Original protocol

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OPENS-2: A phase III, multicenter, investigator-initiated, open-label, randomized, parallel-group, superiority trial to assess the clinical effectiveness of trophic enteral nutrition with supplemental parenteral nutrition versus full enteral feeding in patients with acute severe stroke.

Trial sponsor: Xijing Hospital, The Fourth Military Medical University
Changle West Road 127, Xincheng district, Xi'an City, China
Trial Funder(s): Shaanxi Special Support Program for Leading Talents (2020-44)
Shaanxi Cerebrovascular Diseases Clinical Medical Research Center (2021LCZX-11)
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Name&Role:	Signature:	Date:
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1. Study synopsis

Study Title	A phase III, multicenter, investigator-initiated, open, randomized, parallel-group, superiority trial to assess the clinical effectiveness of trophic enteral nutrition with supplemental parenteral nutrition versus full enteral feeding in patients with acute severe stroke.
Public title	Optimizing Early Nutrition Support in Severe Stroke -2
Contact for queries	Public queries: Dr. Xuan Wang Phone: +86 18791988671 E-mail: wangxuan@fmmu.edu.cn Scientific queries: Pro. Wen Jiang Phone: +86 13991905538 E-mail: jiangwen@fmmu.edu.cn
Countries of recruitment	China
Health condition	Acute Stroke requiring intensive care
Arms and Interventions	Caloric requirements will be calculated based on body mass index (BMI). For patients with a BMI between 18 and 30 kg/m², the daily caloric target is actual body weight (in kilograms) multiplied by 25 kcal; for patients with a BMI below 18 or above 30 kg/m², the formula (height [cm] - 105) × 25 kcal will be applied15. Caloric delivery will follow a stepwise escalation: one-third of the target on intervention day 1, half on day 2, and the full target from day 3 to day 7. An acceptable delivery range is 70% to 100% of the target. The protein intake target for all participants is set at 1.2 to 1.5 grams per kilogram of body weight per day. • Experimental: Trophic enteral feeding combined with supplemental parenteral nutrition. Patients will receive the trophic enteral feeding with a caloric target of 500kcal/d (≤20

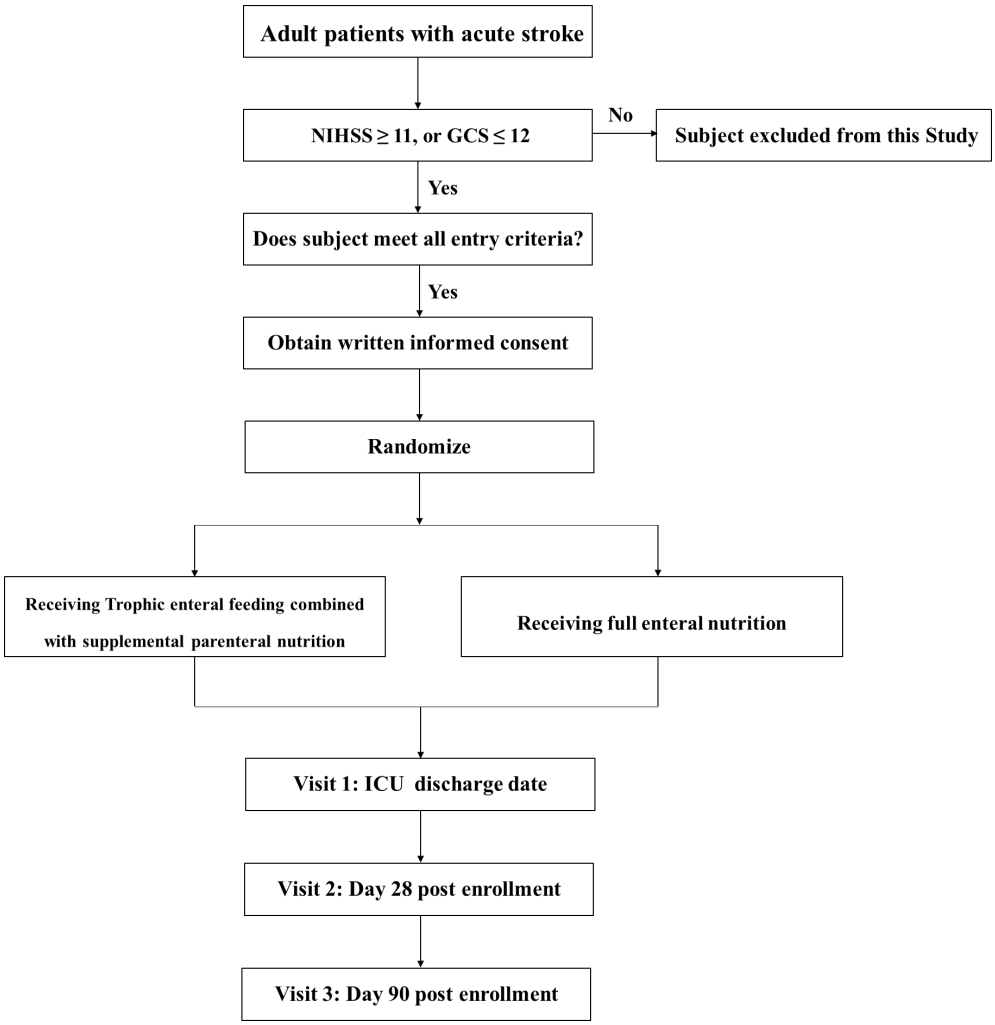
	ml/h), and the remaining caloric-protein requirement are supplemented by parenteral nutrition. • Active Comparator: Full enteral feeding. Patients will receive full enteral feeding through nasogastric tube or nasointestinal tube.
Inclusion Criteria	1. Age≥18 years; 2. Definite diagnosis of acute stroke (GCS≤12 or NIHSS≥11); 3. The randomized nutritional treatment could be initiated up to 72 hours after symptom onset; 4. Any cases of profiles #3 through 5 in Water Swallowing Test or with disorder of consciousness; 5. Plan to receive enteral feeding for at least 7 days; 6. Informed consent.
Exclusion Criteria	1. Receiving parenteral nutrition support 2. Contraindications of enteral nutrition 3. Complicated with the disease which only have life expectancy < 7 days 4. Dementia or severe disability (mRS>4) before stroke 5. Presence of coexisting medical conditions that could interfere with outcome assessment and/or follow-up (a. advanced cancer; b. severe pulmonary dysfunction [forced expiratory volume in 1 second < 50% or/and moderate to severe acute lung injury (PaO2/FiO2)<200mmHg]; c. cardiac insufficiency (NYHA class > I; cardiac structural and/or functional abnormalities such as EF< 50%, abnormal cardiac chamber enlargement, moderate/severe ventricular hypertrophy, or moderate/severe valvular stenosis); d. Severe liver failure [Child-Pugh score≥7]; e. Severe renal failure [glomerular filtration rate ≤30mL/min or serum creatinine ≥4mg/dL]

	6. Currently participating in other clinical trial 7. Pregnant woman 8. Patient who is considered highly likely not to adhere to the study treatment or follow-up protocol.
Study Design	Phase III, investigator-initiated, randomized, open-label, blinded-endpoint multicenter trial
Sample size	546
Primary Efficacy outcome	Incidence of post stroke pneumonia from randomization to day 7.
Secondary Efficacy outcomes	• Time from randomization to onset of the post-stroke pneumonia within 7 days post-randomization • Daily calorie and protein delivery during the first 7 days post-randomization • Insulin dosage during the first 7 days post-randomization • The usage rate of prokinetic agents during the first 7 days post-randomization • Occurrence of nosocomial infections from randomization to ICU discharge • Length of ICU stay • Incidence of tracheotomy, mechanical ventilation, continuous renal replacement therapy, and venous thrombosis from randomization to ICU discharge • Usage rate of vasoactive agents from randomization to ICU discharge • The score of National Institute of Health stroke scale at ICU discharge • Glasgow Coma Scale at ICU discharge • Modified Rankin scale at ICU discharge • Modified Rankin scale at 90 days

Safety Endpoints	• All-cause mortality during ICU stay • All-cause mortality at 28 days • Incidence of cardiac failure from randomization to ICU discharge • Incidence of gastrointestinal complications (Vomiting, diarrhea, gastric retention, gastrointestinal bleeding) during the first 7 days post-randomization

2. Flow chart and schedule of assessment

2.1 Flow Chart



2.2 Schedule of Assessments

	Trial period					
	Enrolment		Treatment	Follow Up		
Timepoint	**V0**	**R**	**Intervention Period** [a]	**V1** ICU Discharge date	**V2** (28±3d)	**V3** (90±7d)
Enrolment						
Eligibility screen	X					
Informed consent	X					
Randomization		X				
Intervention or comparator						

Nutritional support intervention			X			
Assessments						
Demographic data	X					
Medical History	X					
Physical examination	X					
Pre-stroke mRS	X					
NIHSS	X			X		
GCS	X			X		
NRS-2002	X					
APACHE-II			X			
BMI			X			
mRS				X		X
Vital signs	X		X	X		
Brain CT/MRI	X					
Chest CT or X-ray	X					
12-lead ECG	X					
Echocardiography	X					
White blood cell count	X					
Local laboratory result	X					
Blood glucose			X			
Gastric residual volume			X			
Pneumonia Monitoring [b]			X	X		
Complication monitoring			X	X		
Adverse events			X	X	X	X

V = Visit; R = Randomization; d = day

[a] or death, extubation, ICU discharge if < 7 days.

[b] items including temperature, breathing, sputum, blood oxygen saturation. If necessary, check white blood cell count and perform chest CT or X-ray.

3. List of Abbreviations

AE	Adverse Event
AIS	Acute Ischemia Stroke
APACHE	Acute Physiology and Chronic Health Evaluation
BMI	Body Mass Index
CEC	Clinical Events Committee
CT	Computed Tomography
CRF	Case Report Form
CRRT	Continuous Renal Replacement Therapy
DSMB	Data and Safety Monitoring Board
EAB	Ethics Advisory Board
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
EN	Enteral Nutrition
GCP	Good Clinical Practice
GCS	Glasgow coma scale
GRV	Gastric residual volume
ITT	Intention To Treat
LAR	Legally Authorized Representative
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIHSS	National Institute of Health stroke scale
NRS	Nutritional Risk Screening
PI	Principal Investigator

PN	Parenteral nutrition
PP	Per-Protocol
QC	Quality Control
RCT	Randomized controlled trial
RR	Relative Risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPN	Supplemental Parenteral nutrition
TEN	Trophic Enteral Nutrition
TMC	Trial Management Committee
TSC	Trial Steering Committee
PSP	Post stroke pneumonia

4. Background

Stroke has become the leading cause of death and disability among adults in China, imposing a heavy medical and economic burden on society and families[1]. Actively optimizing comprehensive management measures for the acute phase of stroke is of great significance for improving disease prognosis. Stroke-associated pneumonia (SAP) is the most common complication of stroke, with an incidence rate as high as 40% in patients with severe stroke during the acute phase[2]. SAP is an independent risk factor for death and poor prognosis in stroke patients potentially increasing 30-day mortality by threefold[3,4,5,6]. Therefore, reducing the incidence of SAP will help lower stroke mortality.

Due to impaired consciousness and swallowing dysfunction, patients with severe stroke often require nutritional support, thus establishing it as a critical component of comprehensive management. Currently, nutritional support for critically ill patients primarily involves enteral nutrition (EN) and parenteral nutrition (PN). EN helps protect gastrointestinal function[7,8], but carries a significant risk of aspiration during implementation, which can lead to aspiration pneumonia[9,10,11]. Trophic feeding, an EN strategy that provides minimal nutrients, may reduce the incidence of reflux in critically ill patients[12]. However, relying solely on trophic feeding for patients with severe stroke often fails to meet their caloric demands. Our previous multi-center RCT, published in *Lancet Neurology*, demonstrated that low-calorie feeding during the first week after severe stroke was associated with increased mortality[13]. Conversely, while PN can ensure adequate energy delivery, it is associated with complications such as intestinal mucosal atrophy, gut microbiota disruption, and deep vein infections, which may consequently increase mortality risk[14]. Thus, the identification of an optimal nutritional support regimen for patients with severe stroke, which effectively balances gastrointestinal protection, adequate nutrient delivery, and SAP risk reduction, is of paramount importance to improving prognosis.

4.1 Lack of effective clinical measures to prevent SAP

SAP is the most common complication of stroke and a significant risk factor for stroke-related mortality[3,4,5]. International epidemiological data indicate a SAP incidence ranging from 7% to 38% [15,16,17]. Data from China's National Stroke Registry shows SAP incidences of 11.4% for ischemic stroke and 16.9% for hemorrhagic stroke[18,19]. The incidence rises significantly in severe stroke cases, reaching up to 40% within the first week[2]. SAP is an independent risk factor for death and poor prognosis in stroke patients, potentially tripling 30-day mortality and being associated with increased one-year mortality[6]. Aspiration resulting from impaired consciousness and swallowing dysfunction post-stroke is a key pathogenic mechanism[20]. This condition, common in severe stroke, involves weakened protective reflexes and poor respiration-swallowing coordination, which allow secretions or gastric contents to enter the lungs.

Given the significant burden of SAP, international researchers have explored preventive strategies, among which prophylactic antibiotic use has been a focus. However, two major randomized controlled trials, the STROKE-INF study and the PASS study, did not yield positive results. The STROKE-INF study found that prophylactic use of ceftriaxone for 7 days in stroke patients with swallowing dysfunction did not reduce the incidence of SAP within 14 days post-stroke[21]. The PASS study found that prophylactic use of ceftriaxone for 4 days after stroke onset also did not improve functional outcomes at 90 days[22]. Currently, there is a lack of effective clinical measures for preventing SAP, highlighting a critical gap in stroke care that awaits innovative solutions.

4.2 Clinical dilemma of EN vs. PN in severe stroke

While EN is endorsed as the first-line therapy by guidelines from ESPEN and China[23], with recommendations for initiation within 24-48 hours, its application is frequently complicated by aspiration risk and gastrointestinal intolerance, which can interrupt feeding and prevent the achievement of nutritional goals[9,10,11]. In recent years, owing

to its improved safety profile and demonstrably superior nutritional target attainment rates, early PN has gained considerable endorsement in critical care settings[24,25]. Thus, a core clinical dilemma in nutritional support for critically ill patients is the trade-off between EN, which preserves gut integrity but often faces poor tolerance, and PN, which ensures nutrient delivery but carries its own distinct risks. The latest ASPEN consensus states that no significant difference in clinical outcomes between EN and PN during the first week of critical illness, affirming both as acceptable options[26]. Developing tailored nutritional approaches for specific subpopulations, such as patients with severe stroke, represents an important area for further research.

4.3 Potential Benefits of Combined Trophic Enteral Nutrition and Supplemental Parenteral Nutrition

Trophic feeding is defined as a nutritional strategy that involves the provision of minimal amounts of nutrients. As a form of EN trophic feeding offers distinct advantages over PN, including preservation of intestinal epithelial integrity, stimulation of brush border enzyme secretion, maintenance of tight junctions between epithelial cells, and prevention of bacterial translocation[12]. Compared to full-dose EN, trophic feeding has been demonstrated to reduce the incidence of gastrointestinal intolerance and decrease reflux episodes in patients with severe acute lung injury[12]. However, in cases of severe stroke, the administration of low-calorie trophic feeding may be associated with increased mortality[15], highlighting the potential risks of relying solely on this approach. While PN ensures reliable nutrient delivery, concerns persist regarding its adverse effects, such as intestinal mucosal atrophy, disruption of gut microbiota, hyperglycemia, and catheter-related bloodstream infections[14]. The combination of EN and PN in critically ill patients represents a strategic approach that integrates the benefits of both modalities while mitigating their individual limitations. A European multi-center RCT demonstrated that supplemental PN added to early EN to achieve full nutritional targets significantly reduced the incidence of nosocomial infections within 28 days among critically ill patients[27]. In addition, our retrospective data suggest that early supplemental PN (SPN) in combination with EN significantly

delays the onset of new-onset pneumonia and nosocomial infections in patients with severe stroke. A meta-analysis comparing combined PN and EN versus EN alone in critically ill patient indicated that the combined regimen did not increase risks such as in-hospital mortality, ICU length of stay, or duration of mechanical ventilation[28]. Although SPN in addition to EN represents an effective nutritional strategy for critically ill patients, its efficacy has yet to be confirmed specifically in those with severe cerebrovascular disease.

5. Study objectives

The OPENS-2 study aims to assess, in a multicenter, randomized, open-label, blinded-endpoint setting, the efficacy and safety of combining trophic EN with SPN for nutritional support in patients with acute severe stroke. The findings of OPENS-2 are likely to have a direct impact on clinical practice, particularly in the domain of nutritional therapy.

5.1 Primary Objectives

To determine whether the combination of trophic EN and SPN reduces the incidence of pneumonia within the first 7 days after enrollment in patients with severe stroke requiring nutritional support.

5.2 Secondary Objectives

- To compare nutritional delivery (caloric/protein intake) and insulin requirements during the first 7 days.
- To assess gastrointestinal tolerance (complications, prokinetic agent use) during the first 7 days.
- To evaluate clinical outcomes, including other infections, ICU length of stay, mortality (ICU & 28-day), and specific complications/interventions.
- To measure neurological function (NIHSS, GCS) and functional status (mRS) at ICU discharge and 90 days.

6. Organizational Structure

OPENS-2 trial is an investigator-initiated study which is organized by the Xijing Hospital, Fourth Military Medical University. The following boards and institutions will assure the success of the clinical trial:

6.1 Trial Steering Committee

The TSC provides strategic oversight and ensures the operational integrity of the study. Its core duties include approving the trial protocol, monitoring overall progress, allocating resources, and addressing critical issues. The TSC will make impartial decisions on trial modifications, early termination, or continuation based on interim data or external evidence. It also oversees the dissemination of trial results to ensure transparency and ethical compliance. By balancing scientific rigor, operational efficiency, and stakeholder accountability, the TSC safeguards the trial's validity and alignment with its original objectives.

6.2 Data Safety and Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) is charged with the ongoing safety review and ethical oversight of the OPENS-2 trial. The DSMB's mandate includes monitoring unblinded safety data (including adverse events and deaths), conducting rigorous risk-benefit evaluations, and recommending actions regarding trial modification or termination. Additionally, it ensures adherence to ethical and regulatory standards and maintains strict independence from investigators to avoid bias. The board is composed of an experienced neurologist, an intensive care physician, and a biostatistician, who are not participants of the OPENS-2 consortium and not involved in the clinical trial in any other way. The DSMB conducts regularly scheduled or ad hoc meetings to review critical safety and efficacy data, providing impartial guidance to ensure participant protection and uphold the trial's scientific integrity.

6.3 Ethics Advisory Board

Given the vulnerable nature of the severe stroke population and the complex risk-benefit considerations in the OPENS-2 trial, an independent EAB will be established to provide specialized guidance on emergent ethical issues. The EAB will work in conjunction with, and does not replace, the officially constituted Ethics Committee that provided initial approval for the trial. The EAB may be convened to advise on critical matters such as protocol revisions or trial termination from a specialized ethics perspective.

6.4 Trial Management Committee

The TMC holds primary responsibility for the comprehensive executive management and operational execution of the OPENS-2 trial. Its key functions encompass maintaining critical liaison with the Coordinating Centre as well as all financial stewardship, including overseeing funding applications and the disbursement of funds. The TMC also holds ultimate authority over the development and final approval of the study protocol, all trial-related materials, and data collection tools. Additionally, it addresses general trial management issues to ensure the study progresses efficiently.

6.5 Data Management and Coordinating Center

The Data Management and Coordinating Center is responsible for the day-to-day execution and coordination of the trial, providing comprehensive support across all study phases. Its responsibilities encompass trial management and coordination, data operations, and administrative and safety oversight, including assistance with ethics applications, budget management, CRF design, protocol training of investigators, management of investigator payments, monitoring and close-out site visits, organization of investigator meetings, handling of serious adverse event reporting and data analysis and collaboration on publications.

6.6 Imaging Core Laboratory

The Core Imaging Laboratory serves as the central blinded facility for all imaging assessments in the trial. During patient enrollment, the laboratory reviews baseline

chest images to identify and exclude subjects with pre-existing pulmonary infections. For all suspected pneumonia cases during the trial, the laboratory conducts standardized assessments through dual-reader review with adjudication when required. The laboratory team consists of a senior imaging director who provides final arbitration, 2 staff radiologists who perform primary image interpretation, and a data manager who handles image processing and quality control. All personnel remain blinded to clinical data and treatment allocation throughout the trial.

6.7 Endpoint Adjudication Committee

The independent EAC is composed of experts in intensive care medicine, neurocritical care medicine, and respiratory and critical care medicine. The committee is selected for their independence from trial implementation and sponsorship to prevent any potential conflicts of interest. All members undergo comprehensive training on standardized criteria for diagnosing pneumonia, ensuring consistency in their evaluations. The committee systematically adjudicates cases using predefined criteria and remains strictly blinded to treatment assignments throughout the process.

6.8 Clinical Events Committee

The CEC consists of three independent physician experts not involved in the trial conduct at any investigational sites. The committee will perform all assessments while blinded to treatment group assignment. Its responsibilities include validating all complications occurring during the study and categorizing each for severity and relatedness to the study intervention according to predefined criteria in the protocol. The CEC may request any additional source information and images to assist with the adjudication process.

7. Trial Design

OPENS-2 is a Phase III, multicenter, investigator-initiated, randomized, open-label, blinded-endpoint (PROBE) trial designed to assess the superiority of combined

trophic EN with SPN versus full EN in critically ill patients with AIS. Eligible participants will be randomly assigned (1:1) to one of the two nutritional strategies. The intervention will be administered for 7 days, unless interrupted by the initiation of exclusive oral feeding, discharge from the ICU, or death. All other aspects of clinical management will follow standard care at the discretion of the treating physician.

The primary study center will be the Neuro-intensive care Unit at Xijing Hospital, Xi'an City, China. Upon approval, other selected centers will be approached for participation. Each site must demonstrate expertise in neurocritical care and severe stroke management, supported by a dedicated stroke team. Prior to patient enrollment, all sites will undergo mandatory training, covering study protocol adherence, nutritional risk screening, water drinking test administration and standardized assessments (GCS, NIHSS, mRS).

8. Selection of participants

Patients will be recruited from university and non-university, adult, neuro-intensive critical care units in China. Enrollment must be completed within 24 hours of their initial ICU admission. A local PI, who will be responsible for all trial-related activities, will be identified at each participating unit.

8.1 Inclusion Criteria

- Age≥18 years;
- Definite diagnosis of acute stroke (GCS ≤12 or NIHSS≥11);
- The randomized nutritional treatment could be initiated up to 72 hours after symptom onset;
- Any cases of profiles #3 through 5 in Wate r Swallowing Test or with disorder of consciousness;
- Plan to receive enteral feeding for at least 7 days;
- Informed consent.

8.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from study enrolment.

- Receiving parenteral nutrition support
- Contraindications of enteral nutrition
- Complicated with the disease which only have life expectancy < 7 days
- Dementia or severe disability (mRS>4) before stroke
- Presence of coexisting medical conditions that could interfere with outcome assessment and/or follow-up (a. advanced cancer; b. severe pulmonary dysfunction [forced expiratory volume in 1 second < 50% or/and moderate to severe acute lung injury (PaO2/FiO2)<200mmHg]; c. cardiac insufficiency (NYHA class > I; cardiac structural and/or functional abnormalities such as EF< 50%, abnormal cardiac chamber enlargement, moderate/severe ventricular hypertrophy, or moderate/severe valvular stenosis); d. Severe liver failure [Child-Pugh score≥7]; e. Severe renal failure [glomerular filtration rate ≤ 30mL/min or serum creatinine ≥4mg/dL]
- Currently participating in other clinical trial
- Pregnant woman
- Patient who is considered highly likely not to adhere to the study treatment or follow-up protocol.

9. Informed Consent

9.1 Patients with Capacity to Consent

Once eligibility has been confirmed, and if the patient is competent to give informed consent, an authorized unit doctor will describe the OPENS-2 trial to the patient. A standard Patient Information Sheet will be provided which will identify the title of the trial and include information about: the purpose of the trial, funding, the consequences of participating or not, use of personal data, patient confidentiality, data security and the future availability of the results of the trial. Patients will be encouraged to review

the information, ask questions, and discuss any concerns. A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence; and that consent is given for accessing records, collection and storage of personal information, information to be gathered from the medical record system, to be contacted and for follow-up. After ensuring full comprehension, the clinician will invite the patient to sign the consent form and provide a reliable means of contact within the research team for further communication.

9.2 Patients Lacking Capacity to Consent

Based on prior experience from the OPENS trial in severe stroke, only a minority of patients are expected to retain the capacity to provide informed consent. If, as is most likely, the patient will not be competent to give informed consent, his/her legally authorized representative (LAR) will be regarded as the legitimate representatives capable of providing informed consent. Authorized unit doctors will provide the LAR with the same informed consent process as that for the competent patients. The standard Patient Information Sheet will be given to the LAR, which will include details about the title of the trial, its purpose, funding sources, the consequences of participation or non-participation, the use of personal data, patient confidentiality, data security, and the future availability of the trial results. Potential risks and benefits of the OPENS-2 trial will be clearly communicated. The clinician will ensure the LAR fully understands the information, allow sufficient time for review and questions, and explicitly clarify that participation is voluntary and may be withdrawn at any time without detriment to clinical care. Following this discussion, written consent will be obtained. The LAR will also be provided with contact details of the research team for further inquiries. If and when the patient regains decision-making capacity, their direct consent for continued participation in the trial will be sought without delay. This procedure ensures that the rights, safety, and well-being of patients without decision-making capacity are rigorously protected.

10.Imaging

Chest imaging is essential for determining patient eligibility in the OPENS-2 trial. All patients undergo chest CT scans unless exceptional circumstances preclude it, in which case bedside chest X-rays are performed to assess for infection. Imaging must be performed within 24 hours prior to randomization to exclude patients with active pulmonary infection. The chest imaging results of patients intended to be enrolled must undergo review and confirmation by the Core Imaging Laboratory. During the 7-day intervention period, when clinical symptoms suggest respiratory infection requiring antibiotic therapy, attending physicians should promptly order chest imaging (CT preferred or X-ray) to guide clinical management. These images are used for real-time clinical decision-making by trained site staff and are separate from the endpoint adjudication process. For endpoint determination, all chest images from suspected pneumonia cases undergo centralized, blinded review by the Core Imaging Laboratory using predefined diagnostic criteria, providing the primary imaging evidence for the Endpoint Adjudication Committee's final pneumonia adjudication.

Prior to study initiation, all site investigators complete standardized training in chest imaging evaluation, focusing on the recognition of radiological signs of pneumonia.

11.Randomization procedures

Randomization will be performed using a web-based system accessible through mobile devices or computers (http://www.epiedc.com/kf.php). The system will assign participants in a 1:1 ratio to either trophic EN with SPN group or full EN group with stratification by study site. The block size will not be disclosed, to ensure concealment. Once eligibility is confirmed and informed consent procedures are completed, randomization will occur immediately, with the aim of initiating nutritional support within 24 hours after the patient’s admission to the intensive care unit. Each randomized patient will receive a unique trial identification number. The randomization list will be generated by the independent statistical center using SAS 9.4 software.

12.Blinding/Unblinding

Given the practical nature of the nutritional interventions, this trial adopts an open-label design. The treating clinical team is aware of treatment assignments to ensure proper protocol implementation, while most severe stroke patients are expected to experience impaired consciousness during the intervention period. To ensure objective endpoint assessment and data integrity, blinding is strictly maintained for the Endpoint Adjudication Committee, Core Imaging Laboratory personnel, and study statisticians throughout the trial period. These parties remain completely unaware of treatment group allocations until database lock and completion of the final analysis.

13.Trial interventions

Nutritional support will be initiated as soon as possible after randomization, with a maximum allowed window of 24 hours. The actual start time must be documented.

13.1 Calculation of Caloric and Protein Requirements

Caloric requirements will be estimated using predictive equations based on BMI. For patients with a BMI between 18 and 30 kg/m², the daily caloric target is actual body weight (in kilograms) multiplied by 25 kcal; for patients with a BMI below 18 or above 30 kg/m², the formula (height [cm] - 105) × 25 kcal will be applied[13]. Caloric delivery will follow a stepwise escalation: one-third of the target on intervention day 1, half on day 2, and the full target from day 3 to day 7. An acceptable delivery range is 70% to 100% of the target. When calculating total caloric intake, calories derived from intravenous dextrose and propofol will be included. The protein intake target for all participants is set at 1.2 to 1.5 grams per kilogram of body weight per day. The specific dose will be determined by the attending physician based on clinical factors such as renal function and metabolic stress.

13.2 Full enteral feeding

In the full-feeding group, EN will be initiated at 20 mL/h and advanced to goal rates as rapidly as tolerated, following a standardized protocol. EN was sourced from the unit's standard suppliers in accordance with local hospital policies and procedures. The pharmacy or dietetic department (where applicable), along with all research staff, ensured the use of this product followed the manufacturer's guidelines.

13.3 Trophic EN combined with SPN

Patients randomized to the trophic EN with SPN group will receive enteral nutrition at a fixed rate of ⩽20 mL/h, providing approximately 500 kcal per day. To meet the full calculated caloric and protein targets, the deficit not covered by EN will be supplemented with PN, administered via central or peripheral venous access.

13.4 Delivery and Management of EN and PN

The assigned nutritional strategy will be maintained for 7 days, until death, discharge from the ICU, or removal of the feeding tube (if clinically indicated). OPENS-2 will not mandate a single brand of EN or PN but will require that all products and protocols used by participating sites fall within the following common boundaries:

The protocol for delivery of EN will cover:

- Initial nasogastric/nasojejunal tube insertion/positioning in accordance with relevant clinical guidelines[29].
- Use of standard formula within the specified caloric and nitrogen ranges;
- Adjustment of total volume according to fluid balance requirements;
- Monitoring for nutritional-related complications (e.g. diarrhoea, gastrointestinal intolerance)
- Gastric residual volume (GRV) will be monitored every 4 hours in patients receiving gastric feeding. If the gastric residual volume is below 200 mL, the

aspirate may be returned and feeding continued as planned; a volume exceeding 100 mL warrants consideration of a prokinetic agent like metoclopramide, though it does not necessitate interruption of feeding[13], and the use of erythromycin for this purpose should be avoided. If GRV exceeds 200 mL and is accompanied by other signs of intolerance, such as vomiting, distension, ileus, feeding should be held. For a single, resolved episode where symptoms abate completely within 2 hours, feeding may resume at the previous rate. If the initial episode is severe, characterized by large-volume or recurrent vomiting, or if the problem recurs, feeding should be restarted at half of the previous rate and gradually increased back to the target after 6 hours of tolerance. If intolerance persists after restarting at half of the rate, an intensified management phase will be initiated: the EN rate will be further reduced to a minimal maintenance level (e.g., 20–25 mL/hour), an abdominal imaging study may be performed to assess gastrointestinal motility, and conversion to post-pyloric feeding should be actively considered. EN will only be completely stopped if recurrent aspiration occurs despite the minimal rate, with attempts to restart after the underlying cause is addressed. Every effort should be made to maintain feeding continuity; interruptions should only occur for procedures that pose a direct risk of aspiration or that require strict fasting.

- Minimize periprocedual feeding interruptions.

The protocol for delivery of PN will cover:

- Central venous catheter insertion and care with a dedicated lumen for PN;
- Use of standardized commercial PN solutions or individualized formulations prepared by the hospital pharmacy, adhering to protocol-specified macronutrient, electrolyte and micronutrient requirements tailored to the participant's metabolic needs. All PN solutions (commercial or compounded) must meet pharmacopeial standards and undergo sterility and stability verification prior to administration.
- Total volume adjusted according to fluid balance requirements;
- Regular monitoring for PN-related complications (e.g., electrolyte imbalances,

hyperglycemia, catheter-related infections).

13.5 Blood Glucose Management[30, 31]

Glycaemic control should be implemented per international guidelines. The target blood glucose range for this trial is to be maintained between 7.8-10 mmol/L. Monitoring and control procedures should follow local institutional policies and guidelines. Blood glucose will be monitored at least every 4–6 hours, with intravenous insulin protocols used as needed to maintain targets, following local institutional guidelines.

14. Study Schedule

The schedule of assessments conducted during the study is shown in Part 2 (Flow Chart and Schedule of Assessments). The study includes three periods: Enrollment (Visit V0, Randomization), treatment and follow up (V1, V2, V3).

Time points for data collection

- Pre-enrollment (Screening)
- Randomization (Baseline)
- Daily during the 7-day intervention period
- At discharge from the critical care unit (or on Day 7 if still in ICU)
- At 28 days post-randomization (±3 days)
- At 90 days post-randomization (±7 days)

14.1 Enrollment period (Visit V0, Randomization)

14.1.1 Pre-enrollment (Visit V0)

After written informed consent is obtained from the patient or their legally authorized representative, data from standard-of-care assessments will be collected for screening and baseline characterization. The investigator shall document detailed information of all consented subjects to confirm final eligibility and record reasons for screening failures.

- Age
- Diagnostic information and medical history
- Physical examination
- Determination of the pre-stroke mRS via interview of the patient or the patient's legal representative
- NIHSS and GCS scores
- NRS-2002 score
- Measurement of vital signs including blood pressure, heart rate, and respiratory rate
- Laboratory tests
- Arterial blood gas analysis
- 12-lead ECG
- Echocardiography
- Non-contrast CT scan or MRI scan
- Checking of inclusion and exclusion criteria

14.1.2 Randomization (R)

Eligible patients will be randomized following confirmation that all inclusion criteria are met and no exclusion criteria apply.

Data collected at randomization:

- Patient identification code
- Sex
- Height, weight and BMI
- APACHE-II score

14.2 Treatment period

The following data will be collected daily for the duration of the 7-day intervention period.

- Nutritional support access: for PN (central venous catheter site); for EN (feeding tube type and placement)
- Nutritional delivery (formula type, volume, total calories and protein delivered);
- Insulin administration (total daily dose)
- Lowest and highest blood glucose
- Use of prokinetic drugs
- Signs, diagnostic tests, and results for new-onset pneumonia
- Other infectious and non-infectious complications
- Use of antibiotics
- Vital signs
- Survival status
- Adverse events and serious adverse events

14.3 Critical Care Unit Discharge (Visit V1)

- Date of discharge
- Routes of Nutritional Administration during the ICU Stay
- Infectious and non-infectious complications during the ICU Stay
- Acute stroke treatments administered
- Survival status
- Hospitalization expenses
- Adverse events

14.4 Follow Up period

14.4.1 At 28 days post-randomization (Visit V2)

- Survival status
- Adverse events

14.4.2 At 90 days post-randomization (Visit V3)

- Survival status
- Functional outcome: mRS

15. Outcomes

15.1 Primary efficacy outcomes

- Incidence of post-stroke pneumonia from randomization to day 7.

15.2 Secondary efficacy outcomes

- Time from randomization to onset of the post-stroke pneumonia within 7 days post-randomization
- Daily calorie and protein delivery during the first 7 days post-randomization
- Insulin dosage during the first 7 days post-randomization
- The usage rate of prokinetic agents during the first 7 days post-randomization
- Occurrence of nosocomial infections from randomization to ICU discharge
- Length of ICU stay
- Incidence of tracheotomy, mechanical ventilation, continuous renal replacement therapy, and venous thrombosis from randomization to ICU discharge
- Usage rate of vasoactive agents from randomization to ICU discharge
- The score of National Institute of Health stroke scale at ICU discharge
- Glasgow Coma Scale at ICU discharge
- Modified Rankin scale at ICU discharge
- Modified Rankin scale at 90 days

15.3 Safety outcomes

- All-cause mortality during ICU stay
- All-cause mortality at 28 days
- Incidence of cardiac failure from randomization to ICU discharge
- Incidence of gastrointestinal complications (Vomiting, diarrhea, gastric retention, gastrointestinal bleeding) during the first 7 days post-randomization

16. Assessment

16.1 Assessment of efficacy

- **Pneumonia**

The primary outcome is the incidence of post stroke pneumonia, occurring from randomization until the end of the 7-day intervention period. Pneumonia will be defined and adjudicated using predefined criteria established by the Centers for Disease Control and Prevention (CDC), encompassing ventilator-associated pneumonia (VAP), non-ventilator-associated pneumonia, and other lower respiratory tract infections[32]. If a patient dies within 7 days, pneumonia is counted only if it occurred before death. If a patient is discharged from the ICU or transitions to oral feeding within 7 days, pneumonia occurring after that point but still within the 7-day window is included. The time from randomization to the onset of post-stroke pneumonia within the first 7 days was prespecified as a secondary endpoint. All investigators at participating sites will be trained to identify and report all potential pneumonia events throughout the study period. The EAC will adjudicate all reported potential pneumonia events while blinded to treatment assignment. The Committee will review all supporting documentation, including the blinded imaging assessment from the Core Imaging Laboratory, to determine the final diagnosis based on predefined criteria.

- **Nosocomial infections**

The analysis for this objective will utilize a binary endpoint of all new-onset, infections (including sepsis, urinary tract infections, bacteremia, etc.) from randomization to ICU discharge, defined by CDC/NHSN criteria[32]. This composite endpoint, as a key secondary outcome, will be tested for statistical significance under a pre-specified multiple testing strategy.

- **Daily calorie and protein delivery**

This endpoint assesses the adequacy of nutritional support by measuring daily caloric (kcal/day) and protein (g/day) delivery from all nutritional sources (EN and PN) during the 7-day intervention period. Total caloric intake will specifically include contributions from both nutritional formulations and non-nutritional intravenous sources, such as dextrose and propofol.

- **Insulin Dose**

This endpoint was defined as mean daily insulin dose during the 7-day intervention period.

- **The usage rate of prokinetic agents**

The overall proportion of patients receiving at least one dose of a prokinetic agent (e.g., erythromycin, metoclopramide, mosapride) throughout the 7-day intervention.

- **Length of ICU stay**

This endpoint measures the duration from randomization to final discharge from the intensive care unit (ICU), calculated in whole days with any partial day rounded up (e.g., 6.3 days recorded as 7 days). Discharge is defined as transfer to a non-ICU setting (e.g., general ward), or death during the ICU stay. However, the actual timing of ICU discharge may be influenced by the availability of beds on regular wards, which could introduce bias. To more objectively reflect the patient's clinical recovery, this study will primarily evaluate the time to readiness for ICU discharge. This metric is defined as the duration from randomization to the time when the patient first meets all predefined clinical criteria for ICU discharge. A patient is considered ready for discharge upon meeting all the following conditions: a. No longer in need of, or at risk for needing, invasive mechanical ventilation; b. No longer in need of, or at risk for needing, vasoactive support; c. No agitation or altered consciousness requiring close monitoring and management; d. No severe acute metabolic or haematological disorder requiring close monitoring and management. All patients weaned from invasive mechanical ventilation and vasoactive drugs will be assessed daily against these readiness criteria. This strategy to mitigate bias from bed availability has been employed previously in ICU nutrition studies[33].

- **The incidence of non-infection complications**

The cumulative incidence of the following clinically significant events occurring from

randomization until ICU discharge: tracheotomy, mechanical ventilation, continuous renal replacement therapy (CRRT), and venous thrombosis. Each complication will be analyzed and reported separately.

-Tracheotomy: Surgical airway creation performed after randomization.

-Mechanical ventilation: Invasive ventilation via endotracheal intubation or tracheostomy, initiated post-randomization and sustained for ⩾24 consecutive hours.. Non-invasive ventilation is excluded.

-CRRT: Any continuous extracorporeal renal support therapy (e.g., CVVH, CVVHD, CVVHDF) initiated post-randomization and lasting ⩾24 hours.

-Venous thrombosis: Radiologically confirmed deep vein thrombosis or pulmonary embolism, occurring de novo after randomization.

- **The usage rate of vasoactive agents**

The overall proportion of patients receiving at least one dose of vasoactive agents from randomization until ICU discharge. Vasoactive agents include norepinephrine, epinephrine, vasopressin, dopamine, dobutamine, and other catecholamine or non-catecholamine vasoactive drugs administered intravenously. Only intravenous administrations lasting ⩾1 hour will be included.

- **The National Institutes of Health Stroke Scale**

The NIHSS is a standardized assessment tool for evaluating neurological deficits, which serves as a valid and reliable measure of disability and recovery after acute stroke. Scores range from 0 to 42, with higher scores indicating more severe neurological impairment. The scale encompasses multiple dimensions including level of consciousness, extraocular movements, motor and sensory functions, coordination, as well as language and speech capabilities. In this study, NIHSS assessments will be performed at baseline, daily during the intervention period, and on the day of discharge from the ICU. All assessors must undergo standardized training in NIHSS administration and pass a certification examination before participating in the rating

process. At each study site, NIHSS evaluations will be conducted by investigators who are blinded to treatment group assignments (See appendix 1).

- **The Glasgow Coma Scale (GCS)**

The GCS is a standardized neurological assessment tool used to objectively evaluate a patient's level of consciousness based on three behavioral responses: eye opening, verbal performance, and motor responsiveness. Scores range from 3 to 15, with lower scores indicating a deeper level of impairment. In this study, assessments are scheduled at baseline, daily during the intervention period, and at ICU discharge, performed by blinded and trained assessors (See appendix 2).

- **The modified Rankin Scale (mRS)**

The mRS score is a validated and reliable clinician-reported measure of global disability, widely used to evaluate functional recovery after stroke. It assesses the degree of disability or dependence in daily activities, with scores ranging from 0 (no symptoms) to 6 (death). In this trial, the mRS will be assessed at two time points: on the day of discharge from the ICU and at 90 days (±7 days) after randomization. Premorbid mRS status will be retrospectively obtained and documented on the CRF. All follow-up assessors at each study site must undergo standardized training and certification in mRS administration, including the use of the Modified Rankin Scale–9 Questions (mRS-9Q) questionnaire, prior to participating in the trial. Only those who successfully pass the certification process will be permitted to perform mRS evaluations. All assessors will remain blinded to treatment group assignments throughout the study. The mRS-9Q questionnaire will be employed as a structured interview tool to enhance the consistency and objectivity of the ratings. A written record of each assessment will be maintained (See appendix 3). The primary analysis for functional outcome will be the distribution of mRS scores at 90 days, analyzed using an ordinal logistic regression model (ordinal shift analysis).

16.2 Assessment of safety

- **All-cause mortality**

Mortality serves as a key safety endpoint in this trial, with assessment spanning two timeframes: all-cause mortality during the entire ICU stay (from randomization until ICU discharge) and all-cause mortality at 28 days (within 28±3 days after randomization). Mortality rates will be calculated as the number of deaths during each period divided by the total number of randomized subjects in each treatment group.

- **Cardiac failure**

Cardiac failure is defined as the onset or worsening of clinically significant cardiac dysfunction occurring between randomization and ICU discharge, diagnosed according to adapted AHA/ACC/HFSA criteria[34]. Diagnosis requires compatible clinical features (e.g., dyspnea, elevated jugular venous pressure, pulmonary crackles, or peripheral edema) supported by at least one objective criterion: elevated cardiac biomarkers (BNP $\geqslant$400 pg/mL or NT-proBNP $\geqslant$2000 pg/mL), echocardiographic evidence of structural or functional abnormality (e.g., new LVEF <40%, severe valvular dysfunction), or initiation of specific intravenous therapy (diuretics, vasodilators, or inotropes) for $\geqslant$24 hours for acute heart failure management. All events will be adjudicated by Clinical Events Committee blinded to treatment allocation.

- **Gastrointestinal complications**

The incidence of gastrointestinal complications will be assessed for events newly occurring from day 1 to day 7 post-randomization. These complications are defined as: vomiting, defined as the visible passage of enteral formula into the mouth, outside the mouth, or into the airway without nursing care or patient mobilization[33]; diarrhea, defined as $\geqslant$3 loose or liquid stools or more than 300 mL of liquid stool per day)[35]; gastric retention, defined as GRV >200 mL on two consecutive measurements despite prokinetic therapy), or the occurrence of overt vomiting or regurgitation; and

gastrointestinal bleeding, evidenced by haematemesis, coffee ground emesis, melaena, haematochezia, or bloody nasogastric aspirate[36]. All events require clinical documentation and adjudication by Clinical Events Committee, with pre-existing complications at baseline excluded.

17. Data management guidelines

17.1 Case Report Forms (CRFs) and data entry

All study data for the OPENS-2 trial will be primarily captured on paper CRFs at the participating sites. The completed paper CRFs, along with any required supplemental forms (e.g., Withdrawal of Consent, Serious Adverse Event reports), will be submitted to the central Data Management and Coordinating Center. The hospital medical records and the original paper CRFs will serve as the source documents for the trial. The Chief Investigator is responsible for the data overall. Each participating center retains ownership of their local site data. Principal Investigator at each research site is accountable for the accuracy, completeness, and timeliness of data entry onto the CRFs. This responsibility may be delegated to authorized and trained site personnel, with oversight remaining with the PI.

Following trial completion, a complete, cleaned, and de-identified final dataset will be created under the supervision of the Chief Investigator. This dataset will be stored securely with access controls. Investigators will have direct access to their own site's data; access to the full dataset or data from other sites will require a formal request and approval from the OPENS-2 Steering Committee.

The investigators propose to use the following statement in the final manuscript. Non-identifiable individual participant data generated in this trial will be made available for sharing from 3 years from 9 months to 36 months after publication. The data will be accessible only to researchers who submit a written proposal for data use, which must be approved by the OPENS-2 Investigator Committee as

methodologically sound. Proposals should be directed to jiangwen@fmmu.edu.cn.

17.2 Data quality and control

To ensure the accuracy, completeness, and reliability of data in the OPENS-2 trial, standard operating procedures for data collection will be developed. Prior to study initiation, all site investigators will receive standardized training in CRF completion and must pass a certification assessment. During the study implementation phase, a three-tier quality control system will be enforced: investigators will perform immediate self-check upon CRF completion to verify data completeness and logical consistency; study coordinators will conduct secondary review, focusing on internal data consistency; and project monitors will perform periodic source data verification and process compliance audits. All issues identified through the quality control (QC) process will be formally communicated to the respective sites, requiring investigators to provide a formal response with supporting evidence. Prior to database locking, a final data cleaning process will be implemented to resolve all data discrepancies, followed by a review before final database lock. QC activities will be thoroughly documented and archived, establishing a traceable, closed-loop quality management system.

17.3 Data security and storage

The processing of personal data will be conducted in compliance with Chinese data protection laws and regulations, as well as relevant international legislation and established good practice. Robust measures will be implemented to ensure comprehensive data security, with special emphasis on protecting sensitive participant information. The study database will contain only de-identified data, with no personally identifiable information stored at any stage. All paper materials, including CRFs are stored in specially designed cabinets that are waterproof and fireproof, and only authorized staff have access to them. Discarded paper materials are shredded using specialized equipment, and the shredding process is supervised by two people. All paper source records will be retained for a minimum of 10 years from the point of

publication of data on the primary outcome.

18. Safety

18.1 Adverse Events

Usually, AEs are defined in accordance with ICH E2A guidelines as any untoward medical occurrence in a patient receiving an investigational intervention, regardless of causal relationship. In the ICU setting, it is recognized that patients frequently exhibit abnormalities in laboratory values, signs, and symptoms as a consequence of their underlying critical illness or routine medical care. Such manifestations will not automatically be classified as AEs. An event will be considered an AE only if it meets either of the following criteria: (1) it is assessed as having a possible, probable, or definite relationship to the study treatment, or (2) it is judged to be inconsistent with the patient's expected clinical course in the context of their underlying condition. All such cases will be referred to the Clinical Events Committee for final adjudication.

When reporting, the underlying condition (e.g., "renal failure") should be documented rather than its manifestations (e.g., "hyperkalemia"). AE collection is limited to the period from initiation of study nutrition support until 48 hours after its discontinuation. All AEs must be followed until resolution or until a clinically adequate explanation is obtained, with follow-up frequency determined by the investigator.

18.2 Serious Adverse Events

The OPENS-2 trial enrolls critically ill stroke patients characterized by substantial baseline mortality, attributable to the seriousness of the stroke that required ICU management. This risk of death remains present despite the application of standard best-practice care. In accordance with international standards for ICU research, deaths considered part of the natural disease progression or expected complications of critical illness will not be reported as SAEs. Only those deaths deemed causally related to the study intervention or judged by the investigator to represent a potential

safety concern shall be reported as SAEs. All deaths, regardless of cause, will be thoroughly documented, including the cause of death, timing, and relationship to underlying conditions and undergo formal causality assessment by the investigators. All mortality data will be incorporated into the final analysis dataset for unified statistical analysis and reporting.

The protocol mandates expedited reporting for specifically defined SAEs, with new or worsening heart failure events designated as the primary reportable SAE. Regardless of expectedness, any occurrence must be reported within 24 hours following the predefined SAE reporting procedure. Investigators are required to conduct a comprehensive assessment of the event, including determination of causality to the study intervention (categorized as definitely, probably, possibly, unlikely, or unrelated), and submit complete documentation to the Clinical Events Committee for final adjudication.

18.3 Recording and reporting procedures

All AEs that occur between randomization and 30 days post-randomization must be recorded on the CRFs. The onset date, severity, and assessed causality of any event must be documented using the definitions below. Within 24 hours of the investigator becoming aware of the SAE, all events must be reported to the trial coordinator who is available 24/7, using the trial specific OPENS-2 SAE Reporting Form. All sections of the OPENS-2 SAE Reporting Form must be completed.

OPENS2 security desk Fax: +86 029-84775368.

Table 1. Severity categorization of Adverse Event

Grade	Term	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2	Moderate	Minimal, local, or noninvasive intervention indicated; limiting instrumental Activities of Daily Living (ADL).
Grade 3	Severe	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
Grade 5	Fatal	Death related to the AE.

Table 2. Relationship definitions of Adverse Event

Term	Description
None	The adverse event is clearly and unequivocally due to a cause other than the trial treatment.
Unlikely	The available evidence does not support a causal relationship, as the event onset lacked a plausible temporal association with the trial treatment and is more clearly attributable to alternative factors (such as the patient's underlying medical condition or concomitant therapies).
Possible	The adverse event could be associated with the trial treatment, but the connection is uncertain.
Probable	The adverse event is likely due to the trial treatment.
Definitely	The adverse event is clearly and unequivocally linked to trial treatment and other possible contributing factors can be ruled out

18.4 Follow up

All AEs that lead to study withdrawal or persist at the study conclusion must be

followed up. Any SAE unresolved at the end of the study or at the time of a subject's discontinuation requires ongoing follow-up until one of the following criteria is met: resolution of the event, stabilization of the event, return to baseline status (if applicable), attribution to causes other than the study procedures, or determination that no additional information can be obtained. The delegated local investigator(s) must provide follow-up SAE Report(s) if the SAE had not resolved at the time the initial report was submitted.

18.5 Central processing

Upon receipt of a SAE report, clinical members of the OPENS-2 Clinical Events Committee, on behalf of the PI, will assess the event's severity, relationship to the study intervention, and expectedness to determine whether expedited reporting to the Ethics Committee is required. Concurrently, the Data Management and Coordinating Center will regularly submit safety information reports to the PI, TMG, TSC, and DSMB for review.

19. Withdrawal

19.1 Patient Withdrawal

By consenting to participate in the OPENS-2 trial, the patient or their legally authorized representative agrees to undergo trial treatment, assessments, follow-up, and data collection. However, they retain the right to withdraw from the trial at any time without providing a reason and without any penalty or loss of benefits to which they are otherwise entitled.

19.2 Trial Treatment Withdrawal

The attending clinician may discontinue the trial intervention for an individual participant if it is deemed to be in the participant's best medical interest. The reasons for withdrawal must be documented in detail in the CRF. Unless consent is formally withdrawn, data collection and follow-up should continue in accordance with the trial

protocol. In cases where a patient expresses intent to discontinue trial treatment, the study site should explain the importance of remaining in the trial for data collection and follow-up.

19.3 Withdrawal of Consent

Upon withdrawal of consent for further trial participation, all intervention and data collection must cease immediately. A Withdrawal of Consent Form must be completed and submitted to the TMC. All data collected prior to the withdrawal will be retained for analysis. However, if the patient requests the destruction of all their data, the relevant data shall be securely destroyed. Patients withdrawn from the OPENS-2 trial will not be replaced, and this scenario has been accounted for in the sample size calculation.

19.4 Study Site Withdrawal

If a study site decides to cease patient recruitment before the end of the trial, the local PI must provide written notification to the TSC. All patients already recruited at that site must continue to be followed up in accordance with the OPENS-2 Trial Protocol. The TSC, upon recommendation from the TMC, may suspend or terminate a site's participation for significant or persistent protocol non-compliance. Such a decision will be communicated in writing.

20. Trial Closure

20.1 Timing of Trial Closure

This trial will formally conclude once the last enrolled subject has completed the 90-day follow-up. At this point, the Chief Investigator will submit a Trial Closure Declaration Form to the Ethics Committee.

20.2 Archiving of Trial Documents

Upon trial conclusion, the trial Data Management and Coordinating Center will

archive all central-level trial documents in accordance with ICH GCP guidelines. These documents, which include CRFs and other essential documents, will be securely stored for a minimum of 10 years before confidential destruction. Concurrently, the local PI is responsible for retaining locally held trial documents for the same 10-year duration, or longer if required by applicable regulations. Essential documents are defined as those that enable the evaluation of both trial conduct and data quality, while also serving as evidence of the site's adherence to ICH GCP and other regulatory requirements. All archived documents, whether stored centrally or locally, must be made available for regulatory inspection upon request.

20.3 Early Termination of the Trial

The Trial Steering Committee may recommend early termination of the trial based on recommendations from the DSMB or the TMC. The study may be terminated based on several considerations, including but not limited to:

- Safety findings from this or other studies that indicate an unacceptable risk profile.
- Insufficient enrollment rate or accrual that compromises the trial's feasibility or scientific validity.

In such a case, the TMC will formally notify all study sites and Ethics Committees in writing, stating the reasons for termination and any necessary measures regarding participant treatment. All subjects who have been randomized will continue to complete follow-up as specified in the OPENS-2 trial protocol.

21 Statistics

21.1 Sample size calculation

The sample size is based on the primary efficacy endpoint. We expect an 12.0% absolute difference between patients receiving trophic EN combined with SPN and patients receiving full EN (expected rates of post stroke pneumonia: 28% in patients receiving trophic EN combined with SPN and 40% in patients receiving full EN),

which corresponds to a risk ratio (RR) of 0.70[37,38]. In order to demonstrate the expected treatment effect with a type-1 error alpha of 0.05 (two tailed) and a power of 80%, a sample size of n= 490 patients (n=245 per treatment group) is required. To safeguard against dilution of the treatment effect associated with an approximate 10% attrition rate (due to loss to follow-up, consent withdrawal and other reasons), we plan to enroll n=546 patients (n=273 per treatment group) for this study.

21.2 Analysis population

- **Intention-to-Treat Population**

The ITT population includes all patients randomized into the trial, even if the subject does not receive the correct nutritional support, or does not follow the protocol until completion. This population will serve as the primary analysis set for efficacy endpoints, with all subjects analyzed according to the treatment group assigned during randomization.

- **Per-Protocol Population**

The PP population consists of patients from the ITT population who received the assigned nutritional support as randomized and complied with key trial procedures without major protocol violations that could impact efficacy outcomes. As this is an open-label trial, major protocol deviations will be identified through unblinded review prior to database lock. Patients will be excluded from the PP population based on the following criteria at a minimum:

- **Deviations in Nutrition Support Administration.**

  Failure to achieve 7 days of nutrition support duration, unless the discontinuation is due to patient death, discharge from the ICU, the achievement of adequate oral intake, or is supported by a valid clinical justification;

- **Deviations in Nutrition Route.**

a) Failure to implement the assigned nutritional strategy according to randomization;

b) (Trophic EN with SPN group) Exceeding the enteral nutrition rate limit (as

defined per protocol) for more than 24 consecutive hours;

c) (Full EN group) Initiation of parenteral nutrition without appropriate clinical justification;

d) Cessation of all nutritional support for more than 48 consecutive hours without valid medical reasons;

- **Other Major Deviations.**

a) Violation of inclusion/exclusion criteria with subsequent randomization

b) Failure to perform protocol-required nutrition monitoring and data collection

c) Serious violations of enteral/parenteral nutrition preparation and administration protocols.

All protocol deviations must be thoroughly documented in the CRF(s) with explanations. The Steering Committee will provide final confirmation of all deviations prior to database lock and any analysis by treatment group.

- **Safety Population**

The Safety Population comprises all randomized patients who initiated nutritional support regimen. Patients who violated the randomization protocol will be additionally analyzed according to the actual nutritional strategy they received in a supplementary analysis. The classification of patients for the 'as-treated' analysis must be completed prior to database unblinding. Patients who immediately withdrew consent after randomization without receiving any nutritional support will be excluded from the Safety Population.

21.3 Interim analysis

No interim analysis is planned for this study.

21.4 Analysis of results

The efficacy analyses will be performed on the intention-to-treat (ITT) population. For the primary outcome, a modified Poisson regression model will be used to compare the proportions between treatment groups. The risk ratio (RR) with its 95%

confidence interval (CI) will be reported. An adjusted analysis will also be performed, adjusting for pre-specified baseline covariates (e.g., age, NIHSS at ICU admission, stroke type, and history of diabetes). Subgroup analyses will be conducted to explore treatment effect consistency across the following pre-specified subgroups: age (≤70 vs. >70 years), Stroke severity (NIHSS at ICU admission 11-19 vs. ≥20),stroke type (ischemic vs. hemorrhagic), history of diabetes , consciousness level (GCS 9–12 vs. ≤8), and time from stroke onset to nutrition initiation (≤24 vs. >24 hours), Missing primary outcome data will be handled using multiple imputation. Sensitivity analyses will assess the impact of missing data, competing risks such as death, and potential center effects.

For binary secondary endpoints (e.g., tracheotomy, mechanical ventilation), a modified Poisson regression model will be used to estimate the RR and 95% CI as did for the primary endpoint analysis. For continuous secondary endpoints (e.g., calorie/protein delivery, NIHSS score at ICU discharge), linear regression models with treatment group as the study variable and baseline measurement as covariate if available will be applied to estimate mean differences and 95% CI; if normality assumptions are violated, the win ratio method will be employed. For ordinal secondary outcomes (e.g., 90-day mRS), an ordinal logistic regression model will be fitted to estimate the common odds ratio (cOR) and 95% CI; if the proportional odds assumption is violated, the generalized odds ratio (GenOR) with 95% CI will be reported. Time-to-event secondary outcomes (e.g., time to pneumonia) will be analyzed using survival methods, specifically the Fine-Gray subdistribution hazards model, accounting for competing risks where appropriate. Safety analyses will be performed on the safety population, grouped according to the actual nutritional support received. Safety endpoints (e.g., all-cause mortality, cardiac failure, gastrointestinal complications) will be compared using modified Poisson regression models.

22 Ethical and regulatory consideration

22.1 Ethical compliance

The OPENS-2 trial will be conducted in accordance with the ethical principles of the Helsinki Declaration. Prior to the initiation of the trial, the protocol, informed consent form(s), and all other study materials must receive written approval and authorization from the Ethics Committee of Xijing Hospital, Fourth Military Medical University. Each participating hospital's Research Ethics Board (REB) has also approved the trial protocol and informed consent form(s). No trial procedures may commence at a center before these approvals are in place. All substantial amendments to the protocol will be submitted promptly to the REBs for their review and approval before implementation. The continued oversight of the trial will be ensured through the submission of annual progress reports to the REBs.

The two nutritional strategies under investigation (trophic EN with SPN vs. full EN) are both utilized in clinical practice for the management of acute severe stroke. However, their comparative effects on the incidence of pneumonia and other clinical outcomes remain uncertain, which is the primary scientific question this trial aims to address. Therefore, patient participation is associated with the potential for direct benefit, and investigators are committed to ensuring that all enrolled subjects receive protocol-defined care under close monitoring. The OPENS-2 trial employs an independent DSMB to periodically review accumulating safety and efficacy data. The involvement of this independent body ensures that the safety and well-being of the subjects remain the highest priority at all times.

22.2 Monitoring and Quality Assurance

The OPENS-2 trial will implement a comprehensive, risk-based monitoring strategy. This approach combines ongoing remote oversight with targeted on-site visits to ensure participant safety, protocol compliance, and data integrity, with monitoring

intensity dynamically adjusted based on continuous performance evaluation.

Initial On-Site Assessment

All participating centers will undergo an initial monitoring visit (conducted on-site or remotely) after the enrolment of their first 10-15 patients. The primary objectives of this visit are:

- To verify that data recorded in the paper CRFs are accurate and complete. Key data for 100% of the initial patients will undergo this verification.
- To assess the overall conduct of the trial at the site, including the informed consent process, study nutritional preparation management, and adherence to Good Clinical Practice (GCP).

Continuous Oversight and Performance Evaluation

The monitoring team will regularly contact the centers through field visits, emails or phone calls, and send inspectors to assess the progress of the trial, the compliance of investigators and patients with the trial protocol, and to resolve urgent issues.

- CRF Review: As completed CRF pages are submitted, the data management team will perform checks for completeness, legibility, and consistency. Queries will be generated and sent to the site for resolution.
- Performance Metrics Tracking: Key indicators such as recruitment rates, screening failure reasons, and the timeliness of CRF submission will be monitored to identify centers performing outside of expected parameters.

The findings from the initial monitoring visit, combined with the insights from this continuous centralized oversight, will be used to assign a risk status to each center.

Dynamic, Risk-Based Follow-up Monitoring

The frequency and intensity of subsequent on-site monitoring will be directly determined by the assigned risk status:

- Centers with No Noticeable Findings: Sites demonstrating consistent protocol compliance, high-quality CRF completion, and timely query resolution will be

classified as low risk. These centers will not undergo further routine scheduled on-site monitoring but will remain under continuous centralized oversight.

- Centers with Noticeable Findings: Sites with identified issues in data quality, protocol compliance, or GCP will be classified as elevated risk. These centers will receive a follow-up on-site visit within 4 months to address the specific findings.
- Centers with persistent problems: If significant issues continue, monitoring will be intensified, including on-site visits at least three times per year. During these visits, source data verification (SDV) will be performed on a minimum of 50% of CRFs and associated source data.
- Resolution and De-escalation: Once consecutive monitoring activities confirm that all significant findings have been resolved and site performance has stabilized, the intensified monitoring schedule will be discontinued, and the center's risk status will be downgraded accordingly.

Throughout the trial, the monitor will work closely with site personnel to review CRFs, resolve data queries, and ensure the accurate and complete documentation of all trial data.

22.3 Liability and Insurance

The study sponsor shall maintain an appropriate insurance policy to cover claims arising from trial-related injury in accordance with applicable national laws. A certificate of this insurance will be provided to the investigator of the coordinating center where required.

23. Publication and dissemination policy

23.1 Dissemination Plan

Ongoing trial progress will be communicated to local PIs via regular newsletters, emails, and offline conferences. Final results will be presented at relevant national and international scientific conferences and meetings. The findings will also be submitted

for publication in peer-reviewed scientific journals. A summary of the findings will be made available to patients and the public through patient support groups and the official trial website.

23.2 Reporting Obligations

The Data Management and Coordinating Center is responsible for submitting the trial results to the relevant Regulatory Authorities and Ethics Committees. This includes the provision of an annual safety report and a final study report upon trial completion, in accordance with applicable regulations.

23.3 Publication Policy

The primary manuscript for publication will be based on the pre-defined statistical analysis plan outlined in this clinical trial protocol. All publications and presentations will undergo review by the Trial Steering Committee prior to submission to ensure accuracy and consistency. All patient data will be anonymized prior to any publication or public dissemination. The authorship of the primary manuscript and any major secondary publications will be determined by the Trial Steering Committee based on the ICMJE criteria, with the intention of including key contributors from the participating sites. Investigators are not permitted to publish trial-related data that pertains to the overall trial results independently of the central publication committee to prevent fragmentation of findings. However, investigators retain the right to access and analyze data from their own site for local quality improvement or methodological studies, provided that any such publication is coordinated with the central committee to ensure consistency and avoid overlap with the primary trial outputs.

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25. Appendixes

25.1 Appendix 1 NIHSS

NIHSS page 1

Subject ID ___ ___ ___ ___ ___ ___ ___ ___ ___ ___
Subject Date of Birth ___ ___/___ ___/___ ___
Hospital ID _____
Date of Examination ___ ___/___ ___/___ ___

NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)[1]

Interval: [ ] Baseline
[ ] 7-10 days
[ ] 1 month
[ ] 3 months
[ ] 6 months
[ ] Other _____

Time: ___ ___:___ ___ [ ]am [ ]pm

Person Administering Scale _____

Purpose:
The NIH Stroke Scale (NIHSS) is a standardized neurological examination intended to describe the neurological deficits found in large groups of stroke patients participating in treatment trials.

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do ***not*** go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert**; Keenly responsive. 1 = **Not alert, but arousable** by minor stimulation to obey, answer or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful. stimulation to make movements (not stereotyped). 3 = **Responds only with reflex motor or autonomic effects or totally unresponsive**, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct – there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers both questions correctly**. 1 = **Answers one question correctly**. 2 = **Answers neither question correctly**.	_____

[1] The National Institute of Neurological Diseases and Stroke (NINDS), National Institutes of Health (NIH), Last Revised 01 October 2003 (https://stroke.nih.gov/resources/index.htm).

NIHSS page 2

Instructions	Scale Definition	Score
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only the case of amputation or joint fusion at the hip, should the examiner record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift**; limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift**; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity**; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity**; leg falls to bed immediately. 4 = **No movement**. UN= **Amputation** or joint fusion; explain: _____ 6a= **Left Arm**. 6b= **Right Arm**.	_____ _____
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, should the examiner record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb**. 2 = **Present in two limbs**. UN= **Amputation** or joint fusion; explain: _____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal**; no sensory loss. 1 = **Mild-to-moderate** sensory loss; patient feels pinprick is less sharp or is dull on the affected side, or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total** sensory loss; patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No asphasia**; normal. 1 = **Mild-to-moderate aphasia**; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe asphasia**; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia**; no usable speech or auditory comprehension.	_____

NIHSS page 3

Instructions	Scale Definition	Score
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him/her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Answers both tasks correctly**. 1 = **Answers one task correctly**. 2 = **Answers neither task correctly**.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy**; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation**, or total gaze paresis not overcome by the oculocephalic maneuver.	_____
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss**. 1 = **Partial hemianopia**. 2 = **Complete hemianopia**. 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 sounds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, should the examiner record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift**; limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift**; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity**; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity**; limb falls. 4 = **No movement**. UN= **Amputation** or joint fusion; explain: _____ 5a= **Left Arm**. 5b= **Right Arm**.	_____ _____

NIHSS page 4

Instructions	Scale Definition	Score
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, should the examiner record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal**. 1 = **Mild-to-moderate dysarthria**; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria**; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN= **Intubated** or other physical barrier; explain: _____	_____
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality**. 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality**; does not recognize own hand or orients to only one side of space.	_____

NIHSS page 5

You know how.

Down to earth.

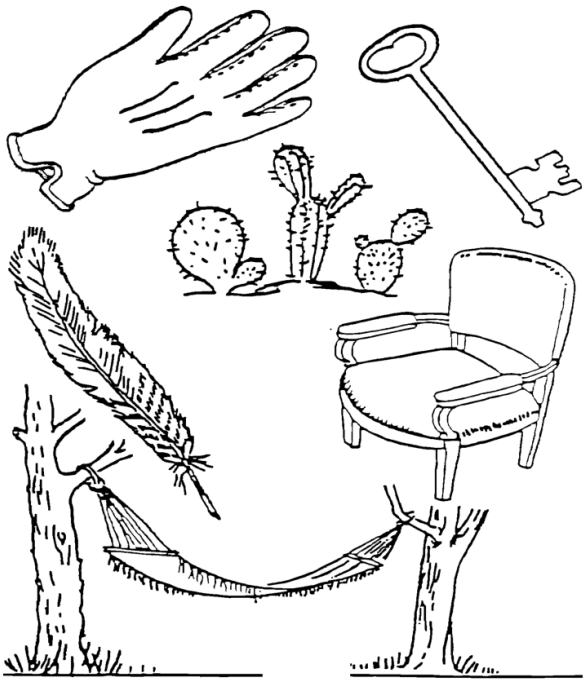
I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

请您读出下列句子：
知道
下楼梯
回家做饭
在学校复习
发表精彩演讲

NIHSS page 6



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

请您读出下列单词：
妈妈
大地
飞机飞机
丝绸
按时开工
吃葡萄不吐葡萄皮

25.2 Appendix 2 GCS

GLASGOW COMA SCALE : Do it this way

GCS EYES VERBAL MOTOR

Institute of Neurological Sciences NHS Greater Glasgow and Clyde

CHECK	OBSERVE	STIMULATE	RATE
For factors Interfering with communication, ability to respond and other injuries	Eye opening , content of speech and movements of right and left sides	Sound: spoken or shouted request Physical: Pressure on finger tip, trapezius or supraorbital notch	Assign according to highest response observed

Eye opening

Criterion	Observed	Rating	Score
Open before stimulus	✔	Spontaneous	4
After spoken or shouted request	✔	To sound	3
After finger tip stimulus	✔	To pressure	2
No opening at any time, no interfering factor	✔	None	1
Closed by local factor	✔	Non testable	NT

Verbal response

Criterion	Observed	Rating	Score
Correctly gives name, place and date	✔	Orientated	5
Not orientated but communication coherently	✔	Confused	4
Intelligible single words	✔	Words	3
Only moans / groans	✔	Sounds	2
No audible response, no interfering factor	✔	None	1
Factor interferring with communication	✔	Non testable	NT

Best motor response

Criterion	Observed	Rating	Score
Obey 2-part request	✔	Obeys commands	6
Brings hand above clavicle to stimulus on head neck	✔	Localising	5
Bends arm at elbow rapidly but features not predominantly abnormal	✔	Normal flexion	4
Bends arm at elbow, features clearly predominantly abnormal	✔	Abnormal flexion	3
Extends arm at elbow	✔	Extension	2
No movement in arms / legs, no interfering factor	✔	None	1
Paralysed or other limiting factor	✔	Non testable	NT

Sites For Physical Stimulation

Finger tip pressure | Trapezius Pinch | Supraorbital notch

Features of Flexion Responses

Modified with permission from Van Der Naalt 2004
Ned Tijdschr Geneeskd

Abnormal Flexion
Slow Sterotyped
Arm across chest
Forearm rotates
Thumb clenched
Leg extends

Normal flexion
Rapid
Variable
Arm away from body

1. Sedated Patients: Assess GCS during daily sedation interruption (DSI) when clinically safe; if DSI is contraindicated, mark “NT (Not Testable – Sedated)”.

2. Intubated Patients: Label verbal subscore as “T” (Intubated); calculate total score as E+M

3. Stimulus Protocol: Prioritize non-destructive pain stimuli (supraorbital pressure > nail bed compression) to avoid skin breakdown.

4. Neuromuscular Blockade: Document use of NM blockers; GCS motor subscore is “NT” until blockade is reversed.

Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness: A practical scale. The Lancet, *304*(7872), 81-84.

https://www.glasgowcomascale.org/download-aid/

25.3 Appendix 3 mRS

Subject ID ___ ___ ___ ___ ___ ___ ___ ___ ___ ___
Subject Date of Birth ___ ___/___ ___/___ ___
Hospital ID _____
Date of Examination ___ ___/___ ___/___ ___

The Modified Rankin Scale (mRS)

(Use web calculator at www.modifiedrankin.com)

0 No symptoms

1 No significant disability; able to carry out all usual activities, despite some symptoms

2 Slight disability; able to look after own affairs without assistance, but unable to carry out all previous activities

3 Moderate disability; requires some help, but able to walk unassisted

4 Moderately severe disability; unable to attend to own bodily needs without assistance, and unable to walk unassisted

5 Severe disability; requires constant nursing care and attention, bedridden, incontinent

6 Dead

References:

Rankin J (May 1957). "Cerebral vascular accidents in patients over the age of 60. II. Prognosis". Scott Med J 2 (5): 200–15

Patel, N., et al. Simple and reliable determination of the modified Rankin Scale in neurosurgical and neurological patients: The mRS-9Q. *Neurosurgery*, published online in advance of print 26 July 2012

Level of Function Survey – mRS-9Q

Q 1: Do you have any symptoms that are bothering you?

☐Yes ☐No

Q 2: Are you able to do the same work as before?

☐Yes ☐No

Q 3: Are you able to keep up with your hobbies?

☐Yes ☐No

Q 4: Have you maintained your ties to friends and family?

☐Yes ☐No

Q 5: Do you need help making a simple meal, doing household chores, or balancing a checkbook?

☐Yes ☐No

Q 6: Do you need help with shopping or traveling close to home?

☐Yes ☐No

Q 7: Do you need another person to help you walk?

☐Yes ☐No

Q 8: Do you need help with eating, going to the toilet, or bathing?

☐Yes ☐No

Q 9: Do you stay in bed most of the day and need constant nursing care?

☐Yes ☐No

mRS-9Q: the mRS calculator (http://www.modifiedrankin.com/)

25.4 Appendix 4 NRS-2002

Nutritional Risk Screening (NRS) 2002

Patient Information

Name:	Gender:	Age (y):	Admission No.:
Height (m):	Weight (kg):	BMI (kg/m²):	Assessment Date:
Clinical Diagnosis:	Albumin (g/L):	Assessor:	Signature:

1.Initial screening

Answer the following questions. If **any answer is "Yes"**, proceed to the final screening. If all answers are "No", the patient is re-screened at weekly intervals. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.

- Is the Body Mass Index (BMI) < 20.5 kg/m²? □ Yes □ No
- Has the patient lost weight in the previous 3 months? □ Yes □ No
- Was nutritional intake reduced in the previous week? □ Yes □ No
- Is the patient severely ill? (e.g., in intensive care) □ Yes □ No

2. Final Screening

Score separately for impaired nutritional status and severity of disease (stress metabolism), then calculate the total score.

A. Impaired Nutritional Status Score (0-3 points)

Score	Criteria	□ Check
0	No impairment of nutritional status	□
1 (Mild)	Weight loss > 5% in 3 months; OR nutritional intake 50-75% of normal requirement in the previous week	□
2 (Moderate)	Weight loss > 5% in 2 months; OR BMI	□

	18.5-20.5 kg/m² + impaired general condition; OR nutritional intake 25-50% of normal requirement in the previous week	
3 (Severe)	Weight loss > 5% in 1 month (or > 15% in 3 months); OR BMI < 18.5 kg/m² + impaired general condition; OR nutritional intake 0-25% of normal requirement in the previous week	□

Subtotal (Nutritional Status): _____

B. Severity of Disease Score (0-3 points)

Score	Criteria	□ Check
0	Normal nutritional requirements (no stress metabolism)	□
1 (Mild)	Hip fracture; chronic diseases with acute complications (e.g., cirrhosis, COPD, chronic hemodialysis, diabetes, oncology)	□
2 (Moderate)	Major abdominal surgery, stroke, severe pneumonia, hematologic malignancy	□
3 (Severe)	Head injury, bone marrow transplantation, intensive care patients (APACHE II > 10)	□

Subtotal (Disease Severity): _____

3. Total Score Calculation & Interpretation

1. Age adjustment: Add 1 point if the patient is > 70 years old (to account for frailty). □ ≥70 y (1 point) □ <70 y (0 point)

2. Total Score = Nutritional Status Score + Disease Severity Score + Age Adjustment Score: _____

3. Interpretation:

Total score ≥ 3: Nutritional risk present; initiate nutritional support planning.

Total score < 3: No obvious nutritional risk; repeat screening weekly.

Reference: Kondrup, J., Allison, S. P., Elia, M., Vellas, B., Plauth, M., & ESPEN. (2003). ESPEN guidelines for nutrition screening 2002. Clinical Nutrition, 22(4), 415-421.

25.5 Appendix 5 APACHE II

Acute Physiology and Chronic Health Evaluation II

Patient Information

Name:	Gender:	Age (y):	Admission No.:
ICU Admission Time:	Assessment Time (within 24h of ICU admission):	Assessor:	Signature:

1. Acute Physiology Score (APS) (0-60 points)

Record the worst value of each parameter within 24 hours after ICU admission. Score 0-4 points for each item; total APS = sum of individual scores.

Parameter	0 Points	1 Point	2 Points	3 Points	4 Points
Temperature (℃)	36-38.4	38.5-38.9	39.0-40.9	≥41.0	≤35.9
Mean Arterial Pressure (mmHg)	70-109	110-139	140-179	≥180	≤69
Heart Rate (bpm)	70-109	110-139	140-179	≥180	≤69
Respiratory Rate (breaths/min)	12-24	25-34	35-49	≥50	≤11
PaO_2/FiO_2 (mmHg)	≥300	-	200-299	<200 (with mechanical ventilation)	-
Arterial pH	7.33-7.49	7.50-7.59	7.60-7.69	≥7.70	≤7.32
Serum Sodium (mmol/L)	130-149	150-154	155-159	≥160	≤129
Serum Potassium (mmol/L)	3.5-5.4	5.5-5.9	6.0-6.9	≥7.0	≤3.4
Serum Creatinine (mg/dL) (×2 for acute renal failure)	≤1.4	1.5-1.9	2.0-3.4	≥3.5	-

Hematocrit (%)	30-45.9	46.0-49.9	≥50.0	-	≤29.9
White Blood Cell Count ($10^3/mm^3$)	3.0-14.9	15.0-19.9	≥20.0	-	≤2.9
Glasgow Coma Scale (GCS)	15	13-14	10-12	7-9	≤6

Acute Physiology Score (APS) Subtotal: _____

2. Age Score (0-6 points)

Age	Score	□ Check
≤44 years	0	□
45-54 years	2	□
55-64 years	3	□
65-74 years	5	□
≥75 years	6	□

Age Score Subtotal: _____

3. Chronic Health Score (0/2/5 points)

Score only if the patient had severe organ dysfunction or immunocompromise before ICU admission.

Condition	Score (Elective Surgery)	Score (Non-Surgery/ Emergency Surgery)	□ Check
No severe chronic organ dysfunction or immunocompromise	0	0	□
Severe organ dysfunction (NYHA Class IV heart failure, chronic hypoxia/obstructive lung disease, chronic dialysis, cirrhosis with portal hypertension, etc.) or	2	5	□

immunocompromise (chemotherapy, radiotherapy, AIDS, leukemia, etc.)			

Chronic Health Score Subtotal: _____

4. Total Score Calculation & Interpretation

4.1 Total APACHE-II Score = APS Subtotal + Age Score Subtotal + Chronic Health Score Subtotal. Total score range: 0-71 points.

4.2 Interpretation: The higher the total score, the more severe the patient's condition and the worse the prognosis.

Score 0-4: Low severity, low mortality risk.

Score 5-9: Mild severity, mild mortality risk.

Score 10-14: Moderate severity, moderate mortality risk.

Score 15-19: Severe severity, high mortality risk.

Score ⩾20: Critical severity, very high mortality risk.

Reference: Knaus, W. A., Draper, E. A., Williams, R. G., & Zimmerman, J. E. (1985). APACHE II : a severity of disease classification system. Critical Care Medicine, 13(10), 818-829.