The Effects of Different Enteral Feeding Regimens on Necrotizing Enterocolitis, Mortality, and Neurodevelopment in Very Preterm Infants: A Multicenter Double-Randomized Trial

Research Proposal

Nov.26, 2025

I. Research Background

Necrotizing enterocolitis (NEC) is one of the most severe and life-threatening gastrointestinal diseases affecting preterm infants, characterized by high mortality, a high rate of surgical intervention, and the risk of long-term neurodevelopmental impairment [1]. In China, it is estimated that 50,000 to 60,000 preterm infants with a gestational age of less than 29 weeks are born each year, among whom several thousand may develop NEC. A significant proportion of these cases require surgical intervention or result in death [2-4]. Additionally, many more preterm infants experience milder forms of NEC, which, although not fatal, can disrupt enteral feeding, prolong hospitalization, increase antibiotic exposure, and lead to substantial healthcare costs.

Feeding practices are considered a key modifiable risk factor for NEC. While own mother's milk (OMM) is the standard feeding recommendation and offers some protective effect, it does not eliminate the risk of NEC: approximately half of the infants who develop severe NEC had been fed exclusively with human milk prior to onset [5]. Due to the immature sucking ability of preterm infants and challenges in sustained maternal lactation, more than 85% of extremely preterm infants require supplementary feeding.

Although pasteurized donor human milk (pDHM) is widely used as a supplement, its clinical efficacy and safety compared to preterm formula (PTF) remain uncertain. Meta-analyses suggest that when used as a sole or supplemental feeding source, pDHM may help reduce the incidence of NEC [6]. However, these studies are often limited by small sample sizes and low methodological quality, and many include only NEC cases treated with antibiotics, which are prone to diagnostic bias. More importantly, no current studies have demonstrated that pDHM reduces mortality or the incidence of invasive infections. Furthermore, several studies have shown that infants fed with pDHM have slower head circumference growth and weight gain [7]. Also, there is recent evidence that pDHM use may result in adverse developmental outcomes[8-10].

To compensate for the nutritional inadequacies of donor milk—particularly its relatively low and variable protein and energy content—many neonatal intensive care units (NICUs) routinely add multi-component bovine-derived human milk fortifiers. However, the use of fortifiers remains controversial: some clinicians are concerned that the bovine proteins they contain may increase the risk of NEC, while others worry that not adding fortifiers will fail to meet the nutritional requirements of preterm infants [11-13]. Additionally, there is concern that routine macronutrient fortification will expose some babies to excessively high protein intakes that are damaging to neurodevelopment [14].

The current evidence base is still limited. Systematic reviews indicate that routine fortifier use does not clearly reduce NEC incidence or improve long-term neurodevelopmental outcomes, though it may offer some short-term benefits in growth.

This study aims to fill these critical evidence gaps through a real-world, stratified, nested, double-randomized trial. The trial will compare: (1) the effects of pDHM and PTF as supplemental feeding options when maternal milk is insufficient; and (2) the outcomes of routine versus non-routine use of nutritional fortifiers. Conducted across multiple neonatal units in China, the study will include preterm infants born at less than 29 weeks' gestational age. By evaluating the impact of these commonly used feeding strategies on NEC, mortality, growth, and neurodevelopmental outcomes, the study seeks to provide robust evidence to inform clinical practice, reduce variations in feeding approaches, and improve health outcomes for preterm infants.

II. Study Objectives

Primary Objectives:

To evaluate the survival without surgery-requiring necrotizing enterocolitis (NEC) at 34 weeks corrected gestational age in preterm infants born at less than 29 weeks of gestation when donor pasteurized human milk (pHDM), or preterm formula (PTF) is used to supplement own mother's milk (OMM) when it is insufficient.

To assess whether routine use of human milk fortifiers (HMF), added to human milk (including both OMM and pHDM), is beneficial for this population of preterm infants.

Secondary Objectives:

To evaluate the effects of supplementing OMM with pHDM, or PTF on language and cognitive development as well as other outcomes at 2 years of age in preterm infants born at less than 29 weeks of gestation.

III. Study Methods

This study is a high-efficiency, nationwide, real-world data-based, multicenter, dual randomization, open-label randomized controlled trial (RCT), embedded within routine clinical care.

The study includes two randomizations: Babies may participate in either or both randomizations.

First randomization (occur when the attending clinician decides a supplemental feed is required because the volume of Own Mother's Milk is insufficient): We will compare the benefits of supplementing with **pHDM versus preterm formula (1:1)** in cases of insufficient breast milk supply. When randomly assigned to the preterm infant formula group, if it was confirmed that milk protein allergy could be treated with hydrolyzed formula [15].

Second randomization (when receiving 60-120 ml/kg of human milk): We will evaluate the differences and benefits between **routine fortification and selective fortification**, which is only considered when the infant meets predefined criteria for growth faltering (Preterm infants exhibit a sustained decline in growth velocity for weight, length, or head circumference, demonstrated by a downward crossing of centiles on growth curves, despite tolerating and consuming at least 180 mL/kg/day of breast milk or formula. Blood urea levels in these infants remain consistently below 1.5 mmol/L, and there are no severe complications such as active sepsis or the need for vasoactive medications to maintain circulatory stability. Chronic sodium depletion has also been ruled out, as this condition alone can lead to growth failure. Additionally, preterm infants are unable to tolerate high-volume feeding of 180 mL/kg/day due to specific reasons, such as severe gastroesophageal reflux or the presence of a high-output stoma following surgical procedures.) (1:1).

Randomization will be carried out electronically using an on-line system managed by the Data Services Team.

Sample Size

Based on institutional data from 2024, the proportion of preterm infants born at <29 weeks gestation who survived to 34 weeks corrected gestational age without requiring surgical intervention for necrotizing enterocolitis (NEC) was 66.3%. To detect an absolute improvement to 73% in this primary outcome with the use of pasteurized donor human milk (pHDM) compared to preterm formula (PTF), the group sample sizes of 736 in group 1 and 736 in group 2 achieve 80.038% power to detect a difference between the group proportions of -0.0670. The proportion in group 1 (the treatment group) is assumed to be 0.7300 under the null hypothesis and 0.6630 under the alternative hypothesis. The proportion in group 2 (the control group) is 0.7300. The test statistic used is the two-sided Z-Test with unpooled variance. The significance level of the test is 0.0500. Under these assumptions, a total of 1,472 infants (736 per group) is required. For the second randomization we target the same minimally clinically important difference of 0.067. we assume 50% co-enrolled into both randomizations. We need a total of 2208. Further accounting for potential loss to follow-up and missing data (5%), we propose increasing the total sample size to approximately 2324 infants.

IV. Study Population

This study intends to include infants with a gestational age as follows:

1. Inclusion Criteria (All of the following must be met):

- Gestational age at birth less than 29 weeks;
- No contraindications to enteral feeding;
- Mother is willing to breastfeed.

2. Exclusion Criteria (Any of the following will result in exclusion):

- For Randomization Group 1: If the infant has already received pasteurized human donor milk (pHDM), preterm formula (PTF), or nutritional fortifiers;
- For Randomization Group 2: If the infant is exclusively fed with preterm formula and the mother has no intention to express breast milk;

3. Withdrawal Criteria

Subjects may voluntarily withdraw from the study at any time for any reason. In addition, the subject will be withdrawn from the study if any of the following occur:

(1) The subject experiences a serious adverse event (SAE) during the study, and the investigator determines that continued participation poses an unacceptable risk;

(2) The subject's condition deteriorates and requires emergency treatment that is inconsistent with the study protocol;

(3) The subject is found to not meet the inclusion criteria or to meet the exclusion criteria after enrollment;

(4) The monitor or ethics committee recommends termination of the subject's participation;

(5) The legal guardian withdraws informed consent or explicitly states unwillingness to continue participation.

4. Termination Criteria

Study termination refers to the complete discontinuation of the clinical trial before its planned completion:

(1) A major safety issue arises during the study, requiring immediate termination;

(2) A critical flaw in the study protocol is discovered, or significant deviations occur, making it difficult to evaluate the intervention's effects;

(3) The sponsor requests to terminate the study.

V. Study Procedures

1. Identification and Recruitment of Participants

After preterm infants are admitted to the neonatal unit, a member of the clinical care team (a neonatologist or nurse with appropriate training and experience) will assess their eligibility. Preterm infants with a gestational age of less than 29 weeks who meet the inclusion criteria will be considered for enrollment.

Informed consent must be obtained from all participants for the following:

- Randomization Group 1

- Randomization Group 2

- Inclusion of the PARCA-R assessment results at 2 years of age in the preterm infant database

2. Randomization and Timing

Participants may be enrolled in either one or both of the randomizations.

Randomization 1 (First week, pHDM vs. PTF, 1:1) will occur when the clinician determines that supplemental feeding is required due to insufficient breast milk supply.

Randomization 2 (Second week) will be conducted when the total daily intake of human milk (including own mother's milk [OMM] and/or pHDM) reaches between 60–120 mL/kg.

- Randomization will be to either routine fortification or no routine fortification in a 1:1 ratio.

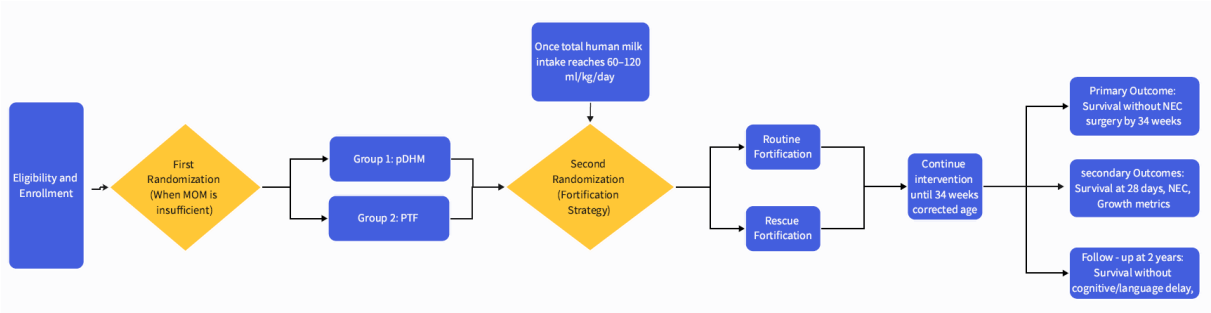
- The term "no routine fortification" is used because "rescue fortification" remains allowed if deemed necessary.

3. Follow-up

No additional study-specific follow-up visits are scheduled.

Cognitive and language development outcomes at 2 years of age will be collected using the digital version of the PARCA-R assessment tool, which is conducted as part of routine clinical care.

Study Flow Diagram



VI. Outcome Measures

Primary Outcome:

- Survival to 34 weeks corrected gestational age without surgical necrotizing enterocolitis (NEC)

Secondary Outcomes:

Assessed at 34 weeks gestational age:

- NEC requiring surgical intervention

Assessed at 28 days after birth:

- Survival

Assessed at discharge from the neonatal unit:

- Survival
- Medically treated NEC
- Treated retinopathy of prematurity (ROP)
- Hearing impairment
- Severe brain injury
- Length of hospital stay
- Number of episodes of bloodstream infection
- Number of days of antibiotic treatment
- Number of days on parenteral nutrition
- Number of days of NPO
- Growth parameters (weight, length, head circumference)
- Breastfeeding status (exclusive breastfeeding and any breastfeeding)

Assessed at 2 years corrected age:

- Survival without moderate to severe cognitive or language impairment
- Growth parameters (weight, length and head circumference)

VII. Risk Prevention and Management

This study involves preterm infants with a gestational age of less than 29 weeks—a high-risk population. Feeding methods and nutritional interventions during the study may impact their health. To ensure the highest level of participant safety, the research team has established a

comprehensive risk prevention and management protocol.

Firstly, strict inclusion and exclusion criteria are set to ensure that only infants with a stable baseline condition are enrolled. All feeding strategies are based on current standard clinical practices and will be implemented through standardized procedures to ensure the safety and controllability of the interventions.

An adverse event monitoring system will be established, and an independent Data and Safety Monitoring Board (DSMB) will be set up to independently assess serious adverse events (SAEs) and regularly review safety data. If serious adverse events occur during the study (such as progression of NEC, infections, or death), they will be promptly reported to the ethics committee and relevant regulatory authorities. The need to discontinue individual participation or the entire study will be evaluated accordingly.

The study has clearly defined withdrawal and termination mechanisms, which include, but are not limited to: clinical deterioration, use of prohibited interventions, or withdrawal of consent by guardians. These provisions ensure that infants receive optimal clinical care under all circumstances.

Regarding data protection, all participant information will be coded, and data collection, transmission, and storage will be encrypted. Access will be strictly controlled to prevent breaches of personal privacy. The informed consent process will be strengthened. Trained research staff will communicate thoroughly with the infant’s guardians, using clear and understandable language to explain the study’s purpose, procedures, potential risks, and benefits. Sufficient time will be given to allow for an informed decision. During the study, guardians may ask questions at any time or choose to withdraw their child from the study. In such cases, the infant will continue to receive standard medical care, and their rights and interests will not be affected.

VIII. Adverse Event Recording and Reporting

During the study, investigators will closely monitor preterm infants for potential adverse events (AEs) that may occur during feeding, with particular attention to complications potentially related to feeding methods, such as abdominal distension, necrotizing enterocolitis (NEC), feeding intolerance, infections, and metabolic disturbances.

In the event of an adverse event (including significant adverse events), investigators must promptly analyze the cause, assess the severity and its potential relationship to the study intervention, and thoroughly document the event. Documentation should include the time of occurrence, clinical manifestations, severity, duration, interventions taken, and final outcome. All relevant medical information and laboratory test results must be accurately recorded in both the original medical records and the study case report forms.

If a Serious Adverse Event (SAE) occurs—such as NEC requiring surgical intervention, severe infection, or death—the investigator must immediately initiate appropriate clinical management, prioritizing the infant's safety. Additionally, a "Serious Adverse Event Report Form" must be completed within 24 hours of the event and submitted to the principal investigator and the ethics committee. All SAEs will be continuously followed up until the infant's condition stabilizes, recovers, or results in death. Each SAE will be independently reviewed by the Data and Safety Monitoring Board (DSMB), which may recommend suspension or termination of the study if necessary.

IX. Data Management

Completion of Case Report Forms (CRFs): The CRFs will be completed by clinical investigators.

Data Entry and Modification: Data entry and management will be handled by Xu Yanping. The REDCap database will be used for data entry and management. To ensure data accuracy, dual data entry and cross-verification will be performed independently by two data managers.

Database Locking: Once the database has been confirmed to be accurate, it will be locked by the principal investigator and the statistical analysis team.

X. Statistical Analysis Methods

This study is a multicenter, double-randomized, open-label real-world randomized controlled trial. It primarily evaluates the effects of using pDHM, or PTF for supplemental feeding in the case of insufficient maternal breast milk, as well as the routine addition of nutritional fortifiers, on survival without surgical NEC by corrected gestational age of 34 weeks and other outcomes in extremely preterm infants (gestational age <29 weeks).

1. Data Handling and Overall Analytical Strategy

All statistical analyses will be conducted based on the Intention-to-Treat (ITT) principle, with Per-Protocol (PP) analysis conducted as a sensitivity analysis. Primary and key secondary outcomes will be analyzed using stratified analysis for the dual-randomization design, taking into account the independent and interaction effects of the two interventions. Center effects will be included in the model as fixed or random effects.

2. Descriptive Statistics

- Continuous variables: Will be presented as mean ± standard deviation (SD) or median (interquartile range), and compared using t-tests or Wilcoxon rank-sum tests depending on distribution.
- Categorical variables: Will be presented as frequencies and percentages, and compared between groups using the χ^2 test or Fisher's exact test.

3. Primary Outcome Analysis

The primary outcome is the proportion of infants who survive to 34 weeks corrected gestational age without requiring surgery for NEC, a binary variable. Between-group comparisons will be conducted using a log-binomial regression model or Poisson regression model with robust standard errors to estimate relative risk (RR) and 95% confidence intervals, adjusting for confounders such as center, birth weight, and gestational age. If substantial center effects are observed, a Generalized Linear Mixed Model (GLMM) will be used for analysis.

4. Secondary Outcome Analysis

- Binary outcomes (e.g., NEC incidence, mortality, infections, ROP): Will be analyzed using χ^2 tests or logistic regression.
- Continuous outcomes (e.g., weight, head circumference, length of hospital stay): Will be analyzed using ANOVA or linear regression models, with log transformation applied if necessary.
- Time-to-event outcomes (e.g., time to first NEC, time to discharge): Will be analyzed using Kaplan-Meier survival analysis and log-rank tests, with further adjustment using Cox proportional hazards models.

5. Missing Data Handling

For the primary outcome, missing data will be handled using Multiple Imputation, and sensitivity

analyses will be performed to assess the impact on results. Reasons for withdrawal or loss to follow-up will be recorded, and follow-up will be pursued as far as possible.

6. Significance Level and Software

All statistical tests will be two-sided with a significance level of α=0.05. Analyses will be conducted using R or SPSS statistical software.

XI Publication Forms of Research Achievements

Upon completion of the study, the research team will prepare manuscripts based on the collected data and submit them for publication in high-impact national and international journals. The publications will cover the primary outcomes, subgroup analyses, monitoring of adverse events, and long-term follow-up results. In addition, the research findings will be presented and shared at national and international academic conferences in the fields of pediatrics and neonatology, in order to enhance the academic impact of the study.

If the study receives funding support, a final report will be submitted as required by the funding agency. Moreover, the results will serve as an important reference for enteral feeding strategies in preterm infants and are expected to contribute to the development of relevant clinical guidelines or expert consensus.

Where ethically permissible, the research data will be made available for international sharing and may be used for further analyses in future studies.

XII Ethical Considerations

1. Risks and Benefits

This study is a comparative investigation of feeding strategies based on routine clinical practice. The interventions involved—such as donor human milk, preterm infant formula, and nutritional fortifiers—are all standard nutritional support methods widely used in current neonatal care, and are generally considered low risk. Potential risks during the study include common complications associated with preterm infant feeding, such as feeding intolerance, infection, and progression of NEC. However, these risks are manageable within the existing medical system and monitoring mechanisms, and clear contingency plans are in place.

The research team will closely monitor the health status of all participants and promptly address any adverse events to ensure maximum safety for the infants. While individual participants may not directly benefit from this study, the systematic evaluation of different feeding strategies on both short- and long-term outcomes in extremely preterm infants will provide critical evidence for optimizing nutritional support. This has the potential to offer safer and more effective feeding approaches for future preterm infants, ultimately improving overall health outcomes. Therefore, participation in this study is of great significance for the advancement of neonatal medicine.

2. Protection of Participant Privacy

Only researchers directly involved in this study will have access to participants' personal medical records. All such personnel are bound by confidentiality agreements or investigator declarations that include confidentiality clauses. Ethics committees and regulatory authorities are permitted to review clinical trial records. During data processing, anonymization techniques will be used to remove personally identifiable information. The publication of research findings will not disclose any personal information of the participants. All medical records will be securely stored in the archives of the Children's Hospital, Zhejiang University School of Medicine, which follows strict data security and confidentiality protocols.

3. Informed Consent and Signing of Consent Forms

Prior to the initiation of the clinical study, investigators must provide the legal guardians of participants with detailed information about the study, including its nature, objectives, potential benefits and risks, to ensure full understanding. The study can only begin after the legal guardian has signed the informed consent form.

Each participant's contact information, including address and phone number, will be recorded in detail. Likewise, the physician will provide their own contact information to ensure that the participant's family can reach the research team at any time.

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The Effects of Different Enteral Feeding Regimens on Necrotizing Enterocolitis, Mortality, and Neurodevelopment in Very Preterm Infants: A Multicenter Double-Randomized Trial

Informed Consent Form

Nov. 26, 2025

Dear Parent or Legal Guardian,

Your child is invited to participate in a research study entitled:” The Effects of Different Enteral Feeding Regimens on Necrotizing Enterocolitis, Mortality, and Neurodevelopment in Very Preterm Infants: A Multicenter Double-Randomized Trial."

Participation in this study is entirely voluntary. This informed consent document provides important information about the study. Please read it carefully before deciding whether your child will participate. If you have any questions or do not understand any part of this document, please ask the study doctor. The research team will answer all of your questions.

This study is being conducted at the Neonatal Intensive Care Unit (NICU) of the Children’s Hospital, Zhejiang University School of Medicine, by Dr. Zheng Chen and his team. The study has been reviewed and approved by the Medical Ethics Committee of the Children’s Hospital, Zhejiang University School of Medicine.

1. Why is this study being conducted?

Extremely preterm infants have immature gastrointestinal function and are prone to various complications during feeding. One of the most serious and potentially life-threatening conditions is necrotizing enterocolitis (NEC). Currently, mother’s milk is considered the most suitable source of nutrition for preterm infants. However, when mother’s milk is insufficient, it remains unclear whether donated human milk or preterm formula should be used as a supplement, and whether nutritional fortifiers should be added.

This study aims to evaluate how different enteral feeding strategies affect health outcomes in

extremely preterm infants, including the incidence of NEC, mortality, growth, and neurodevelopmental outcomes at 2 years of age. Through this research, we hope to identify safer and more effective feeding strategies for preterm infants to improve their survival and developmental outcomes.

2. What needs to be done before participating in the study?

If you and your child decide to participate, you will first be asked to sign this informed consent form before any study-related activities begin. If a new version of the consent form is developed during the study, you will be asked to sign it again.

3. How will the study be conducted?

This is a multicenter study involving several hospitals, aiming to recruit a total of 2,324 participants. Each center will enroll patients competitively. Our hospital aims to recruit at least 200–300 participants.

After signing this consent form, your child will undergo screening. The screening visit involves the following: Gestational age less than 29 weeks; No contraindications to enteral feeding; The mother is willing to express breast milk.

In addition, to avoid interference, infants who have already received donor milk, preterm formula, or human milk fortifier, or who have been exclusively fed with preterm formula and whose mothers are not willing to express breast milk, will be excluded from the study.

After screening, the study doctor will determine if your child is eligible to continue in the study. If your child is not eligible, the doctor will explain the reasons and discuss alternative treatment options with you.

The total duration of your child’s participation in the study will be approximately 24 months.

Your child’s participation will include the following:

1) Participant Identification and Recruitment

After admission to the neonatal unit, a trained and experienced member of the clinical care team (either a neonatologist or a nurse) will assess your child's eligibility.

All participants must provide informed consent for the following:

Randomization 1

Randomization 2

Inclusion of the 2-year cognitive and language development assessment (PARCA-R) results in the preterm infant database

2) Randomization and Timeline

Your child may take part in one or both randomizations:

When the attending doctor determines that supplemental feeding is necessary due to insufficient mother's milk, Randomization 1 will be conducted: Donor human milk vs. Preterm formula (1:1 ratio).

When the total daily intake of human milk (including mother's milk and/or donor milk) reaches between 60–120 ml/kg, Randomization 2 will be conducted: Routine fortification vs. No routine fortification (1:1 ratio).

The term "no routine fortification" means that rescue fortification is still allowed when clinically necessary.

3) Follow-Up

No additional study visits are scheduled beyond routine care. At 2 years of age, your child's cognitive and language development will be assessed using the digital PARCA-R questionnaire, which is conducted as part of routine clinical care.

4. Are there any discomforts or risks in participating in this study? Are there protective measures in place?

This study involves extremely preterm infants with a gestational age of less than 29 weeks, who are considered a high-risk population. However, the feeding strategies used in this study are all standard clinical practices and are not expected to negatively impact your child's health.

To ensure the utmost safety of participants, the research team has implemented thorough risk prevention measures. First, strict inclusion and exclusion criteria have been established to ensure that only infants in stable condition are enrolled. All feeding protocols are based on current clinical practices and will be carried out following standardized procedures to guarantee the safety and controllability of interventions.

In terms of information protection, all participant data will be coded and managed using encrypted data collection, transmission, and storage systems, with strict access control to prevent personal information leaks. The informed consent process will be strengthened by having trained research personnel communicate fully with the child's guardians. They will explain the study's purpose, procedures, potential risks and benefits in clear and understandable language, and allow sufficient time for decision-making.

During the study, guardians may ask questions at any time or choose to withdraw from the study. If you choose to withdraw, your child will continue to receive standard medical care, and their rights and interests will not be affected. This study only collects clinical data and information and does not involve any changes to routine diagnostic or treatment procedures, and therefore poses no additional medical risk to participants.

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

Your child may not receive direct medical benefits from participating in this study, as all feeding methods used are already part of standard clinical care. The purpose of the study is to compare their effectiveness and safety.

However, the information gathered will help doctors and researchers better understand the impact of different feeding methods on preterm infants, particularly in preventing NEC, reducing mortality, and supporting neurodevelopment. The results of this study may provide a more scientific basis for feeding strategies in future cases of preterm infants, potentially benefiting many babies in the future.

Thus, while your child may not benefit directly, their participation is of great significance to the advancement of neonatal medicine.

6. Are there other treatment options besides participating in this study?

Yes. If you choose not to participate, your child will still receive standard neonatal care and feeding management at the hospital. This includes the use of mother's milk, donor milk, preterm formula, and nutritional fortifiers, depending on the child's individual needs.

The feeding and nutritional interventions used in this study are all based on current clinical practices, and the only difference is that they are assigned randomly for the purpose of scientific evaluation. Participation is entirely voluntary, and not participating will not affect the quality of medical care your child receives.

7. What happens if my child is harmed by participating in this study?

All feeding methods and nutritional interventions used in this study are standard in clinical practice, and all medical care will be conducted following established guidelines. Therefore, the risk of research-related harm is very low.

However, if any physical harm related to the study does occur, the research team will take immediate and appropriate medical action to ensure your child receives prompt and proper treatment. The hospital will evaluate the situation according to national and hospital policies and may provide medical assistance or compensation as appropriate.

Your child's safety is always the top priority of this study. If any serious adverse events occur, the research team will report them promptly to the ethics committee and, if necessary, stop the intervention to protect your child's best interests.

Even if you have signed this informed consent form, you still retain all your legal rights.

8. Are there any costs associated with participating in this study?

There are no additional costs for participating in this study. You will only need to pay for routine hospitalization and medical care as usual.

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

There will be no financial compensation or reimbursement provided for participation in this study.

10. Is participation in this study mandatory? Can we withdraw after joining?

No, participation in this study is completely voluntary. You have the right to refuse to allow your child to participate.

You may also withdraw your child from the study at any time during the research process. Withdrawing from the study will not result in any fines, discrimination, or retaliation, and it will not affect your child's future medical care or rights.

If you wish to withdraw your child from the study, please inform us. We will ensure that your child exits the study in the safest possible manner.

11. Under what circumstances may my child be withdrawn from the study?

The study physician has the right to withdraw your child from the study if any of the following situations occur:

You or your child do not follow the instructions provided by the study team, showing poor compliance;

The study physician believes that continued participation would cause unnecessary harm;

The study is terminated by the Ethics Committee or a regulatory authority.

12. What happens if new information about this study becomes available?

During the course of the study, if new information arises that may affect your child's willingness to continue participation, the study physician will inform you and your child in a timely manner. You will be given sufficient time to consider whether you wish to continue in the study.

After the study ends, relevant assessment results will be shared with you and your child.

13. If my child participates in this study, will his/her information be protected?

All documents related to your child's participation in the study will be coded for confidentiality. Any public reports or publications resulting from this study will not disclose any personal information about you or your child.

All data and associated codes will be securely stored by the researcher's institution. Study data will be retained for at least 10 years.

The study records may be reviewed by the researchers, the Medical Ethics Committee of the Children's Hospital, Zhejiang University School of Medicine, and government regulatory authorities.

14. Who should I contact if I have questions about the study?

You may ask questions about any aspect of the study that you do not understand. The study team will answer all your questions. If you feel your questions have not been fully answered or the explanations are unclear, you are encouraged to continue asking questions until you are satisfied. Contact information is as follows:

Chen Zheng, Phone: 13857151000

Xu Yanping, Phone: 13685757726

If you have any concerns regarding your child's rights as a research participant or if you would like to report any dissatisfaction or concerns about the study, you may contact the Ethics Committee:

Name: Medical Ethics Committee of the Children's Hospital, Zhejiang University School of Medicine

Address: No. 3333 Binsheng Road, Binjiang District, Hangzhou, Zhejiang Province

Phone: 0571-86670076

Informed Consent Signature Page

I have read and understood the information in this informed consent form. I have asked questions and am satisfied with the answers provided by the study physician. I have been given sufficient time and opportunity to inquire about the details of the study and to consider whether to allow my child to participate.

I voluntarily agree to allow my child to participate in this study.

Signing this informed consent form does not mean I give up any of my legal rights.

I have been informed that I will receive a signed copy of this document.

I authorize study personnel, the ethics committee, and government regulatory authorities to review my child's medical records.

I ☐ Agree / ☐ Disagree that my child's data from this study may be used in another research.

Participant's Name (Print): _____

Guardian's Name (Print): _____

Relationship to Participant: _____

Guardian's Signature: _____

Date and Time of Signature: _____

Contact Phone Number: _____

(Only one guardian's signature is required for this study)

Statement of Person Obtaining Informed Consent:

I confirm that I have explained the details of this study to the participant's guardian, including their rights and the possible benefits and risks. I have answered the guardian's questions and provided them with a signed copy of the informed consent form.

Name of Person Obtaining Consent (Print): _____

Signature of Person Obtaining Consent: _____

Date and Time of Signature: _____

Contact Phone Number: _____

Impartial Witness Statement (if applicable):

I confirm that the study doctor accurately explained the contents of the informed consent form to the participant's guardian, and that a discussion was held with the guardian. The guardian was given the opportunity to ask questions and voluntarily agreed to allow their child to participate in the study.

Impartial Witness Name (Print): _____

Impartial Witness Signature: _____

Date and Time of Signature: _____

Contact Phone Number: _____

(An impartial witness signature is required if the participant or their guardian is illiterate.)