and accelerated iteration of medical technology, the aging trend in China is severe, and the disease spectrum of residents has also changed significantly. Chronic non-communicable diseases, as the main type of diseases affecting residents' health, have aroused wide attention from medical and public health professionals. The National Health Commission emphasized that early screening, early intervention, and stage-specific standardized management should be strengthened for chronic diseases in the elderly such as diabetes, hypertension, and coronary heart disease, especially degenerative diseases such as Alzheimer's disease (AD) [1-4]. Alzheimer's disease (AD) is an irreversible degenerative disease of the nervous system with insidious onset and progressive progression. It is the most common cause of cognitive impairment, manifested as deterioration of cognitive function and behavioral ability, and eventually affects the patient's daily life and social function [2,5]. Cognitive impairment mainly includes subjective cognitive decline (SCD), mild cognitive impairment (MCI), and dementia. According to WHO reports, 55 million people worldwide suffer from dementia,

with about 10 million new cases each year, and the number is expected to increase to 152 million by 2050. In 2023, the Report on Insights into the Needs of Patients with Alzheimer's Disease jointly released by People's Health Network and the Alzheimer's Disease Branch of the China Association of Gerontology and Geriatrics showed that the total prevalence of dementia in China was 6.04%, with 15.07 million people, among whom AD accounted for 65.2%, about 9.83 million people, and the prevalence of MCI was 15.5%, with 38.77 million people [4]. AD patients are a heavy burden to society and their families. Professor Jia Jianping's team, through an investigation of 3,046 AD patients in 81 institutions in 30 provinces/municipalities/autonomous regions in China, found that the average annual cost per AD patient was about RMB 122,523, and the total socioeconomic burden caused by AD was about USD 167.74 billion per year, 5.95 times the global average level (USD 28.18 billion per year), and it maintained a significant upward trend with age. The construction of a scientific and feasible anti-AD health strategy urgently needs to be completed [1]. Under the influence of factors such as a large population base, increased life expectancy per capita, and accelerated iteration of medical technology, the aging trend in China is severe, and the impact brought by AD will further expand. At present, actively responding to population aging has become an important strategic deployment in China, and around this, a series of measures have been proposed, including strengthening chronic disease management, attaching importance to mental health, and improving primary-level disease prevention and treatment capacity, in order to fully promote the construction of Healthy China. The National Health Commission emphasized that early screening, early intervention, and stage-specific standardized management should be strengthened for chronic diseases in the elderly, especially degenerative diseases such as AD [3,4]. Accordingly, Brain Science and Brain-Inspired Science, namely the China Brain Project, was officially launched in 2021, with 59 guideline directions deployed in the areas of analysis of brain cognition principles, brain-inspired computing and brain-computer intelligence technology, brain intelligence development in children and adolescents, and technology platform construction. Among them, in the field of brain diseases, it is emphasized that multidimensional research systems related to early precise warning and diagnosis, early prevention and intervention, standardized treatment, and efficacy prediction for major brain diseases related to cognitive impairment urgently need to be established [9,10]. It can thus be seen that AD, with its high prevalence, long disease course, complex comorbidities, heavy burden on patients' families, and high socioeconomic cost, is a major issue affecting public health and sustainable social development. How to solve the difficult problem of AD treatment, and thereby reduce the burden on patients' families and control the related socioeconomic costs, has become a major focus of medical development today. However, while the etiology and pathogenesis of Alzheimer's disease have not yet been fully clarified, effective treatments are still lacking. Most current treatments for AD are medical drug therapies, and all are symptomatic treatments, which can only improve cognitive function and treat psychiatric symptoms, but cannot delay disease progression

[2,5]. In recent years, research teams have begun to attempt to improve AD symptoms by intervening in the pathological process of AD. At present, the more widely recognized decisive pathological features of AD are extracellular fibrillar amyloid-beta (Aβ) peptide plaque deposition and tau filaments in intracellular neurofibrillary tangles [5]. Two Aβ-targeting drugs (Aducanumab and Leqembi) have been approved by the FDA for marketing, and have been shown in phase III clinical trials to reduce Aβ plaques in the brains of AD patients and slow the decline of cognitive function and behavioral ability in AD patients [6,7]. The phase III trial results of Donanemab also confirmed efficacy superior to Leqembi [8]. These results prove that Aβ-targeted therapy can delay the progression of AD. However, such drugs have large side effects, including serious adverse effects such as cerebral edema and cerebral hemorrhage. In addition, such drugs are effective only for patients with early mild cognitive impairment, and their efficacy is limited for patients with middle and late-stage dementia [6-8]. The above results suggest that intervening in the pathological process of AD and clearing pathological protein deposition in the brain can delay the AD process to a certain extent, but safer and more effective treatment strategies still need to be found. In 2015, the team at the University of Virginia School of Medicine proposed the existence of a lymphatic drainage system in the central nervous system of the brain [9]. Research proposed that the glymphatic system delivers cerebrospinal fluid (CSF) and nutrients to the brain through periarterial lymphatic pathways, while interstitial fluid (ISF) and metabolic waste leave the brain through perivenous lymphatic pathways and may be drained through meningeal lymphatic vessels to the cervical lymph nodes [10]. The function of the brain lymphatic drainage system is similar to that of a scavenger of metabolic waste in the brain, and is responsible for removing various metabolic proteins from the brain parenchyma, including Aβ [9-11]. Animal experiments have shown that enhancement or reduction of the function of the brain lymphatic drainage system affects the perivascular influx of macromolecules in CSF, the outflow of macromolecules in ISF, and cognitive performance [11]. Other studies have shown that impaired meningeal lymphatic drainage activates microglial inflammatory responses in AD, with activation characteristics similar to those in AD patients, and that enhancement of meningeal lymphatic vessel function combined with anti-Aβ immunotherapy can synergistically enhance the efficacy of AD treatment [12]. The above studies show that dysfunction of the brain lymphatic drainage system plays an important role in the development of the pathological process and cognitive deficits in AD. Experience in lymphatic reconstructive surgery for lymphedema shows that the lymphatic system, as an independent organ, after receiving reconstructive surgery, not only has a local drainage effect, but also has systemic effects that promote lymphatic system function [13]. Combining these experiences with dysfunction of meningeal lymphatic vessels and impaired lymphatic drainage in AD, some scholars have proposed the hypothesis that improving intracranial lymphatic reflux function through extracranial

lymphatic drainage will be beneficial for the excretion of metabolic products out of the skull, thus making the treatment of AD possible [14]. Surgical treatment of AD not only has a theoretical basis, but also already has theoretical practice. Professor Xie Qingping has successfully performed deep cervical lymph vessel/node-venous anastomosis for AD patients, with an average follow-up period of 1 year, and observed significant improvement in behavior, cognitive function, and memory ability, and the related study has been published [15]. At the same time, domestic scholars have also studied the suitability of screening tools for cognitive function in the Chinese elderly, providing a basis for AD clinical screening and classified management [16]. In the preliminary stage, our center has already initially carried out a single-center single-arm clinical study targeting deep cervical lymph vessel/node-venous anastomosis, obtained ethics approval (ethics approval number: SH9H-2024-T41-2), has now completed surgical treatment in 10 patients, and has preliminarily confirmed the effectiveness and safety of this procedure in early follow-up. The high prevalence of Alzheimer's disease (AD), its irreversible progression, and the limitations of existing drugs in delaying disease progression and safety make it urgent to explore innovative treatment pathways. Based on the strong association between dysfunction of brain lymphatic drainage and AD pathology, the preliminary clinical practice of deep cervical lymph vessel/node-venous anastomosis has shown potential for cognitive improvement, but its regulatory mechanism, long-term efficacy, and individualized treatment biomarkers still need systematic verification, and there is still a lack of validation by clinical research with a high level of evidence. This project plans to conduct a standardized multicenter RCT study, prospectively collect multimodal data before and after surgery from patients (cerebrospinal fluid, blood, imaging, and cognitive assessment), and construct a multi-omics biological sample bank for AD, aiming to analyze the dynamic effects of lymphatic reconstructive surgery on pathological biomarkers, neuroinflammation, and lymphatic drainage function, verify the efficacy of this procedure, explore its mechanism of action, further mine biomarkers predictive of efficacy, and optimize surgical indications. This

study not only provides key evidence for elucidating the mechanism of pathological intervention in AD, but also fits the strategic demand of the China Brain Project for precise management of cognitive impairment diseases [9,10]. Through biological sample resource sharing and multicenter collaboration, it will promote the transformation of AD from irreversible to intervenable, and provide scientific support for reducing the social medical burden and achieving healthy aging.

III. Trial Objectives

3.1 Primary Objective

This study aims to investigate the efficacy and safety of deep cervical lymph vessel/node-venous anastomosis combined with oral donepezil, compared with oral donepezil alone, in patients with Alzheimer's disease and moderate dementia.

3.2 Secondary Objectives

To evaluate, in patients with Alzheimer's disease and moderate dementia, the efficacy of deep cervical lymph vessel/node-venous anastomosis combined with donepezil on cognitive function, mental status, activities of daily living, structural brain changes, pathological protein deposition, and fluid biomarker levels relative to the pretreatment baseline, and to compare the efficacy of combined treatment versus oral donepezil alone in these domains; safety will be evaluated through the incidence of adverse events, clinical laboratory examinations, physical examinations, and vital signs.

IV. Trial Methods

4.1 Overall Trial Design

This study is a multicenter randomized controlled trial mainly enrolling patients with Alzheimer's disease and moderate dementia from outpatient clinics, inpatient wards, and health examination centers. Participants are 50 to 80 years of age, have an MMSE score <=24, a CDR-SB score of 9.5-15.5, and are assessed by experienced imaging physicians as beta-amyloid-positive on PET imaging. Patients with contraindications to MRI contrast examination, PET scan, or lumbar puncture; active or acute intracranial lesions; major respiratory, circulatory, or urinary system diseases; severe depression; or potential suicidal risk will be excluded. Complete inclusion and exclusion criteria are detailed below.

All research participants will be randomly assigned to the surgery combined with donepezil group or the donepezil-only group. Participants will undergo preoperative anesthesia assessment, neuropsychological assessment, neuroimaging examination, and relevant physical and laboratory examinations. Eligible participants will receive deep cervical lymph vessel/node-venous anastomosis combined with donepezil or oral donepezil alone. After treatment, standardized systematic follow-up will be conducted, comparing each participant's data with baseline and between groups.

Neuropsychological assessments include MMSE and MoCA for cognitive function, BADL and IADL for activities of daily living, AES, NPI, and CDR for dementia diagnosis and severity grading. Neuroimaging includes MRI to assess hippocampal and temporal lobe volume and glymphatic function, and PET to assess beta-amyloid pathology (AV1/AV45) and Tau pathology (AV1451/PI-2620). Laboratory assessments compare post-treatment changes versus baseline in CSF and plasma Aβ-42, Aβ-40, Aβ-42/Aβ-40, P-tau181, GFAP, NfL, and pTau217, as well as inflammatory markers including IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNFα, IFN-γ, and IFN-α; baseline APOE polymorphism will also be tested. Ultrasound assesses the internal/external jugular vein diameters, maximum flow velocities, and anastomotic status. Lymph nodes and lymphatic fluid that may be collected intraoperatively will undergo gross pathology, immunofluorescence staining, and other tests.

4.2 Sample Size

The primary outcome is the change in CDR-SB at Month 12. Based on the literature, the mean 12-month change from baseline in CDR-SB in patients receiving donepezil alone is 0.75. Combined with preliminary results, surgery combined

with donepezil may improve cognitive function. Conservatively assuming a moderate effect size (Cohen's d = 0.5), a standard deviation of 2 for CDR-SB change, and a between-group mean difference of 1.0 point, the expected 12-month change from baseline in the surgical group is approximately -0.25. With two-sided alpha = 0.05, power = 0.9, and 1:1 allocation, PASS 2021 indicates that 86 participants are needed per group. Allowing for 20% loss to follow-up, 108 participants per group and 216 participants in total are planned.

4.3 Randomization

Central randomization and stratified block randomization will be used, with study center and age group (50-64 years and 65-80 years) as stratification factors. Enrollment is competitive. After a participant is selected, designated personnel at the participating center enter basic information through the network platform, and the central randomization system automatically generates a random number and completes allocation according to the prespecified stratified block scheme. The allocation code is strictly maintained by the central randomization system.

4.4 Control and Blinding

Participants assigned to the control group will receive oral donepezil once daily at bedtime, starting at 5 mg/day and adjusted to 10 mg/day after 6 weeks if tolerated. If not tolerated, 5 mg/day will be maintained for 6 weeks, and escalation to 10 mg/day will be attempted again. Treatment continues for 18 months; participants who cannot tolerate the higher dose may remain on 5 mg/day for 18 months.

Because of the nature of the surgical intervention, participants and surgeons cannot be blinded. Efficacy evaluators and imaging readers will remain blinded to ensure objectivity and reliability of the study results.

4.5 Visit Time Points

Screening period: After signing informed consent, participants enter screening. Investigators collect basic information and clinical data, including medical history, medication history, surgical history, allergy history, tumor history, prior clinical study participation, and previous relevant medical examination results. Interview, physical examination, and necessary auxiliary examinations are used to determine eligibility and any condition unsuitable for participation.

Screening examinations include: 1) interview, physical examination, and general assessment, including age verification, vital signs, neurological interview and examination, mental status, and compliance assessment; 2) neuropsychological and functional scales including MMSE, CDR-SB, BADL, IADL, HAMD, and Hachinski; 3) blood tests including blood routine, C-reactive protein, coagulation, liver function, renal function, electrolytes, fasting glucose, myocardial injury markers, BNP, thyroid function, tumor markers, HIV, syphilis, and hepatitis-related tests; 4) cardiopulmonary and other auxiliary tests including electrocardiogram, echocardiography, pulmonary function, chest CT, and cervical ultrasound; 5) neuroimaging including enhanced brain MRI and SWI, cerebral CTA, and beta-amyloid PET (Aβ-PET).

Baseline collection stage: After passing screening and before randomization and treatment, complete baseline data are collected. Baseline data serve as the reference for evaluating efficacy, safety, and mechanistic indicators. Even if some tests were performed during screening, any item used for subsequent efficacy, safety, or mechanistic analysis must be clearly recorded in the baseline data.

Baseline collection includes: 1) general data, history, concomitant medication, vital signs, physical examination, and adverse event assessment; 2) gross photographs and videos; 3) neuropsychological, functional, and behavioral scales including MMSE, MoCA, CDR-SB, BADL, IADL, AES, and NPI; 4) neuroimaging including Aβ-PET, Tau-PET, enhanced brain MRI and SWI, and glymphatic MRI research sequences; 5) cervical ultrasound; 6) blood and CSF sample collection and testing, including AD-related pathological proteins and neural injury biomarkers (Aβ-42, Aβ-40, Aβ-42/Aβ-40, P-tau181, pTau217, GFAP, NfL), inflammatory markers (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNF-α, IFN-γ, IFN-α), and APOE polymorphism.

Treatment period: Participants receive surgery plus oral donepezil or oral donepezil alone as detailed in Section 6.1. Post-treatment visits: Participants will have face-to-face follow-up at 1 week, 1 month, 3 months, 6 months, 12 months, and 18 months after treatment; the detailed visit plan is shown in Section 6.2.

V. Selection, Withdrawal, and Management of Research Participants

5.1 Diagnostic Criteria

According to the Revised Criteria for Diagnosis and Staging of Alzheimer's Disease (2024) updated by the National Institute on Aging and the Alzheimer's Association (NIA-AA), diagnostic criteria for MCI and dementia include positive Aβ-PET or abnormal CSF Aβ-42/40, objective cognitive impairment, documented decline from baseline, and functional criteria distinguishing MCI due to AD from AD with dementia.

5.2 Inclusion Criteria

(1) The patient or guardian signs the informed consent form;

(2) Age 50-80 years (≥50 years, ≤80 years), male or female;

(3) The first diagnosis is Alzheimer's disease with dementia;

(4) MMSE score ≤24;

(5) Positive β-amyloid protein PET imaging findings;

(6) HAMD score ≤17;

(7) Hachinski score ≤7;

(8) No AD-related drug treatment has been received within the past 1 month;

(9) ASA grade 1-3 (≥ grade 1, ≤ grade 3);

(10) CDR-SB score of 9.5-15.5.

5.3 Exclusion Criteria

(1) Presence of contraindications to MRI, ICG angiography, or PET scan;

(2) Presence of contraindications to lumbar puncture;

(3) Severe heart disease or unstable hemodynamic status;

(4) Severe lung disease, including severe obstructive, restrictive, or mixed ventilatory dysfunction, or acute inflammation within 3 months;

(5) Hepatic insufficiency, AST or ALT >3 times the upper limit of normal;

(6) Renal insufficiency, GFR <60 mL/min or need for blood purification treatment;

(7) MRI indicates active or acute intracranial lesions, including intracranial infection, space-occupying lesions, major hemorrhage, and ≥4 lobar microbleeds, etc.;

(8) History of cerebral hemorrhage or cerebral infarction with severe residual neurological dysfunction;

(9) Blood diseases, bleeding/coagulation disorders, coagulation dysfunction;

(10) Abnormal thyroid function;

(11) Moderate or severe stenosis of intracranial or cervical vessels with severe residual neurological dysfunction;

(12) Severe hypertension not effectively controlled, systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg;

(13) The disease requires systemic use of steroids;

(14) Drug addiction (including alcohol, narcotics, and alcohol dependence);

(15) Severe infectious diseases, including HIV positivity, severe infection, etc.;

(16) Severe psychiatric disease or potential suicide risk;

(17) Within 3 years after radical surgery for malignant tumor;

(18) Participation in other interventional clinical trials within the past three months;

(19) In the physician's judgment, poor compliance, inability to complete, or unwillingness to cooperate with regular postoperative follow-up;

(20) Other circumstances that the physician considers unsuitable for this clinical trial;

(21) Anti-Aβ monoclonal antibody treatment has been received within half a year;

(22) Previous neck surgery.

5.4 Criteria for Removal and Withdrawal

Removed cases include participants who violate important enrollment criteria or do not receive deep cervical lymph vessel/node-venous anastomosis treatment. Withdrawal criteria include other diseases affecting study observation, participant request to withdraw, or investigator judgment that termination is necessary. Complete clinical data of withdrawn participants will be retained and reasons will be recorded in the case report form.

5.5 Conditions for Trial Termination

The trial may be terminated for serious violation of the protocol, withdrawal of informed consent, loss to follow-up, or other circumstances affecting efficacy and safety evaluation.

5.6 Management of Research Participants

Participants will be recruited by the main center and subcenters through outpatient clinics, inpatient wards, and health examination centers. After sufficient explanation of study purpose, research content, and risks, eligible candidates voluntarily sign informed consent and complete the basic information questionnaire.

VI. Trial Process

6.1 Surgical Procedure and Medication Procedure

1. After randomization, participants enter either the deep cervical lymph vessel/node-venous anastomosis plus oral donepezil group or the oral donepezil group.

2. For the combined intervention group, surgery is performed under general anesthesia maintained with total intravenous anesthesia. The patient is placed supine with the head turned to one side and shoulders elevated. A transverse neck incision is made along a neck crease approximately 4 cm from the mandibular margin.

3. The external jugular vein, great auricular nerve, platysma, sternocleidomastoid muscle, carotid sheath, internal jugular vein, and surrounding lymphatic composite tissue flaps are carefully exposed and protected. Deep cervical lymphatic composite flaps in the IIA and IIB/III regions are prepared, with care to protect the accessory and vagus nerves.

4. Lymphatic revascularization reconstruction includes end-to-end anastomosis between the IIA-region lymphatic flap and branches of the common facial vein or external jugular vein when appropriate, and end-to-side anastomosis between the IIB/III-region lymphatic flap and the internal jugular vein or external jugular vein when appropriate. Hemostasis is confirmed and the incision is closed cosmetically.

5. Oral donepezil in the combined group begins on postoperative day 1, once daily at bedtime, starting at 5 mg/day and adjusted to 10 mg/day after 6 weeks if tolerated. If intolerance occurs, 5 mg/day is maintained, followed by another attempt at 10 mg/day after 6 weeks; total treatment duration is 18 months. The same dosing regimen is used in the oral donepezil group.

6.2 Treatment Course and Visit Time Points

Visit Schedule for the Combined Intervention Group

Item	Preoperative	Immediately postoperative	1 week post-op ±1 day	1 month post-op ±7 days	3 months post-op ±14 days	6 months post-op ±14 days	12 months post-op ±14 days	18 months post-op ±14 days
Signed informed consent	√							
Gross photographs/videos	√		√	√	√	√	√	√
Adverse events	√	√	√	√	√	√	√	√
CDR	√		√	√	√	√	√	√
Neuropsychological scales (MMSE, MoCA, AES, NPI, BADL, IADL)	√		√	√	√	√	√	√
HAMD, Hachinski	√							
PET	√					√	√	√
MRI plain	√		√	√	√	√	√	√
MRI contrast-enhanced	√					√	√	√
Cervical ultrasound	√			√	√	√	√	√
CSF	√		√			√	√	√
Blood	√		√	√	√	√	√	√
Lymph nodes/lymphatic fluid		√ (intraoperative)						

CSF and blood examination indicators include Aβ-42, Aβ-40, Aβ-42/Aβ-40, P-tau181, GFAP, NfL, pTau217, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNFα, IFN-γ, and IFN-α. Approximately 8-9 mL of blood and 6 mL of CSF are collected at each relevant follow-up. During surgery, 1-2 angular, level II, and level III cervical lymph nodes are planned to be collected, and 0.5-3 mL of lymphatic fluid from each side may be drawn.

Visit Schedule for the Medication-Only Group

Item	Before medication	Treatment start day	1 week after treatment ±1 day	1 month after treatment ±7 days	3 months after treatment ±14 days	6 months after treatment ±14 days	12 months after treatment ±14 days	18 months after treatment ±14 days
Signed informed consent	√							
Gross photographs/videos	√		√	√	√	√	√	√
Adverse events	√	√	√	√	√	√	√	√
CDR	√		√	√	√	√	√	√
Neuropsychological scales (MMSE, MoCA, AES, NPI, BADL, IADL)	√		√	√	√	√	√	√
HAMD, Hachinski	√							
PET	√					√	√	√
MRI plain	√		√	√	√	√	√	√
MRI contrast-enhanced	√					√	√	√
Cervical ultrasound	√							
CSF	√		√			√	√	√
Blood	√		√	√	√	√	√	√

CSF and blood examination indicators include Aβ-42, Aβ-40, Aβ-42/Aβ-40, P-tau181, GFAP, NfL, pTau217, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNFα, IFN-γ, and IFN-α. Approximately 8-9 mL of blood and 6 mL of CSF are collected at each relevant follow-up.

VII. Evaluation Indicators

7.1 Baseline Indicators

1. Demographic data: name code, sex, age, education years, and related basic information.

2. General safety data: vital signs, physical examination, adverse events, concomitant medication, and necessary routine laboratory tests.

3. Pretreatment imaging and video data: gross photographs and videos, Aβ-PET, Tau-PET, enhanced brain MRI and SWI, glymphatic MRI research sequences, and cervical ultrasound.

4. Pretreatment scale data: MMSE, MoCA, CDR-SB, BADL, IADL, AES, and NPI.

5. Fluid indicators: AD-related pathological proteins and neural injury biomarkers in blood and CSF, including Aβ-42, Aβ-40, Aβ-42/Aβ-40, P-tau181, pTau217, GFAP, and NfL; inflammatory indicators; and APOE polymorphism.

7.2 Efficacy Evaluation

Primary and key secondary clinical endpoints will be assessed by trained blinded evaluators according to standardized procedures. Key endpoint data will be submitted to an independent endpoint adjudication committee for centralized review and consistency interpretation.

7.2.1 Primary Evaluation Indicator

Change from baseline in the Clinical Dementia Rating Sum of Boxes (CDR-SB) at Month 12.

7.2.2 Secondary Evaluation Indicators

1. At Month 18: changes in CDR-SB, MMSE, MoCA, AES, NPI, BADL, and IADL.

2. Neuroimaging at Month 18: PET assessment of beta-amyloid and Tau; MRI assessment of hippocampal and temporal lobe volume and glymphatic system function; ultrasound assessment of internal/external jugular vein diameters, maximum flow velocity, and anastomotic status.

3. Fluid biomarkers at Month 18: changes in CSF and blood pathological protein indicators Aβ-42, Aβ-40, Aβ-42/Aβ-40, P-tau181, GFAP, NfL, and pTau217; changes in CSF and blood inflammatory indicators IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNFα, IFN-γ, and IFN-α.

4. Pathological examination of lymph nodes/lymphatic fluid collected intraoperatively, including gross pathology, immunofluorescence, pathological proteins (P-tau181, Aβ-42, Aβ-40), and neural injury factors (GFAP, NfL).

7.3 Safety Evaluation

Safety evaluation includes vital signs, adverse reactions, surgical or medication-related complications, and adverse event recording and handling. Potential risks include postoperative infection, bleeding, local vascular or nerve injury, lymphatic leakage, and donepezil-related adverse reactions such as drug allergy, diarrhea, muscle cramps, fatigue, nausea, vomiting, insomnia, headache, rash, psychiatric symptoms, or gastrointestinal bleeding. Adverse events will be graded using CTCAE principles and managed according to predefined procedures.

VIII. Data Quality Assurance

Quality control of data collection and collation will include unified training, predefined data requirements, double checking, centralized entry, deduplication, cleaning, and collation. Data verification will be conducted in the early, middle, and late stages. Missing values and abnormal values will be handled according to prespecified procedures. Data managers will establish the database according to protocol requirements, develop logical validation procedures, and issue data queries when needed.

Biological samples collected at each center, including blood, CSF, lymph nodes, and lymphatic fluid, will undergo strict transport and quality monitoring. Samples will be processed, aliquoted, stored at -80°C, and transported every 3 months by professional cold-chain logistics to the main-center biobank. The first three cases of samples at each center in every 3-month period will undergo early quality inspection to detect degradation, hemolysis, contamination, or cold-chain problems, followed by corrective retraining if needed.

IX. Statistical Analysis

9.1 Analysis Datasets

The Full Analysis Set (FAS) follows the intention-to-treat principle and includes all randomized participants who receive at least one intervention and have at least one post-baseline primary outcome assessment. The Per-Protocol Set (PPS) includes participants who complete specified interventions and primary follow-up strictly according to the protocol and is used for sensitivity analyses. The Safety Set (SS) includes all participants who receive at least one surgery or medication intervention and is used for safety analyses.

9.2 Statistical Methods

Statistical analysis will be performed using R version 4.0. The primary efficacy analysis will use change from baseline in CDR-SB at Month 12 as the primary endpoint. A mixed-effects model for repeated measures (MMRM) will be used, with change from baseline in CDR-SB at each follow-up visit as the dependent variable, baseline CDR-SB as a covariate, and group, visit, age stratum, ApoE carrier status, group-by-visit interaction, and baseline-score-by-visit interaction as fixed effects. Least-squares mean differences, 95% confidence intervals, and P values will be reported.

For secondary efficacy analyses, continuous neuropsychiatric scale outcomes will use the same MMRM approach. Continuous neuroimaging indicators will be analyzed using ANCOVA or MMRM with adjustment for baseline values. Categorical variables will be compared using Fisher's exact test or the chi-square test. Laboratory biomarkers in blood and CSF will first be summarized descriptively. Normally distributed data will be presented as mean ± SD, and skewed data as median (interquartile range). Within-group comparisons will use paired t tests or Wilcoxon signed-rank tests, and between-group comparisons will use independent-sample t tests or Mann-Whitney U tests according to distribution. Safety indicators and laboratory test results will be summarized descriptively; adverse events will be summarized by number and incidence.

All tests will be two-sided, with $P<0.05$ considered statistically significant. For multiple endpoints, no multiplicity adjustment will be performed and nominal P values will be reported. The primary endpoint will be subjected to sensitivity analyses based on FAS and PPS; multiple imputation, LOCF, and mixed-effects models with center random effects may be used to assess robustness. Subgroup analyses will be based mainly on FAS and will use interaction tests to explore consistency and heterogeneity of treatment effects; all subgroup analyses are exploratory.

9.3 Subgroup Analysis Content

Prespecified exploratory subgroups include demographic factors, APOE genotype, baseline biomarker burden, disease-related factors, comorbid diseases and risk factors, subcenter factors, and intraoperative factors in the intervention group. Interaction terms will be used to evaluate heterogeneity, and findings will be interpreted as hypothesis-generating.

X. Ethical Requirements and Informed Consent Form

This protocol, written informed consent form, and materials directly related to research participants must be submitted to the ethics committee. The study may begin only after written ethics approval is obtained. Investigators will submit annual reports when applicable, report protocol or informed consent changes, and report serious adverse events according to applicable regulations.

Investigators must provide participants or legal representatives with an understandable ethics-approved informed consent form and sufficient time to consider participation. No participant may be enrolled before signed written informed consent is obtained. Updated informed consent documents will be provided as needed and retained as essential study documents.

An interim safety evaluation will be performed when approximately half of the participants in the surgery group have completed treatment. Results will be submitted to the ethics committee for review before the decision to continue subsequent study procedures. An independent Data and Safety Monitoring Board may review study progress, safety events, and data quality and provide recommendations regarding continuation, modification, or termination.

XI. Insurance

This multicenter RCT applies deep cervical lymph vessel/node-venous anastomosis combined with donepezil or donepezil alone after standardized training and assessment. Appropriate clinical trial insurance will be provided. During treatment and follow-up, the project will cover protocol-related surgical, anesthesia, medication, examination, and assessment costs as specified in the informed consent form, and will provide transportation reimbursement and CSF examination subsidies according to protocol rules.

XII. Quality Control and Quality Assurance

Investigators participating in the clinical trial will be relatively fixed and must have the professional expertise, qualifications, and capabilities required for clinical trials. Before the clinical trial, investigators will receive training to ensure consistent understanding of study indicators and standardized procedures. Participants will return for visits according to the protocol time points; investigators will actively reduce dropout rates and monitor adverse reactions.

A collaborative research coordination committee, academic expert committee, and quality control system will be established. Monitors with medical background and GCP training will supervise the clinical trial, verify data and documents, ensure protection of participant rights and data accuracy, and ensure that the trial follows the approved protocol and applicable regulations.

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