Statement on the Registration of the "Study on the Effects of Oral Nutritional Supplementation Combined with Resistance Exercise on Nutritional and Physical Function Status in Hospitalized Frail Older Patients"

To the review experts of ClinicalTrials:

This statement aims to clarify the relationship between the registered study "**Study on the Effects of Oral Nutritional Supplementation Combined with Resistance Exercise on Nutritional and Physical Function Status in Hospitalized Frail Older Patients**" (hereinafter referred to as "this registered study") and the approved parent study "**Promotion of Appropriate Technologies for Early Screening and Standardized Management of Multimodal Interventions in Older Frailty Patients**" (Ethical Approval No.: 2023 Clinical Trial No. (21K), hereinafter referred to as "the parent study").

1. Nature of the Study: This registered study constitutes a **pre-specified subgroup analysis and in-depth investigation** within the framework of the aforementioned parent project. The parent project aims to promote comprehensive management techniques for frailty in the elderly. This registered study focuses specifically on evaluating the efficacy and exploring the mechanisms of a core combination intervention (oral nutritional supplementation combined with resistance exercise) within that broader initiative.

2. Basis of Association: The research protocol of the parent project (attached with this document), in **Chapter 4 "Research Content", section 2.2 "Multidimensional Intervention",** explicitly lists **"nutritional intervention (including oral nutritional supplementation, ONS)"** and **"exercise training (including resistance exercise)"** as standard management measures for frail patients. This registered study constitutes an evaluation and post-hoc analysis of the effects of this specific combination of interventions in a particular population (hospitalized patients).

3. Ethical Coverage: All data sources, patient interventions, and sample collections in this registered study strictly adhere to the established protocol of the parent project and are conducted within the scope authorized by its ethical review approval (No.: 2023 Clinical Trial No. (21K)) and informed consent forms. This study imposed no interventions or risks on subjects beyond those specified in the original protocol.

4. Protocol Supplement: The retrospective analytical approach employed in this registered study—specifically, grouping participants based on changes in SPPB scores to assess treatment efficacy and comparing baseline characteristics between groups—is a pre-specified, in-depth secondary analysis plan utilizing the parent project database. This analytical plan is designed to deepen the understanding of heterogeneity in intervention effects and serves as a reasonable extension and scientific supplement to the overall research protocol of the parent project.

In summary, this registered study is entirely reliant on the approved parent project in terms of ethics, data, and interventions, and constitutes an integral part of its scientific objectives. This is hereby state

I.Research Title: Promotion of Appropriate Technologies for Early Screening and Standardized Management of Multimodal Interventions in Older Frailty Patients

II.Research Objective: Frailty refers to an increase in vulnerability and a decline in the ability to maintain intrinsic homeostasis in older individuals, manifested by reduced physiological reserve and diminished resistance to stressors[1]. It is associated with increased susceptibility to adverse health outcomes, including falls[2], fractures[3], disability[4], loss of independence[5], nursing home admission[6], and death[7]. Frailty has a high global prevalence and poses a significant threat to the health of older adults[8]. However, only half of older adults with frailty receive effective interventions[9]. Studies have shown that the difference in healthcare costs between frail and non-frail individuals amounts to €1,917[10,11]. Importantly, frailty is potentially reversible, particularly in its early stages. Early screening and appropriate management of frailty may reduce disability, decrease nursing home admissions, lower the need for long-term care, and reduce medical and social costs. Pre-frailty can be reversed to a robust state, and even some cases of frailty can be reversed to pre-frailty[12]. In the context of China's strained healthcare resources, routine screening and standardized management of frailty are rarely implemented in hospitals. The dissemination of this appropriate technology will improve professionals' understanding of frailty and enhance both the quality of care and outcomes for frail older adults.

III.Research Background： The clinical management principles for frailty include: (1) screening for frailty using validated assessment tools; (2) prescribing moderate-intensity resistance training exercises; (3) identifying causes of weight loss or fatigue in older adults, which involves adjusting dietary patterns, increasing nutritional supplements, and correcting poor eating habits; and (4) conducting comprehensive geriatric assessments to uncover underlying health problems and integrating multidisciplinary resources to develop diversified intervention strategies. The ICFSR guidelines strongly recommend frailty screening for all older adults. The guidelines provide specifications on frailty screening and assessment, the selection of appropriate screening tools, the qualifications required for screening and assessment, and the development of comprehensive care plans. These recommendations are intended to guide clinical and practical care for frail older adults and promote person-centered care. Although international clinical practice guidelines have

charted a clear direction for the clinical management of frailty in older populations, variations in hospital size and medical capacity across different regions in China have led to inconsistencies in the specific procedures for frailty assessment, intervention approaches, and the overall level of nursing care.

IV.Research Content: The active implementation of frailty assessment and management helps effectively delay the onset and progression of frailty in older adults, improve health outcomes, and enhance quality of life. This provides a foundation for promoting appropriate technologies for early screening and standardized management of frailty in older populations. **Figure 1 presents the management flowchart.**

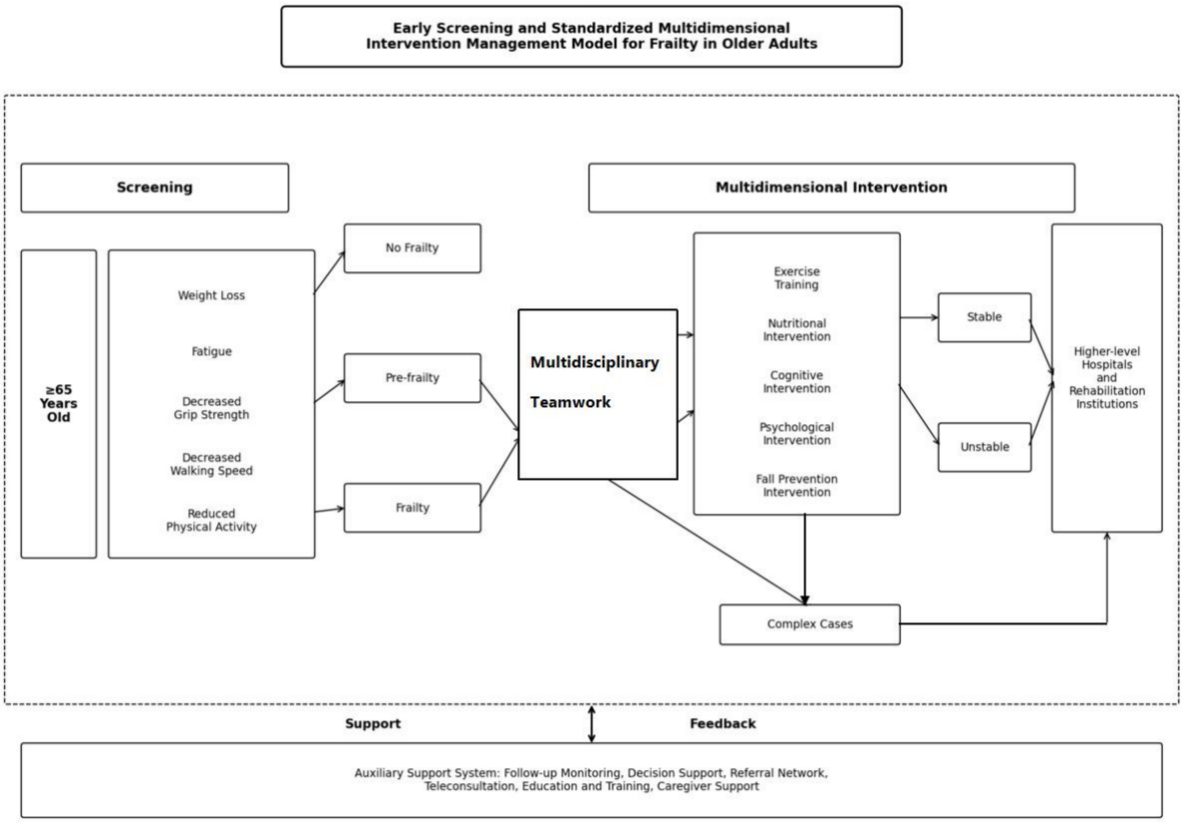

Figure 1 Standardized Management Model for Early Screening and Multidisciplinary Intervention of Frail Older Adults

1. Frailty Screening Using the Fried Frailty Phenotype： All elderly patients aged 65 years and older undergo frailty screening. The Fried frailty criteria consist of five components based on frailty-related symptoms: (1) unintentional weight loss, (2) exhaustion, (3) decreased grip strength,

(4) reduced walking speed, and (5) decreased physical activity. Individuals meeting one or two criteria are classified as pre-frail, those meeting three or more criteria are classified as frail, and those meeting none of the criteria are considered non-frail healthy older adults.

2. Standardized Management of Frailty

2.1 Identifying Reversible Causes in Older Adults Who Screen Positive for Frailty

For older adults who screen positive for frailty, first identify underlying, untreated factors that may contribute to fatigue, weight loss, or reduced nutritional intake; provide early intervention for reversible causes, avoid reduced physical activity and inadequate nutrition, and use pro-catabolic medications with caution to prevent muscle loss.

2.2 Multidimensional Intervention

For patients who screen positive for frailty, identify reversible causes and develop a multidimensional intervention plan based on the individual's preferences, goals, and frailty level. This primarily includes: exercise training; nutritional intervention; cognitive and psychosocial intervention; fall prevention intervention; and management of polypharmacy.

2.2.1 Exercise Training

Based on aerobic exercise combined with resistance exercise, may be supplemented with flexibility training and balance function training.

2.2.2 Nutritional Intervention (Calorie and Protein Supplementation)

Calorie supplementation: In general, basal metabolism declines and physical activity is relatively reduced in older adults aged 65 years and above. Calculated based on light manual labor, the recommended calorie intake is 25-30 kcal/kg/d. When older patients adhere to daily exercise lasting 30 minutes or more, it is advisable to consider appropriate energy supplementation, which may include oral nutritional supplements (ONS) containing high-quality protein, providing an additional 400–600 kcal of energy intake per day.

Protein supplementation: Protein is essential for older adults, and the requirement should not be lower than that for younger adults. The recommended protein intake is 1.0-1.5 g/kg/d, preferably from high-quality protein sources. When food intake is less than 80% of the target amount, oral nutritional supplements (ONS) are recommended. ONS should be taken between meals, providing 400–600 kcal/d, to achieve nutritional supplementation without interfering with regular meals. When oral intake falls below 60% of the target amount, continue ONS, closely monitor the

patient's condition, and consider tube feeding if necessary.

2.2.3 Cognitive and Psychological Intervention

Assist in maintaining and improving instrumental activities of daily living (IADL); encourage participation in work within limits to preserve the ability to live independently. Support the development of hobbies based on personal interests. Encourage participation in social activities and reminiscence.

2.2.4 Fall Prevention Intervention

Education: Raise awareness of fall prevention, provide education on fall prevention knowledge, and instruct on adhering to regular physical exercise.

Assistive device selection: Assist the elderly in choosing appropriate assistive devices, and place canes, walkers, and frequently used items within easy reach.

Footwear guidance: Instruct on wearing loose, well-fitting clothing and shoes, and avoid slippers, high heels, and shoes that are prone to slipping, etc.

2.3 Follow-up

Frail older adults derive the greatest benefit from standardized frailty management interventions. Therefore, frail-positive older adults should receive follow-up every 12 weeks, to monitor and reinforce the implementation of multidimensional intervention measures.

V. Research Methods

1. Selection of Participating Hospitals

This appropriate technology will be disseminated and applied across the province in two tertiary hospitals and three secondary hospitals that meet the selection criteria.

Inclusion criteria for participating institutions: ①The implementing institution must be located within Zhejiang Province; ②The institution must meet the relevant requirements for secondary and tertiary hospitals as stipulated in the Zhejiang Provincial Measures for the Grading and Evaluation of Medical Institutions; ③The institution must consent to the implementation of this technology.

2.Baseline Assessment

Baseline evaluations will be conducted in the five designated secondary and tertiary hospitals to assess: The current status of frailty among hospitalized older patients; Medical staff's level of

knowledge regarding frailty in the elderly; Their awareness of frailty assessment components; The current screening rate for frailty in the elderly.

3. Technical Training and On-Site Guidance

Training plans and on-site guidance programs will be developed, and medical staff from the five hospitals will receive training and instruction in batches. Training content includes: ①Theoretical Training on Frailty in the Elderly; ②Early Screening and Assessment for Frailty; ③Exercise Training for Frail Older Patients; ④Nutritional Supplementation for Frail Older Patients; ⑤Integrated Care Model Based on Multidisciplinary Team Collaboration.

5. Program Implementation Content

(1) Develop training course materials, create frailty assessment forms for the elderly, and design questionnaires to evaluate geriatric medical staff's competency in early frailty assessment and standardized management.

(2) Deliver centralized training sessions to disseminate relevant theoretical knowledge to participating partner hospitals, enabling medical staff to master early frailty assessment and standardized management in the elderly.

(3) The prevalence of frailty was calculated by applying this technique to screen about 600 elderly frail cases. A total of 200 older patients were randomly selected as the intervention group for standardized multidimensional intervention management, while another 200 matched older patients with similar age and gender characteristics served as the control group. The frailty, nutritional and functional status, falls, mortality, and other adverse outcomes were monitored over a one-year follow-up period. Collect clinical data, perform statistical analysis, evaluate efficacy, and write papers.

(4) Conduct on-site effectiveness assessments at the partner hospitals during the mid-to-late stages of the dissemination program, using methods such as theoretical examinations or case analyses to evaluate implementation outcomes; administer questionnaires to medical staff and patients, and adjust subsequent implementation priorities based on collated feedback.

(5) Sustain the dissemination efforts to establish a standardized, multidimensional management model for frailty in the elderly.

VI.Name and Address of the Sponsor, Trial Sites, and Name, Qualifications, and Address of

the Investigator

Sponsor: Zhejiang Hospital (Sandun Campus)

Address: No. 2996 Guangye Street, Xihu District, Hangzhou City

Investigator Name: Chen Lingyan

Investigator Qualifications: (Deputy Chief Nurse)

VII.Inclusion Criteria, Exclusion Criteria, Subject Selection Procedures, and Subject Allocation Methods

Inclusion Criteria: ①Aged 65 years or older, regardless of sex; ②Possess basic reading comprehension skills; ③ Ability to walk independently or with assistive devices; ④Voluntarily sign the informed consent form; ⑤Relatively stable medical condition.

Exclusion Criteria: ①Patients with unstable conditions such as recent acute infection or acute organic brain disease; ②terminal illnesses; ③severe cognitive impairment (determined by the ward's doctor and physiotherapists)

VIII.Research Risks and Risk Management Plan

The operational procedures of this project are not complicated, and the process of frailty assessment and standardized management poses no adverse impact on either researchers or participants. As long as the medical staff conduct assessments using the designated screening tools and implement the standardized management protocol accordingly, safety outcomes are assured. In the event of any injury occurring in connection with this clinical trial, the research team will provide compensation and indemnification in accordance with the relevant laws and regulations of China.

IX. Statistical Analysis Methods

All data will be entered using EpiData 3.1 and analyzed with SPSS 25.0. Missing data will be denoted by "-". Measurement data conforming to a normal distribution will be described as mean ± standard deviation, while those with a skewed distribution will be expressed as median (25th percentile, 75th percentile). Count data will be presented as constituent ratios or rates. Statistical analyses will include one-way ANOVA, chi-square test, rank-sum test, correlation analysis, and

regression analysis, as appropriate. A P-value < 0.05 will be considered statistically significant.

X. Provisions for Data Management and Data Traceability

Data management for this study shall be the responsibility of the research team to ensure the authenticity, integrity, confidentiality, and traceability of clinical trial data. Information shall be entered into the Case Report Form (CRF) by the Principal Investigator or other authorized researchers; only researchers with medical qualifications may enter original clinical assessment and safety data. After original data entry, any modifications made to the CRF by the Principal Investigator or other authorized researchers shall be documented. For any approved data modifications, the researcher or authorized personnel making the change shall sign their name, the date of modification, and the reason for the modification (if the change is not substantial).

XI. Quality Control of the Trial

The investigators will implement standard operating procedures to ensure the implementation of quality control and quality assurance systems for the clinical trial. All observations and findings during the clinical trial will be verified to ensure data reliability and to confirm that all conclusions drawn from the trial are derived from source data. Quality control will be applied at every stage of data processing to ensure that all data are reliable and have been correctly processed.

XII. Ethical Requirements

Before the initiation of the clinical trial, the study protocol must be reviewed and approved by the Ethics Committee. The trial may only commence upon issuance of a written approval.

During the trial, the study shall adhere to the WMA Declaration of Helsinki (2013), the CIOMS International Ethical Guidelines for Health-related Research Involving Humans (2016), and the National Health and Family Planning Commission's Measures for the Ethical Review of Biomedical Research Involving Humans (2016).

Any modifications to the clinical study protocol, informed consent form, recruitment materials, or other relevant documents during the trial period must be reviewed and approved by the Ethics Committee prior to implementation.

Prior to enrollment, the researcher must provide each potential subject with a detailed explanation

of the study purpose, procedures, duration, examinations and interventions involved, anticipated benefits and risks, potential time and financial costs, and the possibility of assignment to different groups. The researcher must also inform the subject that participation is entirely voluntary and that they have the right to withdraw from the trial at any stage without discrimination or reprisal, and that their medical care and rights will not be affected.

After full and detailed explanation of the trial, the subject or their legal representative (for subjects lacking capacity) shall sign and date the informed consent form. The researcher conducting the informed consent process must also sign and date the form. The informed consent form shall be completed in duplicate, with one copy retained by the subject and the other by the researcher.

The researcher shall ensure that no personally identifiable information of subjects appears in any study reports, publications, or public materials. Strict measures shall be taken to protect subject privacy in accordance with Chinese laws and regulations.

XIII. Expected Progress and Completion Date of the Clinical Study

Phase	Timeline	Key Activities
Preparation	Nov 2022 –Feb 2023	Protocol finalization, ethics approval, contracts signed, baseline survey, recruitment
Intervention & Follow-up	Mar 2023 – Feb 2025	Training, on-site guidance, multidimensional intervention implementation, 3-month follow-ups, mid-term evaluation
Data Analysis	Mar –May 2025	Data cleaning, statistical analysis, efficacy evaluation
Summary & Acceptance	Jun–Dec 2025	Paper writing, dissemination report, SOP booklet, project acceptance

XIV. Responsibilities of All Parties and Other Relevant Provisions

In the event of any injury occurring in connection with this clinical trial, the research team will provide compensation and indemnification in accordance with the relevant laws and regulations of China.

XV. References

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[2] Cheng M H, Chang S F. Frailty as a Risk Factor for Falls Among Community Dwelling People: Evidence From a Meta-Analysis[J]. J Nurs Scholarsh, 2017, 49(5): 529-536. PMID: 28755453

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[8] Clegg A, Young J, Iliffe S, et al. Frailty in elderly people (vol 381, pg 752, 2013)[J]. Lancet, 2013, 382(9901): 1328. PMID: 23395245

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[12] Yu P L, Wang J Y. Strengthening the research on prevention and treatment of frailty syndrome in the elderly[J]. Chinese Journal of Geriatrics, 2015, 34(12): 1281.

Informed Consent Form • Information Sheet

Dear Sir/Madam:

You are invited to participate in a clinical trial entitled "**Promotion of Appropriate Technologies for Early Screening and Standardized Management of Multimodal Interventions in Older Frailty Patients**". Before you decide whether to participate, please read the following information carefully. It will help you understand the purpose, procedures, potential benefits, risks, and discomforts associated with this study. This study has been reviewed and approved by the Ethics Committee of Zhejiang Hospital and complies with relevant Chinese laws and regulations as well as ethical principles for the protection of human subjects, such as the Declaration of Helsinki.

Study Introduction

1. Research Background

Frail older adults are more susceptible to falls, disability, delirium, cognitive impairment, and hospital readmission than their non-frail counterparts, posing greater challenges and demands on healthcare services. Moreover, the mortality rate in frail older adults is significantly higher than in non-frail individuals, with an average increase in mortality risk of 15%–50%.

Prefrailty can be reversed to a robust state, and some frailty states can also be reversed to prefrailty. This helps prevent frailty-related loss of independence and other adverse outcomes, maximizes the preservation and restoration of functional capacity in older adults, improves quality of life, reduces the burden on individuals, families, and society, and minimizes the waste of healthcare resources.

2. Research Objectives

Active assessment and management of frailty can effectively delay its onset and progression, improve health outcomes, and enhance the quality of life in the elderly. Standardized clinical management of frailty includes: (1) screening for frailty using validated assessment tools; (2) prescribing moderate-intensity resistance training exercises; (3) necessary nutritional interventions, including adjusting dietary structure, providing nutritional supplements, and correcting poor eating habits; (4) identifying potential health problems in older adults through comprehensive assessment, and integrating multidisciplinary resources to develop Multidisciplinary interventions.

3. What will I need to do if I participate?

If you meet the inclusion criteria and agree to participate, you will be asked to cooperate with physicians/nurses in completing the following: ①Complete a frailty screening questionnaire and permit access to your research-related medical data via the hospital information system.

②If you are identified as frail, healthcare professionals will conduct an in-depth comprehensive geriatric assessment and provide a comprehensive intervention plan based on the results. You will be required to undergo follow-up visits 3 days before the official start of the study and at 24 weeks thereafter, and cooperate with the researchers in completing the relevant examinations.

4. What are the inclusion and exclusion criteria?

Inclusion Criteria: ①Aged 65 years or older, regardless of sex; ②Possess basic reading comprehension skills; ③ Ability to walk independently or with assistive devices; ④Voluntarily sign the informed consent form; ⑤Relatively stable medical condition.

Exclusion Criteria: ①Patients with unstable conditions such as recent acute infection or acute organic brain disease; ②terminal illnesses; ③severe cognitive impairment (determined by the ward's doctor and physiotherapists)

5. What are the potential benefits of participating in this study?

①Your condition may or may not improve as a result of participating in this clinical study.

②You will receive no direct benefit from participating in this clinical study.

6. What are the risks of participating in this study?

①The primary risk associated with participation in this clinical study is the potential breach of privacy. We will implement a series of measures to protect your privacy; for example, only your initials will appear on the case report form, and no personally identifiable information will be disclosed.

②Other potential risks include falls and exercise-related injuries. We will take various measures to ensure your safety, such as using safety harnesses during gait assessments. Exercise prescriptions will be evaluated and supervised by qualified specialists.

7. Will participation in this study increase my medical expenses?

Participation in this study involves multidisciplinary treatment that is part of routine clinical diagnosis and treatment. The questionnaire surveys conducted as part of this research are provided free of charge. Therefore, this study will not impose any additional financial burden on you.

8. Will I receive any compensation for participating in this study?

Due to limited research funding, you will not receive any financial compensation for participating in this study.

9. Compensation for Injury

If you experience any injury related to this clinical trial, the research team will provide compensation and indemnification in accordance with relevant national laws and regulations.

10. Is my personal information kept confidential?

All information related to your participation in this study will be recorded in the study medical records/case report forms. All trial results appearing in original medical records (including personal data, laboratory reports, etc.) will be kept strictly confidential to the extent permitted by law. Your name will not appear on the CRF; only your initials and the subject number assigned to you upon enrollment will be used. In relevant study summaries, publications, or public materials, only your initials and subject number will appear, if necessary.

If required, the drug regulatory authorities, the Ethics Committee, or the project funding agency may access the participants' research data in accordance with regulations. However, without authorization, they will not use the data for other purposes or disclose it to other entities.

11. How can I obtain more information?

You may ask any questions regarding this clinical trial at any time by contacting the physician (name_____) at the following number (Mobile phone number_____).

If important new information becomes available during the trial that may affect your willingness to continue participation, your physician will notify you promptly.

12. Must I participate in this study, and can I withdraw midway?

Whether or not to participate in this study is entirely voluntary. You may refuse to participate. You have the right to withdraw from this study at any time during the research process. If you refuse to participate or withdraw midway, your benefits will not be affected, and you will not be discriminated against or retaliated against. If you choose to participate, we hope that you will complete the entire trial process.

Your physician or the researcher may terminate your participation in this trial at any time, in your best interest.

13. What should I do now?

Whether to participate in this clinical trial is your own decision. You may discuss it with your family or friends before making a decision.

Before deciding to participate, please ask your physician as many questions as necessary until you fully understand this clinical trial.

14. Ethics Committee

If you have any concerns or complaints regarding the study, please contact the Ethics Committee of Zhejiang Hospital.

Ethics Committee Office: 3rd Floor, Building 8, Zhejiang Hospital (Sandun Campus)

Contact Number: 0571-81595231

Contact Person: Xie Xiaoping

Thank you for reading the above information. If you decide to participate in this clinical trial, please inform your physician, who will arrange all study-related matters for you.

Please keep this document for your records.

Informed Consent Form • Signature Page

Statement of Consent

1. I have read this informed consent form. The responsible project personnel have provided me with a detailed explanation of the purpose, content, risks, and benefits of this trial.
2. I have discussed and asked questions regarding this study, and I am satisfied with the answers provided.
3. I have had sufficient time to make my decision.
4. I voluntarily agree to participate in the clinical study described herein.
5. If I withdraw midway due to reasons related to this study, I will inform my physician promptly of any changes in my condition.
6. If my condition requires any other treatment, I will consult my physician in advance or truthfully inform my physician afterwards.
7. I agree to allow the drug regulatory authorities, the Ethics Committee, or the project funding agency representatives to access my research data.
8. I will receive a copy of this informed consent form signed and dated.

Finally, I hereby decide to voluntarily participate in this clinical trial and agree to comply with the medical instructions.

Subject Signature: _____ Date: _____ Year ____ Month ____ Day
Subject Contact Number: _____

Legal Guardian Signature: _____ Date: _____ Year ____ Month ____ Day
Relationship with Subject:_____
Legal Guardian Contact Number:_____

I confirm that I have thoroughly explained the details of this study to the subject, including their rights and the potential benefits and risks, and have provided them with a signed copy of the informed consent form.

Physician Signature: _____ Date:_____ Year ____ Month ____ Day
Study Physician Contact Information: _____

(This page is an essential part of the subject informed consent form. Each copy of the "Subject Informed Consent Form" is valid only if signed and dated by the subject or legal guardian and the study physician.)