Informed Consent Form

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informed consent

(ICF Template)

Project Title: Comparison of Protein Absorption Efficiency Between Short-Peptide and Whole-Protein Enteral Nutrition Formulations in High-Risk Patients with Pancreatic Exocrine Dysfunction in the ICU: A Multicenter Randomized Controlled Study

Research institution: Tongji Hospital Affiliated to Tongji University

Principal Investigator: Wang Sheng

You are invited to participate in a clinical study. This informed consent form provides you with essential information to help you decide whether to participate. Please read it carefully, and if you have any questions, please consult the investigator responsible for the study.

This study has been approved by the Ethics Review Committee of Shanghai Tongji Hospital. Shanghai Tongji Hospital is a tertiary Grade A general hospital and a drug clinical trial institution accredited and registered with the National Medical Products Administration (NMPA). The principal investigator of this study is Dr. Wang Sheng, Chief Physician at the Intensive Care Medicine Center.

This study plans to enroll a total of 250 participants, with three hospitals participating in the study, among which Tongji Hospital affiliated to Tongji University serves as the lead institution. The participating hospital itself intends to enroll 100 subjects.

1. Research Objective (Why is this study being conducted?):

1.1 Main Research Objectives:

Using targeted amino acid metabolomics and gut microbiota co-metabolomics as core quantitative metrics, this study systematically evaluated whether short-peptide-based versus whole-protein-based enteral nutrition (EN) formulations can enhance protein absorption efficiency in high-risk patients with pancreatic exocrine insufficiency (PEI) on the intensive care unit.

1.2 Secondary Research Objectives:

Compare the effects of two EN formulations on the pancreatic exocrine function, gastrointestinal tolerability, associations with intestinal barrier function and gut microbiota metabolic profiles, as well as clinical outcomes in study subjects.

2. Research Background and Significance:

In intensive care units (ICUs), critically ill patients often face a dual challenge of hypermetabolism and impaired protein absorption due to their state of severe stress, which interacts to create a vicious cycle. This leads to rapid skeletal muscle atrophy, delayed wound healing, significantly increased risks of infectious complications, prolonged mechanical ventilation duration, and extended ICU hospitalization time, severely compromising patient recovery and long-term prognosis—a critical issue requiring urgent resolution in critical care medicine. Our previous epidemiological data indicate that the incidence of pancreatic exocrine insufficiency (PEI) among ICU patients reaches as high as 52.2%, with severe PEI accounting for 18.3%. Shock, sepsis, cardiac arrest, hyperlactatemia, and invasive mechanical ventilation are identified as high-risk factors for PEI in the ICU setting. PEI refers to dysfunction of the pancreatic exocrine glands, resulting in insufficient secretion of digestive enzymes and thereby impairing digestion and absorption processes; thus, individuals at high risk for PEI represent a subpopulation with a heightened susceptibility to protein absorption disorders. Moreover, conventional nutritional therapies administered to critically ill patients with concurrent PEI not only fail to correct malnutrition but may also exacerbate gastrointestinal burden, inducing adverse effects such as abdominal distension, diarrhea, and pancreatic enzyme secretion disturbances, further deteriorating patient outcomes. Consequently, implementing enteral nutrition therapy in critically ill patients exhibiting both "ICU stress state" and "high PEI risk" characteristics presents greater challenges and carries higher risks of poor prognosis.

Enteral nutrition (EN), as a nutritional support approach that aligns with the physiological principles of digestion and absorption in humans, has been explicitly recommended by numerous clinical guidelines as the preferred method for nutritional support in ICU patients. Among these, short-peptide formulations and whole-protein formulations are currently the two most widely used EN preparations in clinical practice. Short-peptide formulations primarily utilize small-molecule peptides as their protein source, requiring no extensive enzymatic digestion by pancreatic enzymes; they can be directly absorbed via the PepT1 transporter on the surface of intestinal mucosal epithelial cells, making them theoretically more suitable for individuals with insufficient pancreatic enzyme secretion or impaired digestive function. Whole-protein formulations, on the other hand, contain complete proteins as their core component, which require digestion by pancreatic enzymes such as trypsin and chymotrypsin for absorption. These formulations offer advantages including low cost, comprehensive nutritional composition, and broad applicability; however, in cases of pancreatic exocrine insufficiency (PEI), their digestibility and absorption efficiency may be significantly compromised, failing to meet patients 'nutritional needs. Currently, the selection of EN formulations for high-risk PEI populations in clinical practice largely relies on clinicians' empirical judgment, lacking robust evidence-based support. Moreover, previous related studies exhibit significant limitations: First, the study populations predominantly focused on general ICU patients or patients with chronic protein malabsorption (PEI) (e.g., postoperative patients with chronic pancreatitis or pancreatic cancer), failing to specifically address the dual pathophysiological characteristics of "ICU stress state + high risk of PEI," resulting in poor clinical generalizability of the findings; second, most studies were single-center, small-sample retrospective observational studies with low evidence quality, and

core evaluation metrics primarily centered on feeding tolerance (e.g., diarrhea, abdominal distension, gastric retention), lacking precise quantitative assessment of protein absorption efficiency; third, evaluation methods were limited to macroscopic parameters such as nitrogen balance and plasma total amino acid concentrations, which cannot effectively distinguish the impacts of different pathological mechanisms—including insufficient pancreatic enzyme digestion, intestinal absorption disorders, and increased muscle catabolism—on protein metabolism, thereby hindering identification of the underlying pathophysiological basis for differences in absorption between the two formulations.

The 2025 Nutrition Guidelines for Severe Patients issued by the American Society for Parenteral and Enteral Nutrition (ASPEN) explicitly state that targeted nutritional interventions should be investigated for populations with specific pathological conditions in the ICU (e.g., high-risk groups for postenteric infection [PEI], patients with acute gastrointestinal injury, etc.). Priority should be given to enteral nutrition (EN) formulations tailored to their digestive and absorptive capacities to enhance the clinical efficacy of nutritional support and improve patient outcomes. Meanwhile, rapid advancements in targeted amino acid metabolomics have provided novel technical foundations for precise quantification of protein absorption efficiency. This technology enables systematic evaluation of the entire protein "digestion-absorption-metabolism" chain by accurately measuring changes in concentrations of specific metabolic markers such as branched-chain amino acids (BCAAs) and citrulline in plasma, combined with analysis of fecal microbiota co-metabolites, thereby overcoming the limitations of traditional assessment methods. Given these clinical challenges, existing research gaps, and technological constraints, this study focuses on high-risk populations with pancreatic exocrine insufficiency in the ICU, using whole-protein EN formulations as controls. Through a multicenter prospective cohort study, we aim to systematically evaluate the effects of short-peptide EN formulations on protein absorption efficiency, pancreatic exocrine function, gastrointestinal tolerance, relationships with intestinal barrier function and gut microbiota metabolic profiles, as well as clinical outcomes in high-risk PEI patients. The findings will provide high-quality evidence-based data to guide individualized EN formulation selection strategies and promote the transition of critical care nutrition from an "empirical" to a "precision-based" approach.

3. Selection Criteria and Exclusion Criteria (Who is eligible to participate in this study?):

You may participate in this study if you meet the following requirements: (specific requirements)

- Patients aged ⩾18 years, regardless of gender, who meet the temporal requirements for baseline data collection and intervention implementation.
- Meets the definition of high-risk populations for PEI and satisfies any one of the following criteria: ① APACHE II score ⩾15, indicating severe disease status, significant stress response, and a high risk of pancreatic dysfunction; ② Postoperative period ⩽7 days following major abdominal surgery (including gastrointestinal, hepatobiliary, or pancreatic surgeries), during which postoperative

stress may readily impair pancreatic function; ③ Concurrent severe acute pancreatitis meeting the diagnostic criteria of the Atlanta Classification (2012 edition); ④ Diagnosis of sepsis (SOFA score ≥2) accompanied by elevated serum pancreatic lipase/starchase levels (>1.5 times the upper limit of normal reference values), suggesting pancreatic involvement; ⑤ Prolonged fasting (≥72 hours) associated with gastrointestinal dysfunction (gastric retention>200 mL/4 h or diminished/absent bowel sounds), indicating impaired digestive and absorptive functions.

- The patient is hemodynamically stable (maintained with a norepinephrine dose of ≤ 0.2 μg/kg/min or an equivalent dose of other vasoactive agents, blood lactate concentration ≤2 mmol/L, urine output ≥0.5 ml/kg/h), and has an AGI score ≤ grade II, meeting the criteria for initiating enteral nutrition therapy.
- The duration of enteral nutrition support is expected to be ≥7 days, with feeding administered via nasogastric tube or nasoenteric tube, ensuring continuous implementation of intervention measures and effective monitoring of outcome indicators.
- The study subject or their legally authorized family member signs the informed consent form.

You are not eligible to participate in this study if you meet the following criteria: (specific requirements)

- Patients with a definitive diagnosis of PEI (fecal elastase-1 <200 μg/g) or those with concurrent chronic pancreatic diseases (including chronic pancreatitis, pancreatic cancer, etc.) exhibit chronic and persistent pancreatic dysfunction, which contradicts the high-risk population for acute stress-induced PEI identified in this study.
- There are contraindications to enteral nutrition therapy, including paralytic ileus, active upper gastrointestinal bleeding, short bowel syndrome, severe intestinal ischemia, etc., making enteral nutritional support unsuitable.
- Patients with severe combined hepatic and renal dysfunction (Child-Pugh liver function score ≥ grade C, stage 3 acute kidney injury [AKI] without renal replacement therapy [RRT] or RRT duration>7 days) may experience significant impairment of hepatic and renal function, which could affect protein metabolism and the accuracy of laboratory test results.
- In patients with combined amino acid metabolic disorders (e.g., maple syrup urine disease), severe malnutrition (BMI <16 kg/m²), or cachexia, there are congenital or severe pathological abnormalities in protein metabolism that may interfere with study outcomes.

- Within 7 days prior to enrollment, patients had received pancreatic enzyme replacement therapy (PERT) or used medications that may affect protein absorption (e.g., long-term use of glucocorticoids>1 week at doses exceeding 20 mg/day equivalent to prednisone); such drugs may interfere with the assessment of pancreatic function and protein absorption efficiency.
- Patients with an anticipated ICU stay of <7 days, those scheduled for transfer to another medical institution, or those whose family members have explicitly declined active treatment are unlikely to complete the full intervention and follow-up process.
- Women who are pregnant or breastfeeding, those with mental disorders who cannot cooperate with the study investigators, individuals at risk of ethical issues in the study, or cases where study implementation poses significant challenges.
- Participated in other interventional clinical studies during the same period.

4. Research Process (What does participation in this study require?):

This study employed a multicenter, randomized controlled trial design. Participants were randomly assigned to groups without mandatory interventions and the study was conducted strictly in accordance with standard clinical practice principles to ensure the real-world applicability of the results. All subjects were recruited from the intensive care units of tertiary Grade A hospitals in China, totaling approximately 250 patients, with at least 100 cases included in this center. Patient recruitment lasted for 18 months, and follow-up concluded 28 days after enrollment.

During the screening/baseline phase, informed consent forms were obtained and inclusion/exclusion criteria were verified. A total of 100 patients were planned to be enrolled, with systematic collection of the following data: demographic characteristics (age, gender, height, weight, BMI, etc.), clinical baseline parameters (types of underlying diseases, APACHE II score, SOFA score, surgical history, presence of sepsis diagnosis, etc.), laboratory baseline values (pancreatic enzyme levels, liver and kidney function tests, complete blood count, baseline plasma amino acid levels), and gastrointestinal functional status prior to initiation of enteral nutrition (gastric retention volume, bowel sound intensity, etc.), thereby establishing a comprehensive baseline database for all study participants.

Study subjects meeting the inclusion criteria were randomly assigned to either the short peptide group or the whole protein group, with the specific allocation scheme as follows:

1） 1) Short peptide group: Patients received short-peptide-enriched EN formulations for nutritional support therapy. The selected formulations contain 5 g of protein per 100 ml, composed entirely of hydrolyzed whey protein, which can be absorbed by the intestines without requiring full digestion with pancreatic enzymes;

2） 2) Whole Protein Therapy: Nutritional support is provided using whole protein-enriched EN formulations, with a selected formulation containing 5 g of protein per 100 ml, all composed of complete protein components that are digested and absorbed via pancreatic enzymes secreted by the pancreas.

Both study groups strictly adhered to the 2025 ASPEN Guidelines for Nutritional Therapy in Critically Ill Patients and the expert consensus on critical care nutrition in China when administering nutritional support therapy. Apart from differences in enteral nutrition (EN) formulations, all other therapeutic interventions—including anti-infective therapy, organ function support therapy, gastrointestinal motility regulation therapy, and sedation/analgesia—were rigorously implemented in accordance with standard ICU clinical protocols, ensuring consistent baseline treatment conditions between the two groups.

The total study duration was set at 18 months, divided into two phases: the first phase (enrollment period) lasted 16 months, during which all subjects underwent screening, enrollment, and intervention implementation; the second phase (follow-up period) lasted 2 months, ensuring that all enrolled subjects completed follow-up visits 28 days after intervention completion and enabling comprehensive collection of outcome data.

Monitoring of clinical parameters after initiation of study medication:

On the day of enrollment intervention (D0): Record baseline values of pancreatic enzyme levels, liver function, renal function, complete blood count, plasma amino acids, gastric retention volume, bowel sounds, and measure femoral rectus muscle thickness by ultrasound.

Days 1 – 7 after enrollment and intervention (D1 – D7): Record the infusion rate, dosage of enteral nutrition (EN), and feeding tolerance (including symptoms such as diarrhea, abdominal distension, or gastric retention). On days 3 and 7 of the intervention, collect 5 mL of fasting venous blood, 5 g of fresh fecal sample, and perform 24-hour urine analysis for amino acid metabolomics profiles, pancreatic function parameters, and intestinal barrier function indicators. Subsequently, initiate enteral nutrition infusion and collect venous blood samples at 0.5, 1, 2, 3, and 4 hours post-infusion to measure plasma BCAA concentrations at each time point and calculate the AUC_{0-4} h.

On day 14 after enrollment and intervention (D14): Record the infusion rate, dosage of EN infusion, and feeding tolerance (including symptoms such as diarrhea, abdominal distension, or gastric retention); collect 5 mL of fasting venous blood, 5 g of fresh fecal sample, and 24-hour urine samples for analysis of amino acid metabolomics profiles, pancreatic function parameters, and intestinal barrier function indicators; perform ultrasonography to measure femoral rectus muscle thickness and assess muscle atrophy severity.

On day 28 (D28) after enrollment and intervention: Follow-up was conducted via telephone to assess the patients' survival status, place of residence (home/rehabilitation facility/hospital), and occurrence of infection recurrence.

The follow-up period lasted until 28 days after patient enrollment. In the event of patient death, the time of death was recorded; if the patient survived, the duration of mechanical ventilation, ICU hospitalization time, total hospital stay duration, and occurrence of infection complications (ventilator-associated pneumonia, catheter-related urinary tract infection, catheter-related bloodstream infection) were documented.

From the initiation of intervention to the conclusion of the study, all adverse reactions related to enteral nutrition (including vomiting, aspiration, upper gastrointestinal bleeding, allergies, etc.) must be documented. Each adverse reaction should be recorded in detail, including the occurrence time, severity, management measures, and outcome.

5. Potential risks and discomforts associated with participating in the trial:

1) Blood sampling: (pain, bleeding, swelling, infection, etc.)

During blood drawing, a bruise may form at the site where the needle penetrates the skin. In rare cases, syncope or infection may occur. If the injection site becomes red or swollen at any time, you should inform your physician or the ward nurse.

2) Adverse reactions after intervention: (diarrhea, abdominal distension, allergic reactions, etc.)

This study is a prospective randomized controlled trial that employed clinically standard short-peptide and whole-protein enteral nutrition formulations as intervention measures, without additional invasive procedures. The study protocol strictly adhered to clinical practice guidelines. The primary research risks involved mild adverse reactions associated with enteral nutrition (e.g., diarrhea, abdominal distension), which were rare and could be effectively managed with symptomatic treatment, making the overall study risk manageable.

If any discomfort, new changes in the condition, or any unexpected events occur in the study subjects, regardless of their association with the medication/examination, the primary physician should be promptly notified. The physician will assess the situation and provide appropriate medical intervention.

6. Potential benefits (What benefits will this study bring me):

1) For patients, this approach enables the provision of more targeted nutritional support regimens, effectively improving protein absorption, reducing the risk of complications such as muscle atrophy and infections, thereby enhancing prognosis.

2) Clinically, this study fills the evidence gap in nutritional interventions for high-risk populations with PEI in the ICU, provides a scientific basis for clinicians to precisely select enteral nutrition (EN) formulations, and optimizes the critical care nutrition management workflow.

3) For academia, this initiative can drive technological innovation and theoretical advancement in the field of critical care nutrition, providing methodological references and data support for subsequent related research.

7. Possible additional costs or expenses (Do I need to pay any fees for participating in this study?)

Participation in this research project will not incur any additional expenses; all testing fees related to the study are covered by the research funding. However, treatments and examinations required for other coexisting conditions are not included within the free scope of coverage.

8. Medical treatment and compensation for injuries (What to do in case of injury during participation in the study)

If you sustain an injury during the study period or experience an adverse event while receiving medication therapy, please contact your study physician; you will receive prompt medical treatment. For any injury with a causal relationship to this study or the investigational drug, the sponsor will cover all medical expenses and provide appropriate financial compensation in accordance with applicable national laws and regulations.

Even after signing this informed consent form, you retain all your statutory rights.

9. As a study subject, you have the following responsibilities:

Provide accurate information regarding your medical history and current health status; inform the research physician of any discomfort experienced during the study period; refrain from taking restricted medications or consuming prohibited foods; and disclose whether you have participated in other studies recently or are currently participating in any other studies.

10. Privacy and Confidentiality:

If you decide to participate in this study, we will make every effort to protect your personal privacy within the limits permitted by law. No public reports regarding the study outcomes will disclose any of your personal information. Your research physician and investigators will collect your information for use in this study. This may include date of birth, gender, height, weight, health-related information, medical history, diagnoses, as well as data obtained from blood or urine samples and imaging materials (collectively referred to as "personal information"; personal information excludes information that has been anonymized). During and after the study period, your personal information will be collected, processed, and stored.

Your medical records (including original medical charts, laboratory reports, etc.) will be fully retained at the hospital where you received treatment. Within legal limits, monitors, auditors, ethics committee members, and regulatory investigators are permitted to review your original medical records to verify the clinical trial procedures and data, without any disclosure of personal information.

As part of this study, the investigating physician will also record the results of your study-related assessments in your personal medical records. The investigating physician will further review your personal medical records to obtain health-related information, such as past medical history and recent treatments received.

Your personal information is stored exclusively at this research center. Any data provided to external parties will undergo anonymization (your identification information is represented by your date of birth and participant number). Therefore, your personal information will not be disclosed and is protected by a password. This password-protected data is referred to as "research data," with your study physician controlling the password. Your personal information will not be disclosed to any third party unless for your health and benefit, for the health and benefit of other participants, or as required by law. Any public reports regarding the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical information within the limits permitted by law. In accordance with medical research ethics, experimental data may be accessible to the public and shared only through web-based electronic databases, ensuring no personal privacy information is leaked. If you find your information inaccurate or incomplete, you have the right to request corrections or supplements from your study physician.

The anonymized information will be used to conduct and evaluate studies in China or worldwide in accordance with relevant regulatory requirements as per the protocol. Subsequent development phases will involve further research, development, and safety assessment of new products and/or improvements to existing products, with applications submitted for marketing approval and sale of these products anywhere in the world.

The results of this study may be published in medical journals, but we will maintain strict confidentiality of your research records in accordance with legal requirements. No personal information will be disclosed during publication.

If you withdraw your consent, the study physician will no longer use your research data or share it with others. However, research data that you have already shared with the sponsor prior to withdrawing your consent may still be used by the sponsor.

If any of the above requirements regarding the processing and management of your personal information are amended, the investigating physician will promptly inform you of the changes and obtain your renewed consent.

During the study period, we will promptly notify you of any significant new developments or medical information related to your health, including recommendations for additional examinations to confirm such findings. We will also promptly inform you of any new information that may influence your decision to continue participating in the study.

11. Are there any other treatment options currently available, and what are the advantages and disadvantages of the treatment approach employed in this study?

Participation in the study is not your only treatment option. If you choose not to participate, you will still receive other therapeutic interventions and guidance provided by your physician, who will develop a tailored treatment plan based on your individual circumstances and inform you of potential benefits and risks.

12. Subjects' Rights:

Your participation in this study is entirely voluntary. You may refuse to participate or withdraw from the study at any time during its conduct, and your data will not be included in the study results. This will not affect your relationship with your physician, nor will it impact your medical benefits or rights.

If you require additional treatment, fail to comply with the study protocol, experience study-related injuries, or for any other reason, the principal investigator will promptly notify you and terminate your participation in this study. The principal investigator will then provide recommendations for your subsequent treatment plan based on your health status.

If you withdraw from the study midway, for safety considerations, we will complete all required examinations specified in the final safety follow-up as much as possible; however, you have the right to decline. If new information related to your health or rights is identified

after your withdrawal, please promptly inform your research physician, and we will contact you again.

14. Who should I contact if I encounter any problems or difficulties?

If you have any questions related to this study, please contact:

Research Physician:, Contact Number:_____.

If you have any concerns regarding the research process or questions related to your rights and interests, please contact the Secretary of the Ethics Committee at Shanghai Tongji Hospital at telephone: 021-66111243 or email: tongjilunli2012@163.com.

Sign page for the Informed Consent Form

I have read this informed consent form, discussed the study with my physician, and raised any relevant questions. The physician has provided me with a detailed explanation of the study objectives, procedures, potential risks, and benefits, and has addressed all my inquiries. I am fully aware that participation in this study is voluntary.

I confirm that I have had sufficient time to consider this matter, including the potential risks associated with participating in the study. I may consult my physician for further information at any time, withdraw from the study without facing discrimination or retaliation, and ensure that my medical care and benefits remain unaffected by withdrawal. I am also fully aware that if I withdraw from the study during the course of participation—particularly for therapeutic reasons—I must promptly inform my physician of any changes in my condition and complete the required physical and biochemical examinations, which will benefit both myself and the entire study. Should any additional treatment be required due to changes in my condition, I will seek prior consultation with my physician or provide truthful disclosure thereafter.

I voluntarily participate in this study. I consent to the researchers, sponsors, health regulatory authorities/pharmaceutical and food regulatory agencies, and ethics committees accessing my research data. I will receive a signed and dated copy of my informed consent form.

Subject Name (standard Chinese script): _____ Subject Signature:

_____

contact number ： _____ date ： _____days_____sun

Client Name (standard script):_____Client Signature:_____

contact number ： _____Date: _____ Year _____ Month _____ Day

Witness Name (standard script):_____Witness Signature:_____

contact number ： _____Date: _____ Year _____ Month _____

Day

(Note: If the subject is illiterate, a witness's signature is required; if the subject lacks legal capacity, a representative's signature is required.)

I have accurately informed the subject of this document; the subject has thoroughly read the informed consent form and was assured of the opportunity to raise any questions. I confirm that the subject provided voluntary consent.

Researcher's Name (in standard Chinese): _____ Researcher's Signature: _____

contact number ： _____Date: _____ Year _____ Month _____ Day