

Application of improved Clown Care in Nebulization inhalation Nursing in Pediatric Outpatient Clinics

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Research Sponsor: Wu Jun

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1.0	2025-01-08	First Draft
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List of Clinical Trial Center Information

Information of Research Sponsor and Leading Research Unit

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Researcher's Statement and Signature Page

This study is a prospective clinical research. The methodologies, equipment and drugs adopted in the research have been widely used in clinical practice. A strict adverse event monitoring system will be established in this study to carefully record all adverse events and ensure timely and effective handling. If any serious adverse events or important adverse events occur, whether related to the research intervention or not, and whether the intervention has been implemented, the research sponsor must be notified in a timely manner, and a decision on whether to stop the research shall be made in a timely manner according to the situation. The researcher guarantees that the personal data of the subjects will be strictly confidential: all subject information and images will be identified by numbers instead of names; information that can identify the identity will not be disclosed to members outside the research team unless permitted by the subjects; all research members and the research sponsor are required to follow the principle of confidentiality; all research files will be stored in locked file cabinets for access only by researchers; during and after the research implementation, government regulatory authorities or ethics committee members are allowed to conduct random inspections and supervision on the personal data of the subjects in accordance with regulations; when the results of this research are published, no personal data will be disclosed.

Researcher's Signature

I have read and agreed to the plan proposed in this document, recognized the relevant content of the plan, and will strictly abide by the laws, regulations and relevant rules and systems of the People's Republic of China during the trial process, perform the duties of the researcher and abide by the confidentiality regulations.

Research Unit: The First Affiliated Hospital of Zhejiang University
Researcher's Name: Wu Jun
Researcher's Position: Head Nurse
Researcher's Signature:
Signature Date:

Plan Abstract

Item	Content
Research Name	Application of improved Clown Care in Nebulization inhalation Nursing in Pediatric Outpatient Clinics
Research Background	Pediatric outpatients with respiratory tract infections often feel fear, cry and resist the device during nebulization inhalation treatment, resulting in the failure of drugs to effectively reach the lung lesions and affecting the treatment effect. Clown therapy is widely and maturely applied abroad, which can relieve patients' tension, improve nursing experience, and have a significant effect in pediatric perioperative period and other operations. However, clown therapy started late in China, and the related research has problems such as small sample size, lack of multi-center large-sample research, and limited research methods. The applicant has previously carried out professional training on clown therapy for nurses, which has improved the nurses' cognition and operational feasibility of clown therapy. On this basis, this study will be carried out.
Research Objectives	1. To explore the operational feasibility of modified clown therapy in nebulization inhalation nursing in pediatric outpatient clinics. 2. To evaluate the effect of modified clown therapy on relieving anxiety of children and their guardians. 3. To analyze the role of modified clown therapy in improving children's compliance with nebulization treatment.
Research Content	This is a single-center, prospective study. Children aged 2-10 years who are treated with nebulization for the first time or for the first time in nearly a year due to upper/lower respiratory tract infections in outpatient clinics will be selected as research objects and randomly divided into the clown therapy group and the control group. The clown therapy group will have interactions with modified clown volunteers (dressed as plush teddy bear dolls) according to the children's personalities before, during and after nebulization; the control group will receive routine nursing care. Basic information of children and their families will

	be collected, and the FLACC Scale (Face, Legs, Activity, Cry, Consolability), Facial Expression Pain Scale, self-designed Nebulization Compliance (Likert) Rating Scale, and modified SAS (Self-Rating Anxiety Scale) Questionnaire will be used to collect the anxiety score information of children and their families. The effect of clown therapy on the anxiety and pain of children and their families during nebulization treatment of pediatric outpatients with pneumonia will be explored. Finally, after the entire nebulization treatment course, a self-designed satisfaction questionnaire will be used to collect the satisfaction score data of the patients' families on the nebulization (clown) treatment and nursing in the pediatric outpatient clinic.
Characteristics, Composition, Principle and Scope of the "Clown Care" Project	Friendly image: volunteers are dressed as plush teddy bear dolls which are more acceptable in China, making it easy for children to get close. Diverse interactions: they can perform teddy bear fun dances, magic tricks, juggling, etc., and flexibly choose interaction methods according to the children's personalities. Composition: Services are provided by professionally trained modified clown volunteers. The service process includes stages such as communicating and formulating interaction methods during the visit, reducing fear before treatment, establishing a trusting relationship 5 minutes before treatment, and giving rewards after treatment. Principle: Based on psychological and behavioral theories, interesting performances and interactions stimulate the secretion of endorphins in children's brains, regulate emotions, relieve pain, reduce psychological defense, and improve treatment compliance. Scope: Applied in the nebulization treatment process of pediatric outpatients with respiratory tract infections.
Indications, Contraindications and Precautions of "Clown Care"	Indications: Children aged 2-10 years who are treated in outpatient clinics due to upper/lower respiratory tract infections and receive nebulization treatment for the first time or for the first time in nearly a year. Contraindications: Children with cognitive impairment or congenital developmental disorders; children allergic to plush materials; children with severe pneumonia complicated with respiratory failure; children with concurrent insufficiency of other organs such as heart, liver and kidney or other serious diseases. Precautions: Pay attention to the children's emotional and

	physical reactions to avoid excessive interaction; ensure the cleanliness and hygiene of the doll costumes and props, and volunteers should pay attention to personal hygiene; communicate with family members in a timely manner to understand the children's characteristics and taboos; handle and observe the follow-up situation in a timely manner according to the severity of adverse events.
Overall Design	Research Method: A single-center, prospective study with a clown therapy group and a control group. The clown therapy group carries out interactions according to specific processes, the control group receives routine nursing care, and relevant data are collected at different stages. Measures to Reduce Bias: A cluster randomization method will be adopted, and the grouping will be based on different pediatric outpatient doctors (A or B) at the first visit. Clear criteria for judging clinical indicators: positive results of at least two symptoms, signs or laboratory tests related to respiratory tract infections can be judged. Subject Selection: Inclusion criteria: children aged 2-10 years treated in outpatient clinics, suffering from upper/lower respiratory tract infections, conscious, with normal cognition, vision and hearing, receiving nebulization treatment for the first time or for the first time in nearly a year, and receiving diagnosis and treatment by the same doctor and nursing team throughout the process; exclusion criteria include various situations related to the subjects themselves, lesions and combined medications. Study Endpoints: Primary study endpoint: During the period of clown therapy or routine nursing intervention (synchronized with the entire nebulization course, i.e., 2-3 days), the FLACC Scale, a professional children's anxiety scale, is used to evaluate the two groups of children, and the difference in anxiety scores between the clown therapy intervention group and the control group is compared. Secondary study endpoints: During the period of clown therapy or routine nursing intervention (2-3 days of nebulization course), first, the difference in children's cooperation score during nebulization treatment: a self-designed children's cooperation rating scale is used for evaluation, including performance score, number of mask drops and facial pain FPS (Facial Pain Scale) score;

	second, the difference in guardians' anxiety scores: the SAS scale suitable for guardians is used to evaluate the guardians of the two groups of children; third, nursing satisfaction: a self-designed nursing satisfaction scale is used to evaluate the satisfaction difference of guardians.
Research Process	Ethical Principles and Informed Consent: Screen subjects according to inclusion and exclusion criteria, introduce the research content to family members, solicit opinions and sign the informed consent form. Subject Screening: Nursing staff check whether to include in the research based on the children's basic information and condition, and the selected children are randomly grouped. Intervention in the Research Group: Volunteers in the intervention group carry out interactions, and the control group receives routine nursing care. Follow-up after Modified Clown Care Assisted Nebulization Inhalation Treatment: Observe the changes in the children's condition, conduct follow-up according to the primary and secondary study endpoints and record relevant data. Nebulization Treatment Combined with Oral Medication: Pediatric outpatients often receive combined oral medication treatment. Whether to continue medication is determined according to symptoms, and no follow-up is conducted after reaching the study endpoint.
Statistical Considerations	Statistical Software: R4.3.1. Sample Size: A total of 160 cases are expected to be included. 30 cases in each group in the pilot study stage, and 80 cases in each group are determined after calculation. The sample size is appropriately increased considering factors such as loss to follow-up. Significance Level and Power: The significance level α is set at 0.05, and the power is 80%. Statistical Analysis Population and Methods: The analysis population is 2-10-year-old children diagnosed with respiratory tract infections in pediatric outpatient clinics who need nebulization treatment; descriptive statistical analysis is used for data, and appropriate statistical test

	methods are selected according to data types and distributions. Point estimates and 95% confidence intervals of primary and secondary evaluation indicators are calculated. Handling of Missing Values and Outliers: Missing values are handled by deletion method; outliers are identified through boxplots, and corrected, weighted down or carefully deleted according to the situation. Expected Attrition Rate: 10%. Procedure for Reporting Deviations from the Original Statistical Analysis Plan: After finding deviations, evaluate the impact, record the situation, communicate and approve with relevant parties, implement the new analysis after approval, and explain in detail in the report.
Data Recording and Management	Recording Content: Basic information of children and their families, results of various rating scales, etc. Management Method: Establish paper file storage and electronic system preservation, set strict access rights, handle missing values and outliers according to predetermined methods, ensure the integrity, accuracy and traceability of data, and comply with GCP (Good Clinical Practice) specifications.
Criteria and Procedures for Termination of Clinical Research	Termination Criteria: Sufficient sample data (within 200 cases) are collected; subjects voluntarily withdraw informed consent; researchers determine that subjects cannot continue the research; serious adverse events occur that threaten the safety of subjects. Termination Procedures: When the termination criteria are met, researchers notify the sponsor in writing, sort out and save the data, and the principal researcher submits a termination report to the ethics committee for review.
Expected Research Progress	February 1, 2025 - May 1, 2026: Collect 200 eligible samples of pediatric respiratory tract infection cases. May 1, 2026 - August 1, 2026: Process the collected data to ensure data quality. August 1, 2026 - February 1, 2027: Conduct in-depth data processing, form charts, submit manuscripts and fill in gaps according to reviewers' comments.

Evaluation and Reporting of Adverse Events	Definition of Adverse Events: Including adverse events (AE, any unfavorable medical event occurring in subjects), serious adverse events (SAE, such as death, life-threatening, etc.), and major adverse events (events affecting research results or progress). Evaluation: Severity is divided into mild, moderate and severe; relevance to "clown care" is evaluated according to the occurrence time and remission situation. Recording: Detailed information of general adverse events is recorded; serious adverse events are handled immediately and relevant personnel are notified, and the principal researcher reports to the ethics committee within 24 hours. Handling and Follow-up: Corresponding handling measures are taken according to the severity, and follow-up is conducted for subjects with adverse events to record the recovery situation.
Quality Control and Quality Assurance	Quality Control: 1. Intensification of training for the clown medical team: When carrying out clown intervention in nebulization treatment, there should be at least 2 nurses on site to perform professional nebulization treatment operations and record relevant data respectively. 2. Standardization of interaction processes: Formulate detailed videos and standard manuals of interaction processes for clown volunteers, clarifying the interaction methods, time and key points at different stages before, during and after nebulization treatment. 3. Regular evaluation and feedback: Medical staff and children's families fill in evaluation questionnaires to evaluate the interaction effect, children's reactions, and the promoting effect on nebulization treatment. Quality Assurance: Ensure plan compliance, strictly operate according to the plan, and plan revisions need approval; accept external reviews and rectify according to feedback; establish a continuous improvement mechanism to summarize experience and optimize the research.
Deviations from the Clinical Research Plan	Definition and Classification: Deviations between research implementation and the established plan, divided into major deviations (affecting research scientificity and

	subject rights and interests) and general deviations (minor deviations). Reporting Process: After discovering deviations, researchers fill in a report form and submit it, and the quality control team evaluates and formulates corrective measures. Handling Measures: Major deviations require discussion by the research team, suspension of research and approval by the ethics committee to adjust the plan; general deviations are corrected under the guidance of the quality control team.
Regulations on Revisions to the Clinical Research Plan	Reasons for Revision: Emergence of new medical evidence, unreasonableness of the original plan, requirements of the ethics committee, etc. Revision Process: Researchers apply, the research director organizes evaluation, submits to the ethics committee for approval after approval, and trains participants after approval. Recording and Notification: Record the entire revision process and notify relevant personnel.
Direct Access to Original Data	Access Rights: The research director, quality control personnel, ethics committee members and regulatory authorities have the right to access. Access Process: Access personnel apply in advance, and the research director arranges access after review to ensure confidentiality. Recording and Supervision: Record access information, and the quality control team supervises to prevent data leakage and abuse.
Personal Data Protection	Protection Measures: Replace identifiable information with numbers, lock paper data, encrypt and back up electronic data, and restrict access rights. Information Use: Only used for this research, and desensitized when publishing or sharing data. Violation Handling: Launch an emergency response when a violation occurs, handle the person responsible and report.

Confidentiality	Confidentiality Scope: Subjects' personal data, research data, plans, unpublished results, etc. Confidentiality Measures: Seal paper documents, encrypting electronic documents, restrict access, and strictly managing relevant equipment and media. Leakage Handling: Timely control when a leakage occurs, investigate the cause and hold responsible people accountable.
Data Preservation	Preservation Content: Informed consent forms of subjects, original data records and other various data. Preservation Method: Dual preservation of paper and electronic, classified filing, regular backup, and ensuring a suitable preservation environment. Preservation Period: Not less than the specified years (such as 10 years) after the end of the research and destroyed in accordance with procedures after the expiration.
Research Summary and Termination	Summary Report: After the end of the research, the research director organizes the writing, which is reviewed by the team and submitted to the research sponsor and the ethics committee. Termination Process: When the predetermined endpoint is reached, the sample size requirement is met, or unforeseen circumstances occur that make the research impossible to continue, terminate the research according to the standards and procedures, sort out and save the data and notify relevant parties.
Final Report and Publicity Principles	Content of the Final Report: Comprehensively present the research background, objectives, methods, results, safety evaluation, etc., to ensure scientificity and integrity. Publicity Principles: On the premise of protecting privacy and confidentiality, publicize research results through academic journal publication, academic conference reports, etc., and timely notify relevant parties.
Responsibilities of All Parties	Responsibilities of the Clinical Research Sponsor: Provide resource support, participate in the design and review notifying plan, supervise the progress and quality of the research, coordinate relationships, solve problems arising in the research process, and evaluate and transform

	research results. Responsibilities of the Medical Institution Undertaking Clinical Research: Provide venues and facilities, organize and train the research team, implement the research according to the plan, recruit, screen and treat subjects, ensure the rights and interests and safety of subjects, and cooperate with inspections and audits by the research sponsor and regulatory authorities.
Qualifications of the Research Center and Researchers	Qualifications of the Research Center: The First Affiliated Hospital of Zhejiang University has venues meeting the needs, equipped with advanced equipment and space; has professional medical staff, some of whom have received clown therapy training; has established a sound quality control and assurance system, has a mature ethical review mechanism, and standardized research management. Qualifications of Researchers: The principal researcher has rich experience, the members of the research team are professional, have the conditions and capabilities to carry out the research, and take up their posts after training and assessment.

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1 Research Background

Children with pneumonia feel unfamiliar and fearful of nebulization inhalation devices, often crying and resisting wearing masks, which makes it difficult to start treatment smoothly. Some children also cannot stay quiet for a long time during treatment and twist their bodies frequently, resulting in nebulized drugs failing to accurately reach the lung lesions and affecting the treatment effect. How to improve children's compliance during nebulization treatment and reduce their anxiety and pain is an important part of pediatric nursing work [1].

Medical clowns, also known as clown therapy, promote the release of endorphins in patients through professionally designed funny performances and creative humorous interactions, regulate and stimulate the immune system, which can effectively relieve the tension caused by diseases in patients, create a relatively relaxed and pleasant atmosphere in the medical process, and then improve the patient experience in clinical nursing. Clown therapy has a wide range of research in pediatrics, and has been applied in children's perioperative period, intravenous indwelling needle insertion, burn dressing change and other operations, which can effectively reduce children's anxiety and pain, and improve children's compliance in accepting clinical nursing operations.

At present, specialized hospitals have more child-friendly facilities and equipment in the diagnosis and treatment of pediatric diseases. For example, nebulization treatment equipment combined with entertainment TV and small games can meet the needs of children of different ages and reduce children's anxiety and pain by diverting attention. In terms of personnel, medical staff have deeper research on pediatric diseases, and may have a more thorough understanding of the application of clown therapy in pediatric nebulization treatment, which can better cooperate with clown volunteers to carry out work. However, the condition of children in specialized hospitals may be relatively severe and complex, and some children may have low acceptance of clown interaction due to their condition, which may affect the implementation effect of clown therapy. General hospitals have many pediatric patients and a variety of diseases, which can provide a wider range of samples for the research. Hospitals are rich in resources and have strong multi-disciplinary collaboration capabilities, which have advantages in dealing with complex problems arising in the process of clown therapy (such as when children have other systemic diseases). However, pediatric medical staff in general hospitals are busy, and may have limited energy in cooperating with clown volunteers to carry out interactive activities. In addition, the cognition and acceptance of clown therapy may vary among different departments, affecting the consistency and promotion of the research. Finally, by analyzing these differences, it can provide a basis for promoting clown therapy in different types of hospitals and improve the applicability of research results.

At present, clown therapy is widely and maturely applied abroad, but it started late in China and is mostly concentrated in the field of pediatrics. The deficiencies of the research include small sample size in some studies, lack of multi-center large sample research, and the need to enrich research methods. The applicant has previously carried out professional clown therapy training for nurses in pediatric outpatient clinics, which has confirmed that professional training can significantly improve nurses' cognitive level and acceptance attitude towards clown therapy, and improve the feasibility of applying clown therapy in the actual

nursing operations of outpatient nurses. On this basis, the applicant intends to introduce clown therapy into the nebulization treatment of pediatric pneumonia patients, hoping to reduce children's anxiety and pain during nebulization, improve children's compliance and final curative effects, and improve the level of pediatric clinical nursing.

2 Objectives and Contents of Clinical Research

2.1 Objectives of Clinical Research

1. To explore the operational feasibility of modified clown therapy in nebulization inhalation nursing in pediatric outpatient clinics.
2. To evaluate the effect of modified clown therapy on relieving anxiety of children and their guardians.
3. To analyze the role of modified clown therapy in improving children's compliance with nebulization treatment.

2.2 Contents of Clinical Research

This is a single-center, prospective study aiming to explore the effect of clown therapy on the anxiety and pain of children and their families during nebulization treatment of pediatric outpatients with pneumonia.

The research population is pediatric outpatients (aged 2-10 years), mainly suffering from respiratory tract infections, who receive nebulization treatment for the first time or for the first time in nearly a year. The children are randomly divided into the clown therapy group and the control group. The children only receive intervention during nebulization treatment, and their subsequent treatment and follow-up follow the clinical routine diagnosis and treatment process of the research center, without being affected by this research.

3 Characteristics, Composition, Working Principle, Mechanism of Action and Research Scope of the "Clown Care" Service for Research

This study adopts modified clown care to assist the clinical nursing operation of nebulization inhalation. The "clown care" service has the following characteristics:

(1) Friendly Image: Abandoning the exaggerated facial makeup abroad, volunteers are dressed as plush teddy bear dolls which are more acceptable in China, as shown in Figure 1. This image makes it easier for children to get close and reduces their fear of the medical environment.

(2) Diverse Interactions: After training, medical clowns have accumulated rich performance abilities. They will perform teddy bear fun dances to attract children's attention with cheerful rhythms and lovely movements; they will also perform magic tricks and juggling to bring surprises and joy to children. In addition, they can flexibly choose interaction methods according to the personality characteristics of the service objects, such as chatting softly with introverted children, performing more lively and interesting programs for active children, and even letting children familiarize themselves with the nebulization treatment process through role-playing that imitates medical procedures, so as to reduce their psychological burden.

The working principle of the "clown care" service is based on psychological and behavioral theories. Through interesting performances and interactions, it stimulates the secretion of endorphins in children's brains. Endorphins can not only bring a sense of pleasure but also have the functions of regulating emotions and relieving pain, thus effectively relieving the tension and fear caused by diseases and treatments in children. At the same time, the relaxed and pleasant atmosphere can reduce children's psychological defense, increase their trust in medical staff and treatment operations, and then improve treatment compliance.

In terms of relevant research progress, clown therapy is widely and maturely applied abroad, and has been applied in children's perioperative periods, intravenous indwelling needle insertion, burn dressing change and other operations, which can effectively reduce children's anxiety and pain, and improve children's compliance in accepting clinical nursing operations. Although it started late in China, increased attention has been paid to this field of research in recent years. Existing studies have shown that clown therapy has a positive effect in pediatric nursing, but some studies have problems such as small sample size, lack of multi-center large-sample research, and the need to enrich research methods. Based on previous studies, this study hopes to further explore the application value of clown therapy in nebulization inhalation nursing in pediatric outpatient clinics, and provide new and effective strategies for domestic pediatric nursing.



Figure 1: Example diagram of teddy bear dolls and related props used in "clown care"

4 Indications, Contraindications and Precautions of the "Clown Care" for Research

Indications: Applicable to children aged 2-10 years who are treated in outpatient clinics due to upper/lower respiratory tract infections and receive nebulization treatment for the first time or for the first time in nearly a year. Such children often feel unfamiliar and fearful of nebulization inhalation devices during nebulization treatment, and are prone to crying and resisting wearing masks. They also have difficulty staying quiet during treatment, resulting in nebulized drugs failing to effectively reach the lung lesions. "Clown care" aims to relieve the

anxiety and irritability of children and their families, improve children's compliance with nebulization treatment, and then enhance the treatment effect.

Contraindications:

Patient-related factors: Children with cognitive impairment or congenital developmental disorders are not suitable for this service because they may not understand the interactive intention of clown care and it is difficult to achieve the expected comfort and cooperation effect; children allergic to plush materials are also not applicable to "clown care" because volunteers interact dressed as plush teddy bear dolls, which may cause allergic reactions.

Condition-related factors: Children with severe pneumonia complicated with respiratory failure are in critical condition and need to focus on emergency treatment. Clown care may distract medical staff's energy and interfere with the main treatment, so it is not applicable; children with concurrent insufficiency of other organs such as heart, liver and kidney or other serious diseases have complex physical conditions and cannot bear additional emotional fluctuations or interactive stimuli, so they should also be excluded from "clown care".

Precautions:

Interaction Process: During the clown care process, volunteers must always pay attention to the children's emotional and physical reactions to avoid excessive interaction leading to children's fatigue or discomfort. If the child shows obvious boredom and resistance, the interaction should be stopped immediately, and the way should be adjusted or the clown care service should be suspended.

Hygiene and Safety: The costumes and related props of plush teddy bear dolls must be kept clean and hygienic, and strictly disinfected after each use to prevent cross-infection. Volunteers should also pay attention to personal hygiene and do a good job in cleaning and disinfection before and after contacting children.

Communication with Family Members: Medical staff and clown volunteers should communicate with children's family members in a timely manner to understand the children's personality characteristics, special habits and taboos, so as to provide more targeted services. At the same time, they should also explain the purpose, method and possible situations of clown care to family members to eliminate their concerns.

Handling of Special Situations: If a child has adverse events such as excessive emotional fluctuations and over-excitement during the clown care process, medical staff should take corresponding measures in a timely manner according to the severity. For example, mild emotional fluctuations can be relieved through verbal comfort and adjusting interaction methods; if moderate or severe adverse events occur, such as the need to suspend treatment for psychological intervention or cause serious physical symptoms, clown care should be stopped immediately, handled in accordance with the established adverse event handling process, and the child's subsequent situation should be closely observed.

5 Overall Design

5.1 Research Methods

This is a single-center, prospective study. Modified clown volunteers who have received professional training provide nursing care for outpatient children during nebulization

treatment. The modified clown medical service abandons the exaggerated facial makeup abroad, and volunteers are dressed as plush teddy bear dolls which are more acceptable in China. After training, medical clowns have accumulated basic performance abilities such as fun teddy bear dances, magic tricks, juggling, etc. At the same time, they can flexibly choose interaction methods according to the personality characteristics of the service objects, including fun dances, companionship, magic tricks, juggling and role-playing that imitates medical procedures. The service process is divided into 4 stages.

Stage 1: When the child visits the doctor, the doctor and nursing team communicate with the child's family, introduce the content of the modified clown medical service, formulate the clown medical service method according to the child's characteristics with the full informed consent of the parents, and ask the family to sign the informed consent form.

Stage 2: The medical clown accompanies the child into the nebulization treatment room, and reduces the child's fear of the medical place and operation through interaction and companionship support before the start of nebulization treatment.

Stage 3: 5 minutes before nebulization treatment, the medical clown communicates with the child, and establishes a familiar and trusting relationship through various clown activities, such as performing teddy bear fun dances, magic tricks, and fun simulation of wearing nebulization masks.

Stage 4: After the nebulization treatment, the medical clown gives the child a butter teddy bear sticker as a reward, and promises that after the continuous 2-3-day nebulization treatment course, a small toy will be given as a reward. After the interaction, the intervention ends to enhance the child's cooperation with the subsequent entire nebulization treatment course.

The control group receives routine nursing care. The participating doctors and nurses team comforts the child in terms of language and actions according to the child's anxiety and cooperation during nebulization.

Basic information of children and their families is collected before clown therapy intervention or routine nursing care for nebulization treatment.

Evaluation of the primary study endpoint: The child's anxiety and pain level are evaluated by professional nurses using the FLACC Scale (Face, Legs, Activity, Cry, Consolability) and the Facial Expression Pain Scale during each nebulization treatment throughout the nebulization course (2-3 days).

Evaluation of the secondary study endpoints: First, evaluate the child's compliance with treatment. During each treatment throughout the nebulization course (2-3 days), a self-designed Nebulization Compliance (Likert) Rating Scale is used to divide the child's compliance with nebulization into five levels (0-5 points) and record the number of times the child takes off the mask during nebulization. Second, evaluate the anxiety level of the child's family members. Before the start of the nebulization course and after the end of the entire nebulization course, a modified SAS (Self-Rating Anxiety Scale) Questionnaire is used to collect the anxiety score information of the child's family members.

Finally, after the entire nebulization course, a self-designed satisfaction questionnaire is used to collect the satisfaction score data of the patients' families on the nebulization (clown) treatment and nursing in the pediatric outpatient clinic.

5.2 Measures to Reduce or Avoid Bias

5.2.1 Randomization Method

A cluster randomization method is adopted, and the grouping is based on different pediatric outpatient doctors (A or B) at the first visit. Before the start of the research, collect information of all pediatric outpatient doctors participating in the research and divide them into groups A and B. Use a random number table to randomly determine that children corresponding to doctors in group A enter the clown therapy intervention group, and children corresponding to doctors in group B enter the routine nursing group; otherwise, to ensure the randomness of grouping.

At the same time, during the research process, strengthen the management of the nebulization treatment room, set obvious signs to avoid communication between children and their families about the intervention situation during treatment, reduce the impact of confounding factors on the research results, and improve the accuracy and reliability of the research.

5.2.2 Judgment of Clinical Indicators

Pediatric outpatients mainly complain of respiratory tract infection symptoms such as cough, expectoration, fever, wheezing, runny nose, headache and dizziness, and may be accompanied by some positive signs in physical examination: moist rales in lung auscultation, enlargement in throat inspection, enlargement in lymph node palpation, etc.; may be accompanied by positive laboratory test indicators: chest X-ray/CT indicating lung inflammation, or blood routine, CRP and other blood test results indicating an increase in inflammatory indicators, and throat swabs may indicate specific viral infections of the upper respiratory tract. If at least two of the above clinical complaints, physical examination and laboratory test indicators are met, it can be judged as pediatric respiratory tract infection.

5.3 Subject Selection

5.3.1 Inclusion Criteria for Subjects

Subject-related:

1. Age: 2-10-year-old outpatients
2. Upper/lower respiratory tract infection
3. Conscious, with certain cognitive ability, and normal vision and hearing
4. First nebulization treatment or first nebulization treatment in nearly a year
5. Diagnosis and treatment by the same doctor and nursing team throughout the process

5.3.2 Exclusion Criteria for Subjects

Subject-related:

1. Those with cognitive impairment or congenital developmental disorders
2. Allergic to nebulization inhalation treatment drugs

Condition-related:

1. Severe pneumonia complicated with respiratory failure
2. Concurrent insufficiency of other organs such as heart, liver and kidney or other diseases

Exclusion criteria related to combined medications:

1. Patients who have long-term used other therapeutic drugs except those related to respiratory tract infections (oral antibiotics, antipyretics, antitussives)

5.3.3 Criteria and Procedures for Subjects to Terminate the Research

Subjects may withdraw from the research at any stage if any of the following situations occur.

- 1) The subject requests to withdraw the informed consent;
- 2) The researcher judges that the subject cannot continue the research, or the subject's

5.3.4 Expected Overall Duration of Clinical Research

The research is expected to start on February 1, 2025 and end on February 1, 2027.

5.3.5 Expected Participation Time of Each Subject

Each subject will receive clown therapy or control group therapy intervention throughout the entire nebulization treatment process (twice a day nebulization inhalation during the 2-3-day course of treatment).

5.3.6 Number of Subjects Required for Clinical Research

For the subjects collected in this study, the number of patients to be enrolled considers factors such as those who do not meet the enrollment criteria, may withdraw from the research, and have unqualified sample quality, so as to make up the analyzable data set that meets the plan. A total of 200 samples of pediatric respiratory tract infections are expected to be included.

5.4 Study Endpoints

5.4.1 Primary Study Endpoint

During the period of clown therapy or routine nursing intervention (synchronized with the entire nebulization course, i.e., 2-3 days), the FLACC Scale, a professional children's anxiety scale, is used to evaluate the two groups of children, and the difference in anxiety scores between the clown therapy intervention group and the control group is compared.

5.4.2 Secondary Study Endpoints

During the period of clown therapy or routine nursing intervention (2-3 days of nebulization course), first, the difference in children's cooperation score during nebulization treatment: a self-designed children's Nebulization Compliance (Likert) Rating Scale will be used for evaluation, which divides children's compliance with nebulization treatment into five levels (0-5 points), and records the number of times the child takes off the mask during nebulization; second, the difference in guardians' anxiety scores: the modified SAS (Self-Rating Anxiety Scale) Questionnaire suitable for guardians will be used to evaluate the anxiety levels of the guardians of the two groups of children before and after the nebulization

course; third, the difference in nursing satisfaction: a self-designed nursing satisfaction questionnaire will be used to collect the satisfaction scores of the guardians on the pediatric outpatient nebulization treatment and nursing services after the end of the entire nebulization course.

6 Research Process

6.1 Ethical Principles and Informed Consent

Researchers will determine whether subjects are eligible for enrollment in the study based on inclusion and exclusion criteria before conducting subsequent nursing interventions. The diagnosis, subsequent treatment, and follow-up of pediatric patients will follow the routine clinical diagnosis and treatment process of the research center and will not be affected by this study; after introducing and communicating the research content to the family members, their opinions will be solicited and the informed consent form will be signed.

6.2 Subject Screening

Nursing staff will verify the eligibility of subjects for inclusion in the study based on factors such as the basic information and condition of pediatric patients. The screened and enrolled pediatric patients will be randomly divided into the intervention group and the control group.

6.3 Research Group Intervention

Nursing staff in the intervention group will dress up as little bear dolls. Through training, medical clowns have acquired basic performance skills and can flexibly choose interactive methods according to the personality characteristics of the service objects. Clown therapy intervention will be introduced before, during, and after aerosol inhalation therapy. The control group will receive routine nursing care, and the participating nurses will provide verbal and behavioral comfort to the pediatric patients according to their anxiety level and cooperation degree during aerosol inhalation therapy.

6.4 Follow-up of Modified Clown Care-Assisted Aerosol Inhalation Therapy

During the aerosol inhalation therapy cycle of pediatric patients, the medical and nursing team must closely monitor changes in their condition.

During the scheduled clown therapy or routine nursing intervention cycle (synchronized with the entire aerosol inhalation therapy course, i.e., 2-3 consecutive days of daily treatment), the professional pediatric anxiety scale (FLACC scale) will be used to evaluate the pediatric patients in both groups. The difference in anxiety scores between the pediatric patients in the clown therapy intervention group and the control group is the key follow-up content of the primary research endpoint.

Upon completion of the scheduled clown therapy or routine nursing intervention cycle (2-3 days of aerosol inhalation therapy course), three aspects will be evaluated as part of the follow-up for secondary research endpoints: first, the difference in cooperation degree scores of pediatric patients during aerosol inhalation therapy: a self-designed pediatric cooperation degree scoring scale will be used for evaluation, including performance score, number of mask dislodgements, and Facial Pain Scale (FPS) score; second, the difference in anxiety scores of guardians: the Self-Rating Anxiety Scale (SAS) suitable for guardians will

be used to evaluate the guardians of pediatric patients in both groups; third, nursing satisfaction: a self-designed nursing satisfaction scale will be used to evaluate the satisfaction difference of guardians.

The above follow-up will be conducted 2-3 times, during the 2-3 consecutive days of daily aerosol inhalation therapy when the pediatric patients and their families come to the hospital.

During the follow-up process, detailed records of the improvement and recurrence of the pediatric patients' symptoms must be made, and the relevant data must be sorted and filed to provide complete information for the study, ensuring compliance with GCP principles.

6.5 Combined Aerosol Inhalation Therapy with Oral Medication

Pediatric outpatients often visit the hospital due to upper or lower respiratory tract infections, with chief complaints such as cough, fever, or accompanied by examination and test results indicating specific influenza virus infections. Therefore, oral medications are often used in combination during aerosol inhalation therapy to relieve symptoms. If after completing the scheduled clown therapy or routine nursing intervention cycle (synchronized with the entire aerosol inhalation therapy course, i.e., 2-3 days), the professional pediatric anxiety scale (FLACC scale) is used to evaluate the pediatric patients in both groups during the clown therapy or routine nursing intervention period (synchronized with the entire aerosol inhalation therapy course, i.e., 2-3 days), and there is a certain difference in anxiety scores between the pediatric patients in the clown therapy intervention group and the control group, and the primary or secondary clinical endpoints of this study are achieved, no further follow-up will be conducted. This study only includes outpatients and does not involve inpatients, so there is no post-discharge medication.

6.5.1 Combined Oral Medication During Aerosol Inhalation Therapy (Recommended)

1. Oral antibiotics: such as antibacterial drugs (cefalosporins, etc.) and antiviral drugs (acyclovir granules, etc.).
2. Antipyretic drugs: Motrin, Tylenol, etc.
3. Antitussive drugs: Yitanjing, etc.

7 Statistical Considerations

7.1 Statistical Overview

Statistical software: R4.3.1.

Basic principles: Descriptive statistics will be used to analyze all data, including demographic data, baseline data, and various outcome evaluation indicators. For continuous data, mean, standard deviation, median, minimum value, and maximum value will be used for description; for categorical data, frequency and percentage will be used for description. Inter-group comparison of baseline indicators will adopt t-test or Wilcoxon rank-sum test, chi-square test, and Fisher's exact test. For all primary and secondary evaluation indicators, point estimation will be used, and the 95% confidence interval will be calculated.

All statistical inferences will adopt one-sided (two-sided) tests, and the test level will be determined (generally set at $\alpha=0.05$). The 95% confidence interval will be used for parameter estimation. For data that conforms to normal distribution, parametric analysis methods (t-test or one-way ANOVA test) will be adopted; when the data does not meet the conditions of parametric methods, data transformation methods may be used to make it meet the conditions; if it still does not meet the conditions, non-parametric methods (Wilcoxon rank-sum test or Kruskal-Wallis test) may be considered.

7.2 Sample Size and Rationale for Determination

7.2.1 Total Sample Size

This study sets the significance level α at 0.05 and aims to achieve a power of 80% ($1-\beta=0.8$) to detect clinically significant differences between groups. Based on previous studies and clinical experience, it is estimated that the mean FLACC score in unintervened pediatric patients is 2.60 with a standard deviation of 1.90; it is expected that clown therapy will improve the anxiety of pediatric patients by 30% or more. Calculated by 30% improvement, the FLACC score in the clown therapy group is 1.82, and the inter-group difference is 0.78. The two groups are parallel-designed and allocated at a 1:1 ratio. The sample size is calculated by PASS 15.0.5, and each group needs to include 95 subjects to ensure sufficient power to detect real effects. Considering the possibility of treatment interruption and dropout of patients during nursing treatment, the number of pediatric patients in each group is appropriately increased to 100, with a total of 200 pediatric patients to be included.

7.3 Significance Level and Power of Clinical Research

This study sets the significance level α at 0.05, that is, when the P value is less than 0.05, the inter-group difference is considered statistically significant. This choice follows the conventional standards of clinical research to balance the risks of type I and type II errors. This study aims to achieve a power of 80% ($1-\beta=0.8$) to detect clinically significant differences between groups. Through pre-sample size calculation, based on the expected effect size (such as a satisfaction percentage difference of 0.1), the set significance level $\alpha=0.05$, and the estimated data standard deviation, it is determined that each group needs to include 73 subjects to ensure that the study has sufficient power to detect real effects. Considering factors such as loss to follow-up, the sample size is appropriately increased to 80 per group, with a total of 160 pediatric patients to be included.

7.4 Statistical Analysis Population and Statistical Methods

7.4.1 Statistical Analysis Population

2-10-year-old pediatric outpatients diagnosed with respiratory tract infections and requiring aerosol inhalation therapy.

7.4.2 Statistical Analysis Methods

In R4.3.2, descriptive statistics will be used to analyze all data, including demographic data, baseline data, and various outcome evaluation indicators. For continuous data, mean, standard deviation, median, minimum value, and maximum value will be used for description; for categorical data, frequency and percentage will be used for description. Inter-group comparison of baseline indicators will adopt t-test or Wilcoxon rank-sum test, chi-

square test, and Fisher's exact test. For all primary and secondary evaluation indicators, point estimation will be used, and the 95% confidence interval will be calculated.

All statistical inferences will adopt one-sided (two-sided) tests, and the test level will be determined (generally set at $\alpha=0.05$). The 95% confidence interval will be used for parameter estimation. For data that conforms to normal distribution, parametric analysis methods (t-test or one-way ANOVA test) will be adopted; when the data does not meet the conditions of parametric methods, data transformation methods may be used to make it meet the conditions; if it still does not meet the conditions, non-parametric methods (Wilcoxon rank-sum test or Kruskal-Wallis test) may be considered.

7.5 Handling of Missing Values and Outliers

Missing values will be handled by the deletion method. If individual questionnaires in this clinical trial have complete key information except for satisfaction, but the satisfaction data is missing, and the proportion of missing questionnaires is very small, these questionnaires can be directly deleted.

Outlier identification method: For numerical data, boxplots can be drawn, and data points outside the "whiskers" in the boxplot are suspected outliers. After identifying outliers, the cause of the outliers must first be verified. If it is a data entry error, it can be corrected based on the original records. If the outlier is not an error but a real extreme data, lower weights can be considered for it in statistical analysis to reduce excessive impact on the results. For example, when analyzing the relationship between satisfaction and other factors, the influence of outlier samples can be appropriately reduced. When outliers seriously affect the analysis results and there are sufficient reasons to consider them as abnormal situations, they can be deleted with caution. However, detailed records must be made before deletion and the reasons explained in the report. For example, in this trial, if the satisfaction score of individual subjects is significantly different from the overall trend and no reasonable explanation can be found, deletion may be considered, but the potential impact of deletion on the results must be explained.

7.6 Expected Dropout Rate

The expected dropout rate is 10%.

7.7 Procedures for Reporting Deviations from the Original Statistical Analysis Plan

In this study, if there is a deviation from the original statistical analysis plan, to ensure the scientificity, reliability, and transparency of the study, a series of rigorous and standardized procedures must be followed, specifically as follows:

1. Discovery of Deviations

During the data collection, cleaning, and preliminary analysis stages, researchers will closely monitor the actual data situation and analysis process throughout. Once it is found that the original statistical method cannot be smoothly implemented due to significant differences between the data distribution and expectations (such as data not conforming to normal distribution, making the originally planned parametric test no longer applicable) or due to

problems such as partial data missing and outliers, it should be quickly identified and confirmed as a deviation from the original statistical analysis plan.

2. Assessment of Deviation Impact

After discovering the deviation, researchers will quickly organize professionals from multiple fields such as statisticians and clinical experts to conduct in-depth discussions. From a statistical perspective, comprehensively assess the impact of the deviation on the accuracy, reliability, and validity of the research results, and accurately judge whether it will change the research conclusion. For example, when the originally planned t-test is adjusted to a non-parametric test due to data not conforming to normal distribution, it is necessary to carefully assess the potential impact of this change on the test power of inter-group differences and in-depth analyze whether it will cause changes in the probability of type I or type II errors. At the same time, from a clinical significance perspective, in-depth analyze the potential impact of the deviation on the answer to the research question and clinical decision-making, and accurately determine whether the deviation will cause substantial damage to the application value of the research results in clinical practice.

3. Recording of Deviation Situation

Detailed written records of the deviation situation are a crucial step. The recorded content should include the exact time of the deviation, specific description (such as the changed statistical method, adjusted data processing method, and other details), reasons for the deviation (such as unexpected changes in data characteristics, unforeseen situations during the trial, etc.), and preliminary assessment of the impact. These detailed records will become an indispensable important file in the research process, providing a solid basis and strong support for subsequent review and explanation work.

4. Communication and Approval

The research team must promptly and accurately communicate the deviation situation with relevant parties such as the Ethics Committee in an all-round way, clearly and detailedly explain the possible impact of the deviation on the research progress, cost, and result credibility, and submit a detailed and well-organized deviation report to the Ethics Committee, fully explaining the rationality and necessity of the deviation, and actively seeking the approval of the Ethics Committee. The Ethics Committee will conduct a strict review from the key perspectives of protecting the rights and interests of subjects and maintaining research scientificity, and the deviation can only be officially implemented after obtaining its approval.

5. Implementation and Reporting

After obtaining the official approval of the Ethics Committee and other relevant parties, the new statistical analysis will be accurately implemented in accordance with the determined deviation plan. After the analysis is completed, the deviation situation will be fully and comprehensively reported in the process of writing the research report and paper. In the "Materials and Methods" section, the original statistical analysis plan and the deviations that occurred during the research will be described in detail and accurately, including the specific content of the deviation, reasons, and approval process and other key information; in the Results section, the data results obtained based on the post-deviation analysis method will be intuitively and clearly displayed, and a scientific and rigorous comparative analysis will be

conducted with the results that may be obtained from the original plan to in-depth discuss the specific impact of the deviation on the results; in the Discussion section, further in-depth elaboration on the potential impact of the deviation on the research conclusion and the useful enlightenment for future similar research will be made, and every effort will be made to ensure that readers can fully and accurately understand the changes in the research process and their possible multi-faceted impacts, thereby ensuring the integrity and credibility of the research.

8 Data Recording and Management

In this study, researchers should accurately record the basic information of pediatric patients and their families, the results of various scoring scales at each stage, etc. For the collected data, both paper file sealing and a complete electronic system storage are established to ensure the integrity, accuracy, and traceability of the data. Paper data is stored in a sealed research box, and electronic data is backed up in a password-protected hard disk. The data is safe and reliable to prevent leakage and damage and comply with the principle of confidentiality. At the same time, strict access permissions are set for paper and electronic data, and only authorized personnel within the research group can access them. During the data processing process, missing values and outliers should be handled in accordance with the predetermined statistical methods, and the processing process should be recorded in detail to ensure that the entire data management process complies with GCP specifications.

9 Criteria and Procedures for Termination of Clinical Research

Termination Criteria:

1. The study has collected sufficient clinical trial sample data within 200 cases.
2. If the subject takes the initiative to request the withdrawal of informed consent, their wishes should be respected to terminate the study to ensure the rights and interests of the subject.
3. When the researcher determines that the subject cannot continue the study, such as the condition deteriorating beyond the manageable scope of the study or the occurrence of serious psychological problems that are not suitable for continuation, the study must be stopped.
4. If a serious adverse event occurs during the study, and after assessment, it poses a significant threat to the safety of the subject, the study should be terminated immediately, and emergency medical measures should be taken to ensure the life and health of the subject.

Termination Procedures:

Once the termination criteria are met, the researcher must notify the research sponsor in writing as soon as possible and explain the reasons for termination in detail. At the same time, the collected subject data must be sorted out and preserved to ensure the integrity and traceability of the data. The principal investigator must submit a study termination report to the Ethics Committee within the specified time, elaborating on the entire process of study termination and related situations, and accepting the review and supervision of the Ethics Committee to ensure the standardization and legality of the study termination process.

10 Expected Research Progress

February 1, 2025 - May 1, 2026: Conduct formal experiments, collect eligible pediatric respiratory tract infection cases in accordance with the established inclusion and exclusion criteria, and it is expected to include 200 cases.

May 1, 2026 - August 1, 2026: Process the collected data to ensure the accuracy and integrity of the data, and timely discover and solve problems in data collection.

August 1, 2026 - February 1, 2027: Conduct comprehensive and in-depth processing of the research data, form charts to intuitively display the research results, submit the paper for publication, and supplement and verify the data according to the reviewers' comments.

11 Assessment and Reporting of Adverse Events

11.1 Definition of Adverse Events

11.1.1 Adverse Event (AE)

Refers to any unfavorable medical event occurring to a subject during the clinical research process, regardless of whether it is related to the research intervention (modified clown care-assisted aerosol inhalation therapy). For example, in this study, emotional fluctuations and overexcitement of pediatric patients, dependence on modified clown medical care, social pressure of introverted pediatric patients, and anxiety of family members are all within the scope of adverse events.

11.1.2 Serious Adverse Event (SAE)

Refers to the following adverse events occurring under clown care intervention: resulting in death, life-threatening, requiring hospitalization or prolonging hospitalization time, leading to permanent or severe disability or functional loss, congenital anomalies or birth defects. In this study, if a pediatric patient has a serious condition such as cardiovascular and cerebrovascular risks caused by emotional excitement, it can be determined as a serious adverse event.

11.1.3 Major Adverse Event

Refers to an adverse event that has an important impact on the research results or may change the research process, such as an adverse event that occurs frequently and seriously affects the compliance of pediatric patients with aerosol inhalation therapy, which may interfere with the evaluation of the effect of modified clown care.

11.2 Assessment of Adverse Events

11.2.1 Severity of Adverse Events

Divided into mild, moderate, and severe. Mild adverse events have little impact on the subject's daily activities and usually do not require special treatment or only simple symptomatic treatment to relieve; moderate adverse events will have a certain interference with the subject's daily activities and may require certain medical intervention measures; severe adverse events seriously affect the subject's quality of life or health status, and even threaten life, requiring urgent and intensive medical treatment. In this study, if the emotional fluctuation and overexcitement of a pediatric patient can be relieved by simple comfort from medical staff, it can be regarded as mild; if it is necessary to suspend treatment for

psychological intervention, it may be moderate; if it causes other serious physical symptoms such as convulsions, it is severe.

11.2.2 Correlation Between Adverse Events and "Clown Care"

If an adverse event occurs shortly after the intervention and gradually relieves after stopping the intervention, there may be a strong correlation; if the adverse event occurs frequently without intervention or is closely related to the subject's own underlying disease, the correlation is weak. For example, if an introverted pediatric patient shows signs of social pressure during interaction with a clown, the correlation is strong; while the aggravation of respiratory tract infection symptoms that the pediatric patient originally had has no obvious time correlation with clown care, so the correlation is weak.

11.3 Recording of Adverse Events

11.3.1 Recording of General Adverse Events

Detailedly record the time of occurrence, symptom performance, severity, duration, treatment measures taken, and outcome of the adverse event. For example, record the specific time point when a pediatric patient has emotional fluctuations and overexcitement, the form of performance (such as the degree of crying, behavioral abnormalities, etc.), the judged severity level, the duration from occurrence to relief, the comfort method adopted by medical staff, and whether they finally return to calm, etc., to ensure the integrity and accuracy of the record for subsequent research analysis.

11.3.2 Recording and Reporting of Serious Adverse Events

For all serious adverse events during the study, regardless of whether they are related to the clown therapy used in the study, the researcher shall immediately take appropriate treatment measures for the subject and notify the research applicant in writing. After learning of the event, the principal investigator shall report it in writing to the corresponding Ethics Committee within 24 hours. The report content includes the detailed situation of the serious adverse event, the preliminary judgment of the correlation with the research, the emergency treatment measures taken, and the current status of the subject, etc., to ensure that the Ethics Committee can timely understand the whole picture of the event and supervise and guide the subsequent treatment.

11.4 Handling and Follow-up of Adverse Events

11.4.1 Handling of Adverse Events

Corresponding treatment measures will be taken according to the severity and type of the adverse event. For mild adverse events, such as slight emotional fluctuations of pediatric patients, medical staff can handle them on site through verbal comfort, adjusting interaction methods, etc.; for moderate adverse events, such as pediatric patients' resistance to treatment caused by social pressure, it may be necessary to suspend the clown care intervention, and professional psychological staff will conduct psychological counseling before evaluating whether to continue; for severe adverse events, such as cardiovascular and cerebrovascular risks, the emergency medical rescue procedure must be activated immediately, and treatment will be carried out in accordance with the hospital's relevant first-aid procedures to ensure the life safety of the subject.

11.4.2 Follow-up of Adverse Events

Continuous follow-up will be conducted on subjects who have experienced adverse events to observe the subsequent development of the adverse events and whether there are any residual problems. The follow-up interval is determined according to the severity and nature of the adverse event. For mild adverse events, follow-up can be conducted within a short time after treatment (such as 1-2 days); for moderate adverse events, the first follow-up can be conducted 3-5 days later, and then the follow-up interval can be appropriately extended according to the recovery situation; for severe adverse events, close follow-up is required, and evaluations will be conducted at key time points such as 24 hours, 1 week, and 1 month after treatment to record the physical and psychological recovery status of the subject until it is confirmed that the adverse event has been completely resolved or stabilized, providing comprehensive adverse event handling and outcome data for the study.

12 Quality Control and Quality Assurance

12.1 Quality Control

Personnel Training and Qualifications: Comprehensive training will be carried out for the medical and nursing team and modified clown nursing staff participating in the study. The training content includes the basic concepts, theoretical knowledge, operating specifications, and interactive skills of clown therapy, as well as the correct use of evaluation tools such as the FLACC scoring scale and aerosol compliance scoring. Ensure that all personnel are familiar with the research process and master relevant skills, and require medical staff to have professional qualifications in pediatric nursing. The medical and nursing team participating in the study must pass the training assessment to ensure the professionalism and consistency of the services they provide.

Data Quality Control: Formulate strict data recording specifications, requiring researchers to truthfully and accurately record the basic information of pediatric patients and their families, the results of various scoring scales at each stage, and other data. Conduct double backup of paper and electronic data; paper data is stored in a sealed research box, and electronic data is backed up in a password-protected hard disk; strict access permissions are set, and only authorized personnel can access them. Regularly audit the data to verify the integrity and logical rationality of the data, and timely discover and correct possible errors or missing values.

Research Process Supervision: Establish an independent quality supervision team to regularly inspect the implementation of the research process. The supervision content includes whether the screening of pediatric patients meets the standards, whether the grouping is random and fair, whether the intervention measures are implemented in accordance with the plan, and whether the recording and handling of adverse events are timely and standardized. If problems are found, communicate with researchers in a timely manner and require rectification within a time limit to ensure that the research progresses strictly in accordance with the established plan.

12.2 Quality Assurance

1. **Strengthening Training of Clown Medical Team:** On the basis of existing training, add training content on professional knowledge of aerosol inhalation therapy to enable clown

medical staff to have an in-depth understanding of the principle of aerosol inhalation therapy, the mechanism of drug action, and possible adverse reactions. At the same time, carry out emergency treatment training to enable them to master the methods and procedures for dealing with sudden situations of pediatric patients during aerosol inhalation therapy (such as choking, difficulty breathing, etc.), ensuring that problems can be found in a timely manner and assisting medical staff in handling them during the accompany process. Finally, when conducting clown intervention in aerosol inhalation therapy, in addition to the clown medical staff, there should be at least 2 nurses on site to perform professional aerosol inhalation therapy operations and record relevant data respectively.

2. Standardization of Interactive Processes: Develop detailed video and standard manuals of interactive processes for clown volunteers, clarifying the interaction methods, time, and key points at different stages before, during, and after aerosol inhalation therapy. For example, for the interaction 5 minutes before aerosol inhalation therapy, specify the duration of performing the little bear fun dance and the number of times to simulate wearing an aerosol mask, etc., to ensure the consistency and standardization of the interaction and reduce research errors caused by individual differences of volunteers. The standardized process text or video is attached at the end of the document.

3. Regular Evaluation and Feedback: Medical staff and pediatric patients' families will fill out evaluation questionnaires to evaluate the interaction effect, pediatric patients' reactions, and the promoting effect on aerosol inhalation therapy. According to the evaluation results, timely feedback and guidance will be given to volunteers, and rewards will be given to outstanding volunteers to motivate them to improve service quality and ensure the stability of aerosol quality in the clown group.

13 Deviation from Clinical Research Protocol

Definition and Classification: Deviation from the clinical research protocol refers to any deviation from the established research protocol during the research implementation process. Deviations are divided into major deviations and minor deviations. Major deviations include situations that affect research scientificity and subject rights and interests, such as enrolling subjects who do not meet the standards (such as not meeting the age classification, non-respiratory tract infection diseases, or non-first visit/visit within nearly 1 year), and failing to perform random grouping in accordance with regulations; minor deviations include relatively small deviations such as non-standard data recording format and slight delay in the time node of the research process.

Reporting Process: Once the researcher finds a deviation from the research protocol, they must immediately fill out a deviation report form, detailing the time of occurrence, specific situation, reasons for the deviation, and possible impact on the research, and submit it to the research director and quality control team in a timely manner. The quality control team will evaluate the deviation report, judge the severity of the deviation, and formulate corresponding corrective measures.

Handling Measures: For major deviations, the research director must organize a research team meeting to discuss solutions, and if necessary, suspend the research and adjust the research protocol after obtaining the approval of the Ethics Committee; for minor

deviations, the quality control team will guide the researcher to make timely corrections and record the correction process and results to ensure that the research returns to the right track.

14 Provisions on Amendments to the Clinical Research Protocol

Reasons for Amendments: Possible reasons leading to amendments to the research protocol include the emergence of new medical evidence, the discovery of unreasonable aspects in the original protocol during the research process, and requirements put forward by the Ethics Committee. It is clarified that the protocol can only be amended after full demonstration and in line with relevant laws, regulations, and ethical requirements.

Amendment Process: The researcher submits an application for protocol amendment, detailing the content, reasons, and expected impact of the amendment. The research director organizes experts to evaluate the amendment application. After the evaluation is passed, the amended protocol is submitted to the Ethics Committee for approval. After obtaining the approval of the Ethics Committee, the research team will train all participants to ensure that they understand and follow the amended protocol for the research.

Recording and Notification: Detailed records of the entire process of protocol amendment will be made, including relevant documents of application, evaluation, and approval. At the same time, all relevant personnel, such as subjects, research team members, and research sponsors, will be notified in a timely manner to ensure that all parties understand the changes to the protocol.

15 Direct Access to Original Data/Materials

Access Rights: Clearly stipulate that the research director, quality control personnel, members of the Ethics Committee, and personnel from regulatory authorities have the right to directly access the original data and materials. Corresponding access permissions will be set for authorized personnel: paper materials need to be accessed and registered at designated locations, and electronic data will be controlled through a password system.

Access Process: Personnel who need to access the data must submit an access application to the research director in advance, stating the purpose of access, the scope and time of the data to be accessed. After the research director approves the application, arrangements for access will be made to ensure that the access process complies with confidentiality requirements, and the accessing personnel shall not copy or disseminate the data without authorization.

Recording and Supervision: Detailed records of each access to the original data/materials will be made, including the accessing personnel, time, and content of access. The quality control team will regularly check the access records and supervise the access behavior to prevent data leakage and abuse.

16 Personal Data and Data Protection

Protection Measures: Various measures will be taken to protect the personal data of subjects: using numbers instead of identifiable information such as names; storing paper materials in locked file cabinets, and storing electronic data in secure hard disks with

electronic encryption and regular backups; restricting data access permissions, and only authorized personnel can access the personal data of subjects.

Information Use: Clearly stipulate that personal data is only used for purposes related to this study. Without the consent of the subject, their personal data shall not be used for any other purposes. When publishing research results or sharing data, desensitization processing will be performed on personal data to ensure that the identity of the subject cannot be identified.

Violation Handling: Formulate a strict violation handling mechanism. If a violation such as personal data leakage occurs, an emergency response will be activated immediately, measures will be taken to reduce the impact, the relevant responsible persons will be dealt with severely, and the incident will be reported to the subject and regulatory authorities.

17 Confidentiality

Confidentiality Scope: Including the personal data of subjects, research data, research protocols, and unpublished research results. All participants are required to sign a confidentiality agreement, promising to strictly keep confidential information confidential.

Confidentiality Measures: Adopt measures such as sealing paper documents, encrypting original electronic documents; restricting access by irrelevant personnel; strictly managing equipment and storage media involving confidential information to prevent information leakage.

Leakage Handling: Once a leakage incident occurs, measures will be taken immediately to control the situation, such as notifying relevant personnel, evaluating the impact of the leakage, and taking remedial measures, investigating the cause of the leakage, and holding the responsible persons accountable in accordance with laws and regulations.

18 Data Preservation

Preservation Content: Including but not limited to the subject's informed consent form, original data records, research protocol and amendment documents, quality control records, adverse event reports, and research summary report.

Preservation Method: Adopt a dual preservation method of paper and electronic. Paper materials are sorted and filed by category and time sequence and stored in a special file box; electronic materials are stored in a secure server or hard disk and backed up regularly. The preservation environment should meet the requirements of fire prevention, moisture resistance, and insect prevention to ensure the integrity and readability of the materials.

Preservation Period: The preservation period of the materials shall not be less than the specified number of years (such as 10 years) after the end of the research to meet the needs of possible regulatory reviews and data reanalysis. After the expiration of the preservation period, the materials will be destroyed in accordance with the specified procedures.

19 Research Summary and Termination

Summary Report: After the end of the research, the research director will organize the writing of a research summary report, which includes the research purpose, methods, results, conclusions, the occurrence and handling of adverse events, and the problems and

experiences during the research process. The summary report must be reviewed internally by the research team and submitted to the research sponsor and the Ethics Committee.

Termination Process: When the research reaches the predetermined endpoint, the number of subjects meets the requirements, or unforeseen situations occur that make the research impossible to continue, the research will be terminated in accordance with the established criteria and procedures for the termination of clinical research. All research materials will be sorted out and preserved, and the relevant parties will be informed of the termination of the research.

20 Final Report and Principle of Disclosure

Content of Final Report: Comprehensively and detailedly present all aspects of the research, including the research background, purpose, methods, detailed results, data analysis, safety assessment, conclusions and suggestions, etc., to ensure the scientificity and integrity of the report.

Principle of Disclosure: Clearly define the method and scope of disclosure of research results. In accordance with relevant laws, regulations, and ethical requirements, on the premise of protecting the privacy of subjects and research confidentiality, the research results will be disclosed through academic journal publication, academic conference reports, etc., to promote academic exchange and knowledge sharing. At the same time, the research results will be promptly reported to relevant parties such as the research sponsor, medical institutions, and subjects.

21 Responsibilities to be Undertaken by All Parties

21.1 Responsibilities of the Clinical Research Sponsor

Provide financial, material, and other resource support required for the research; participate in the design and review of the research protocol; supervise the progress and quality of the research to ensure that the research is carried out in accordance with the protocol and regulatory requirements; coordinate relations between all parties, solve problems arising during the research process; evaluate and apply and transform the research results.

21.2 Responsibilities of the Medical Institution Undertaking the Clinical Research

Provide research sites and necessary medical facilities; organize and train the research team to ensure that personnel have corresponding professional capabilities; implement the research in accordance with the research protocol, collect and sort out data; be responsible for the recruitment, screening, and treatment of subjects, and ensure the rights and interests and safety of subjects; cooperate with the research sponsor and regulatory authorities in inspections and audits.

22 Qualifications of the Research Center and Researchers

Qualifications of the Research Center

In terms of venue: The First Affiliated Hospital of Zhejiang University has the required venues for aerosol inhalation therapy in the pediatric outpatient department, which can meet the needs of a large number of pediatric patients for aerosol inhalation therapy. At

the same time, it is equipped with observation rooms, data storage rooms, and other spaces for conducting clinical research. It has advanced aerosol inhalation equipment and relevant medical monitoring instruments, such as equipment that can monitor the vital signs of pediatric patients in real time, ensuring the safety of pediatric patients during treatment and research. In terms of personnel: It has a team of medical and nursing staff with rich clinical experience in pediatrics, who can accurately diagnose and treat pediatric respiratory tract infections and other diseases, screen suitable pediatric patients for the research, and provide professional medical care for pediatric patients during the research process. Some nurses have received professional training in clown therapy, which has improved their cognitive level and acceptance attitude towards clown therapy, and they have the ability to apply clown therapy to practical outpatient nursing operations, ensuring the effective implementation of research intervention measures. In terms of research management: A complete quality control and quality assurance system has been established to ensure the scientificity and standardization of the research from multiple aspects such as personnel training, data management, and process supervision. For example, strict data management is implemented through paper file sealing and a complete electronic system storage, and access permissions are set to prevent data leakage and damage. It has a mature ethical review mechanism that can strictly review the research protocol to ensure that the research meets ethical requirements and protects the rights and interests of subjects. There are corresponding standardized processes from the handling of deviations from the research protocol, the provisions on protocol amendments, to the access to original data and data protection, ensuring the orderly conduct of the research.

Qualifications of Researchers

The principal investigator of this project is the head nurse of the Pediatric Outpatient Department of Yuhang Campus of the First Affiliated Hospital of Zhejiang University, who has profound experience in outpatient nursing for decades, and has served as the host and key participant in a number of clinical studies. She has unique insights into the application of clown care in outpatient nursing. The research team members include resident physicians and an experienced nursing team. At the same time, the Pediatric Outpatient Department of Yuhang Campus of the First Affiliated Hospital of Zhejiang University has an integrated outpatient layout and an independent and complete aerosol inhalation therapy room for children, with medical facilities that meet the research requirements; at the same time, the medical and nursing staff of the pediatric outpatient department participating in the research have many years of clinical and nursing experience, and have the experience and ability to carry out clinical research on modified clown care in pediatrics; and they have undergone complete modified clown therapy training before the official intervention, and take up their posts after passing the ability assessment. The medical process has a complete quality control and assurance system.

23 Reference

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