Comparison of high-flow nasal cannula and standard face mask oxygen therapy in children with moderate and severe bronchiolitis requiring oxygen therapy: A randomized controlled trial

Trial Registry NCT04245202

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CLINICAL STUDY PROTOCOL

Protocol Title	Comparison of high-flow nasal cannula and standard face mask oxygen therapy in children with moderate and severe bronchiolitis requiring oxygen therapy: A randomized controlled trial
Trial Registry	NCT04245202
Ethics Approval	17-2.1/18 by the Human Research Ethics Committee of EUMF
Co-ordinating center	Ege University Medical Faculty Pediatric Hospital

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PROTOCOL SIGNATURE PAGE

INVESTIGATORS

I admit to conducting this clinical study following the design and specific provisions of this protocol.

I understand that I may cease or suspend the study's enrolment at any time if it becomes necessary to protect the best interests of the study subjects. This study may be terminated by Ege University Medical Faculty, with or without cause.

I admit to manage or supervise this investigation directly and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

I will conduct the study under Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical, and scientific principles that justify medical research. The study will be conducted under all relevant laws and regulations relating to clinical studies and protecting patients.

I will ensure that the requirements relating to HREC review and approval are met. I will provide EUMF with any material which is supplied to the HREC for Ethical approval.

I admit to maintain adequate and accurate records and make those records available for inspection and audit according to relevant regulatory requirements.

I admit to directly disclose to the HREC any developments in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any modifications in the research without HREC approval, except where needed to provide study participants' safety.

Esen Demir, MD	Signature	Date
Aykut Eşki, MD	Signature	Date
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Caner Turan, MD	Signature	Date
Semiha Özgül	Signature	Date
Figen Gülen, MD	Signature	Date

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ABBREVIATIONS

AE	Adverse event
CI	Confidence interval
CPAP	Continue positive airway pressure
CRF	Case report form
CRS	Clinical respiratory score
ED	Emergency department
EUMF	Ege University Medical Faculty
FiO_2	Fraction of inspired oxygen
FLUA	Influenza A
HR	Heart rete
HREC	Human Research Ethics Committee
HFNCOT	High-flow nasal cannula oxygen treatment
HRV	Human rhinovirus
IMV	Invasive mechanical ventilation
IND	Investigational new drug
IPPV	Intermittent positive pressure ventilation
LOS	Length of hospital stay
LOOT	Length of oxygen treatment
MD	Mean difference
NICE	National Institute for Health and Clinical Excellence
mPCR	Multiplex polymerase chain reaction
PEEP	Positive end-expiratory pressure
PEWS	Pediatric early warning score
ICU	Intensive care unit
PPU	Pediatric Pulmonology Unit
RCT	Randomised controlled study
RR	Respiratory rate
RSV A/B	Respiratory syncytial virus
SO_2	Peripheral oxygen saturation
SOT	Standard oxygen treatment
St-FMOT	Standard face mask oxygen treatment
USA	United State of America
VBG	Venous blood gases

DEFINITIONS

Children

- ✓ In this study, is a child under the age of 24 months

Moderate and Severe bronchiolitis

- ✓ Defined as per CRS reported by Liu and colleagues (Appendices 1)
- ✓ Mild bronchiolitis: 0-4 point
- ✓ Moderate bronchiolitis: 5-8 point
- ✓ Severe bronchiolitis: 9-12 points

Supplemental Oxygen Requirement

- ✓ Peripheral capillary oxygen saturation (SpO_2) <92% while breathing room air

Standard Face Mask Oxygen Treatment (St-FMOT)

- ✓ The gas flow between 6.0 and 10.0 L/min

Rescue Treatment for St-FMOT

- ✓ First-tier, HFNCOT (2 L*kg/min) in the general ward
- ✓ Second-tier, admission to ICU for IMV

High-Flow Nasal Cannula Oxygen Treatment (HFNCOT)

- ✓ The gas flow at 2 L*kg/min or maximum 25 L/min

Rescue Treatment for HFNCOT

- ✓ Admission to ICU for IMV

STUDY SYNOPSIS

Title Comparison of high-flow nasal cannula and standard face mask oxygen therapy in children with moderate and severe bronchiolitis: A randomized controlled trial.

Trial Registry NCT04245202

Study Objectives

A. Primary Objectives

- ✓ To evaluate the effect on HR, RR, and CRS

1. The time it takes for HR to reach its normal range for age (hour)

2. The time it takes for RR to reach its normal range for age (hour)

3. The time it takes for CRS to regress from severe [scores of 9-12] to moderate [scores of 5-8] bronchiolitis, or from moderate [scores of 5-8] to mild [scores of 0-4] bronchiolitis (hour)

B. Secondary Objectives

- ✓ The decrease in HR compared with the baseline value
- ✓ The decrease in RR compared with the baseline value
- ✓ The decrease in CRS compared with the baseline score
- ✓ The effect on LOS and LOOT

C. Safety Objectives

1. The proportion of treatment failure at 4 hours or escalation of care

2. The proportion of admission to ICU for IMV

3. The proportion of adverse event

Rationale

- ✓ There has been insufficient RCT conducted on children with moderate and severe bronchiolitis requiring oxygen therapy in the general ward.

Study Population

A. Inclusion Criteria

- ✓ Children aged between 1 and 24 months with moderate and severe bronchiolitis requiring oxygen supplement.

B. Exclusion Criteria

- ✓ Children with mild bronchiolitis
- ✓ Those with not requiring oxygen therapy
- ✓ Those admitted to ICU for urgent IMV
- ✓ Those who received supplemental oxygen or HFNCOT at other facilities before arrival

- ✓ Those with known comorbidity (such as congenital heart disease, chronic lung disease, neuromuscular disease, metabolic disease, and immunocompromised)
- ✓ Those with a craniofacial malformation, an upper airway obstruction, pneumothorax, or nasal trauma

Study Design

- ✓ Open-label, two-arm, phase 4 randomized controlled trial

Sample size (each group)

- ✓ 55 in each group (HFNCOT and St-FMOT)

Investigational treatment:

- ✓ Fisher & Paykel MR850 with Optiflow™ Junior Nasal Cannula System

Control Group

- ✓ St-FMOT

Duration of Treatment

- ✓ From admission to EUMF Pediatric Hospital to at 15 days of post-discharge

Centre/s

- ✓ Single-center – EUMF/Pediatric Hospital

Statistical Methods

- ✓ Chi-Squared Test, Fisher's Exact Test, Mann-Whitney-U Test, Linear Mixed Model, Bruner Langer Method

SCHEDULE OF OBSERVATIONS AND PROCEDURES

Diagnosis bronchiolitis	Screening ED or PPU	1h	2h	4h	12h	24h	48h	72h	96h	Phone follow-up
Inclusion/Exclusion criteria	X									X**
Informed consent	X									
Medical History	X									
Physical exam	X	X	X	X	X	X	X	X	X	
Bodyweight and length	X									
Body temperature (℃)	X	X	X	X	X	X	X	X	X	
Heart rate (beat per min)†	X	X	X	X	X	X	X	X	X	
Respiratory rate (breath per min)†	X	X	X	X	X	X	X	X	X	
Arterial blood pressure (mmHg)†	X	X	X	X	X	X	X	X	X	
Clinical respiratory score†	X	X	X	X	X	X	X	X	X	
PCR	X									
Blood sample*	X									
VBG*	X			X						
Concomitant Medications	X	X	X	X	X	X	X	X	X	
Medical treatment‡	X	X	X	X	X	X	X	X	X	
Adverse event record	X	X	X	X	X	X	X	X	X	

If the patient was not discharged after 96 hours, the procedures mentioned above were continued.

†All parameters were measured during the resting of children.

*Samples were performed at any time if the clinician deemed it necessary.

**All children included in the study were phoned after 15 days post-discharge.

‡The clinician decides to use medical treatments such as beta2 agonist, systemic steroid, and hypertonic saline.

1. INTRODUCTION

1.1 Background

Acute bronchiolitis is globally one of the most considerable health burdens for children. It is estimated that approximately 34 million children under five years suffer from lower respiratory tract infection, with 3.4 million admissions to hospital and about 199,000 deaths per year, especially in developing countries.[1] In the seminar conducted by Florin and colleagues,[2] they reported that the role of medical therapies in children with bronchiolitis was investigated many times. Still, none of these treatments has shown efficacy. The NICE and AAP guidelines[3] recommend supportive therapies, including oxygen supplementation, respiratory support, and hydration. There are currently three ways of delivering oxygen to pediatric patients;

- ✓ Invasive mechanical ventilation, e.g., IPPV in critical care settings, or
- ✓ Non-invasive ventilation, e.g., CPAP predominantly in critical care settings, or
- ✓ Via nasal cannulae, mask, or head-box in ward settings.

High-flow nasal cannula oxygen treatment (HFNCOT) has become an increasingly widespread practice for managing bronchiolitis in recent years. Still, it is not recommended for treating bronchiolitis, according to the current NICE guidelines.[3] Although HFNCOT has been performed extensively for many years in the neonatal population, support for its safety and efficacy in children is still somewhat limited.[4] Previous observational and physiological studies suggested that HFNCOT may decrease respiratory effort, reduce intubation rates, and improve gas exchange.[5,6] Conversely, other reports showed that HFNCOT results in no significant changes in the RR, LOS, and the quality of ICU admission for IMV.[7–9] Although these reports represent an excellent progression in the daily clinical management of bronchiolitis and contribute valuable information to the literature, the major problem in this area is the lack of an adequate number of RCTs.

1.2 High-Flow Nasal Cannula Oxygen Delivery

Warmed humidified titrated medical air/oxygen is delivered through a non-sealing nasal cannula. The Optiflow™ system manufactured by Fisher & Paykel allows humidified flows of up to 25 L/min to be given. There is wide variation in the flows used and methods used to calculate them; however, flows are more remarkable than the standard maximum of 2 L/min. Those who exceed the patient's tidal volume are usually described as high flow. The effective delivery of high-flow oxygen at optimal humidity with dead space flushing and an element of positive airway pressure is expected to be beneficial in managing acute bronchiolitis.[5] Previously published studies showed that HFNCOT notably decreases in HR and RR relative to St-FMOT.[10–12] In contrast, it was illustrated that children

treated with HFNCOT had identical results in reducing the HR and RR compared with those treated with St-FMOT.[4,13] Otherwise, there are conflicting results in the literature regarding whether HFNCOT decreases CRS compared with SOT. Some prospective trials[14,15] did not show a considerable reduction when comparing between HFNCOT and SOT.

In contrast, others showed that HFNCOT is more effective in reducing CRS than SOT.[16,17] High-flow oxygen has been found to lower intubation rates and decrease the LOS for children in ICU settings.[6,13] The Schibler et al.[6] study followed the introduction of high-flow oxygen for bronchiolitis and found intubation rates dropped from 37% to 7% over four years as usage increased from use in 13% of patients to 66% by 2009. This RCT aims to address the gap in knowledge by studying the Fisher & Paykel® humidification system with Optiflow nasal prongs used in the care of children aged between 1 and 24 months with moderate and severe bronchiolitis requiring oxygen supplementation. Bronchiolitis was selected as there is a significant disease burden in this age group due to a variety of viral causative organisms, and no other effective medical treatment may confound results.

1.3 Study Design Rationale

This study includes a single site longitudinal observational cohort study [HREC (03.14.2017/No: 17-2.1/18)] nested within an open, two-arm randomized control trial HFNCOT compared to St-FMOT in the management of moderate and severe bronchiolitis requiring oxygen supplementation in children aged between 1 and 24 months.

2. STUDY OBJECTIVE

2.1 *Study Question*

In children aged between 1 and 24 months with moderate and severe bronchiolitis requiring oxygen supplementation, does HFNCOT delivered via a Fisher & Paykel MR850 humidifier with Optiflow Junior prongs compared to St-FMOT decrease HR, RR, and CRS during the acute admission?

2.2 *Primary Objectives*

- ✓ The median time it takes for HR to reach its normal range for age (hour)
- ✓ The median time it takes for RR to reach its normal range for age (hour)
- ✓ The median time it takes for CRS to regress from severe [scores of 9-12] to moderate [scores of 5-8] bronchiolitis, or from moderate [scores of 5-8] to mild [scores of 0-4] bronchiolitis (hour)

2.3 *Secondary Objectives*

- ✓ The mean difference in HR decreased compared with the baseline value from randomization to 96 hours (or to discharge)
- ✓ The mean difference in RR decreased compared with the baseline value from randomization to 96 hours (or to discharge)
- ✓ The mean difference in CRS regress compared with the baseline value from randomization to 96 hours (or to discharge)
- ✓ The length of hospital stays [from admission to discharge (hour)]
- ✓ The length of oxygen treatment [from admission to weaning to room air (hour)]

2.4 *Safety Objectives*

- ✓ The proportion of the treatment failure at 4 hours and escalation of care
- ✓ The proportion of the admission of ICU for IMV
- ✓ The proportion of adverse events

3. PATIENT POPULATION

3.1 Sample Size

Sample size calculations were done using a t-test on the primary outcome. Based on our pilot trial to obtain a power of 80% and alpha of 0.05 with a 1:1 proportion of control to intervention groups, the sample size yielded a total of 100 participants for CRS, 38 for RR, and 43 for HR. Given these sample sizes, we chose to recruit a minimum of 100 subjects. However, the final sample size was 110 patients, considering the study's longitudinal aspect (with a 10% attrition rate)

3.2 Inclusion Criteria

- ✓ Consented children aged between 1 and 24 months with a clinical diagnosis of moderate and severe bronchiolitis requiring oxygen supplementation presenting to the EUMF ED or PPU

3.3 Exclusion Criteria

- ✓ Children with mild bronchiolitis
- ✓ Those with not requiring oxygen supplement
- ✓ Those admitted to ICU for IMV
- ✓ Those who received supplemental oxygen or HFNCOT at other facilities before arrival

- ✓ Those with known comorbidity (such as congenital heart disease, chronic lung disease, neuromuscular disease, metabolic disease, and immunocompromised)
- ✓ Those with a craniofacial malformation, an upper airway obstruction, pneumothorax, or nasal trauma

3.4 Withdrawal Criteria

Consenting parents/legal guardians will be informed that they have the opportunity of withdrawing their infant/s from the study at any time with no explanation. Data generated by the drawn infant/s will be censored at the time of withdrawal. They will remain part of the study and will be analyzed by intention to treat and per-protocol approach for adherent patients to their protocol. Withdrawn children who require ongoing supplemental oxygen will receive the standard care for bronchiolitis, and no additional data will be collected after withdrawal.

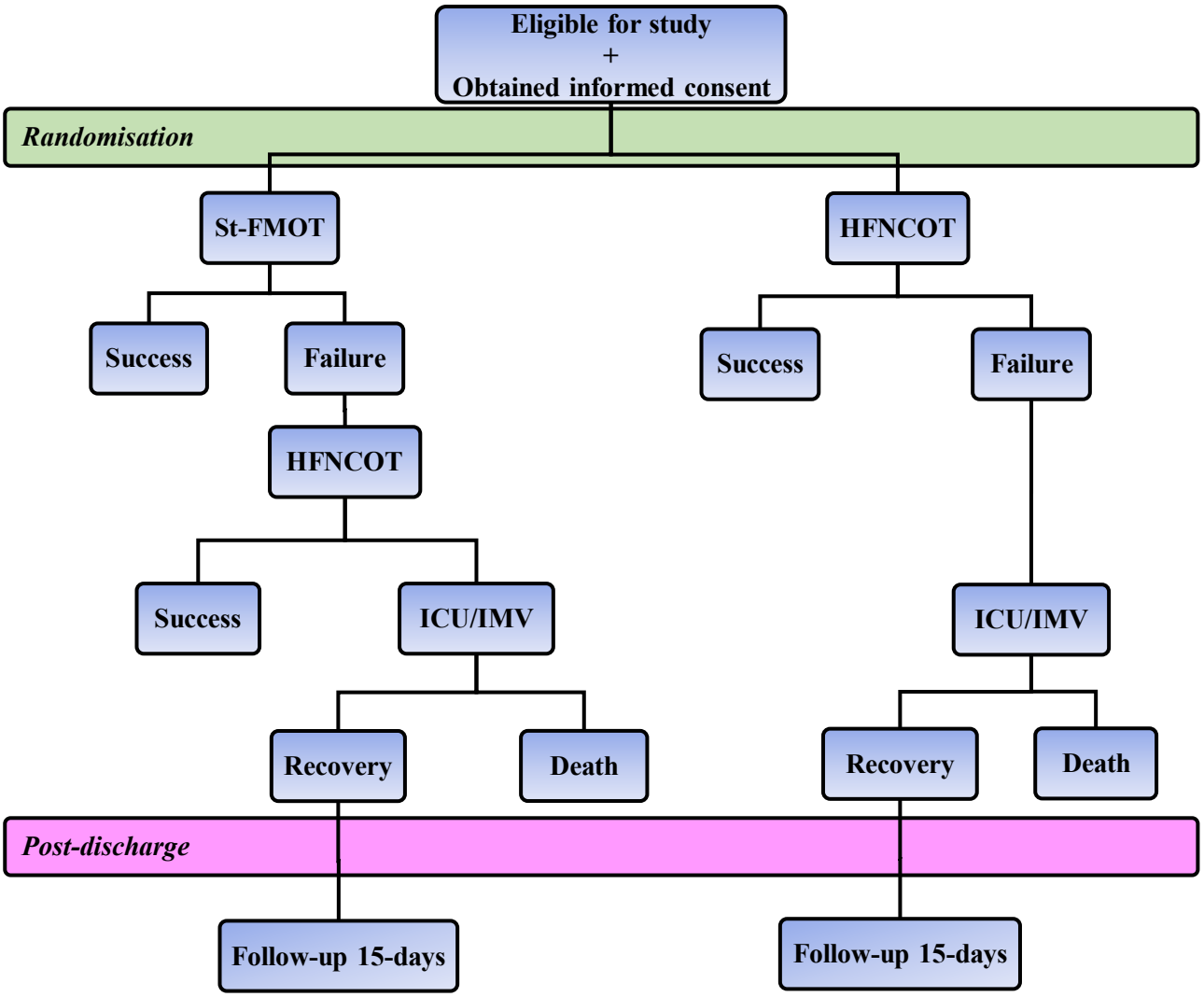
3.5 Participant selection

Children aged between 1 and 24 months with moderate and severe bronchiolitis requiring oxygen supplementation presenting to the EUMF ED or PPU with parents/legal guardians' informed consent will be randomized to experimental (HFNCOT) or standard oxygen therapy (St-FMOT).

3.6 Enrolment/Randomisation

During the clinical and eligibility assessment, and after obtaining written informed consent, we will apply nasal cannula wall oxygen at 2 L/min if a child needs supplemental oxygen. After written informed consent, the physician assigned the participants to either St-FMOT or HFNCOT by using simple randomization. On even-numbered days, patients received the St-FMOT, while on odd-numbered days received the HFNCOT. This trial is an open study because of the inability to blind clinicians, parents, or investigators to the two interventions.

3.7 Study Schema



4. STUDY PROCEDURES

4.1 Duration of Treatment

Treatment will continue from presentation in the ED or PPU to the transfer of care home to the parents/legal guardians.

4.2 Follow up

An investigator will attend telephone follow-up on the first working day after the infant is 15 days post-discharge. The parent/legal guardian will be contacted and asked 7 set survey questions to determine whether an adverse event under therapeutic goods administration requirements, and the treatment has been successful post-discharge (Appendix 2). The investigator will record any identified adverse events relating to the study devices, and the infant will be followed up further if it is clinically indicated.

5. STUDY TREATMENT PLAN

Study procedures will be individually documented in the case report form, available in ED and PPU. This trial will not introduce any invasive procedure or investigation not usually attended as standard care.

5.1 Investigational Treatments

Children will receive maximum therapy for 4 hours, which means that children receive at a flow rate of 2 L*kg/min, but we will let the FiO_2 reduce if children give an excellent response to the treatment. For children on St-FMOT, the FiO_2 will be reduced at any time if children provide a suitable response to the treatment, and the oxygen requirement will be controlled by turning off the flow every hour. Reducing the flow rate should be considered after 4 hours if the children's observations for HR, RR, retraction, SpO_2, feeding ability and tolerability, CRS, and PEWS stabilize or decrease.

- **Control Arm:** Children in the standard-therapy group received supplemental oxygen via a simple face mask, a range of 6-10 L/min, to maintain a SpO_2 level between 92-98%. Those who sustained the SpO_2 >92% in the ambient oxygen concentration were weaned off St-FMOT.

5.2 Experimental Arm: Children in the high-flow group received heated and humidified high-flow oxygen at a rate of 2 L*kg/min (maximum 25 L/min), using an age-appropriate Optiflow Junior cannula and Airvo 2 high-flow system (Fisher and Paykel Healthcare). The initial FiO_2 was set at

40%. The starting flow rate continued for a minimum of 4 hours. According to the patients' clinical response, the flow rate was decreased by 0.5 L*kg/min per hour. The FiO_2 was adjusted to obtain the SpO_2 levels between 92-98%. When the flow rate was at 0.5 L*kg/min, and the FiO_2 was equal to the ambient oxygen concentration, HFNCOT was stopped.

5.3 Treatment Failure and Escalation of Care

- ✓ The clinician will decide on the escalation of care at any time if the Pediatric Early Warning Score (PEWS) is ≥7 points (Appendices 3).
- ✓ Treatment failure at 4 hours is considered when at least three of the following five criteria are present for both groups.
  1. No change or an increase in HR relative to baseline
  2. No change or an increase in RR relative to baseline
  3. Persistence of low SpO_2 (<92%) in the three near independent measurements despite receiving FiO_2 >40% for HFNCOT and at a maximum 10 L/min for St-FMOT
  4. No change or an increase in CRS relative to baseline
  5. Blood pressure of carbon dioxide >60 mm/Hg
- ✓ Children with treatment failure at 4 hours or who need escalation of care will be treated as follows:

- **Control Arm:** Children who deteriorate on the St-FMOT will receive HFNCOT (at 2 L*kg/min) as a rescue treatment in the ward or be transferred to the ICU for IMV.
- **Experimental Arm:** Children who deteriorate on HFNCOT are admitted to the ICU for IMV as a rescue treatment.

5.4 Accountability of Investigational Products

Fisher & Paykel® will provide technical and educational support for the duration of the trial.

5.5 Concomitant Medications and Medical Treatments

Patients on asthma prevention or treatment medications are excluded from this trial due to the confounding effects of existing asthma and its required management. The clinician will use medical treatments such as beta-2 agonist, systemic steroid, and hypertonic saline.

6. SAFETY AND ADVERSE EVENT(S)

During the study, AEs, regardless of relatedness to the study device, will be reported on the AE page of the CRF (Appendices 4). All adverse reactions will be recorded in CRF and registered in the manuscript and clinicaltrial.gov. Open disclosure is paramount to the ongoing efficacy and ethical conduct of the trial, so parents/ legal guardians of participants experiencing AE are to be entirely briefed about the nature and effect of the AE. They are to be informed of likely consequences and alternative facts considered relevant following the standard disclosure duty.

6.1 Definitions and Classification

- ✓ **Adverse Event (AE)**

Any untoward medical occurrence in a patient who is administered a pharmaceutical product or device does not necessarily have a causal relationship with this treatment. An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product.

- ✓ **Suspected Adverse Reaction**

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For IND safety reporting purposes, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies less certainty about causality than an adverse reaction, which means any adverse event caused by a drug.

- ✓ **Adverse Reaction**

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

- ✓ **Unexpected Adverse Reaction**

An adverse event or suspected adverse reaction is considered as unexpected;

- ✓ Not listed in the investigator brochure or is not listed at the specificity or severity that has been observed
- ✓ An investigator brochure is not required or available
- ✓ Not consistent with the risk information described in the general research plan or elsewhere in the current application, as amended.
    - For example, under this definition, hepatic necrosis would be unexpected (under greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis.

- Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (under greater specificity) if the investigator brochure listed only cerebral vascular accidents.

✓ Unexpected as used in this definition, it also refers to adverse events or suspected adverse reactions mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the drug's pharmacological properties, but are not explicitly mentioned with the drug under investigation.

✓ **Serious Adverse Reaction**

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/congenital disability. Important medical events that may not result in death be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one outcome listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

✓ **Life-Threatening Adverse Reaction**

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

6.2 Follow-up 15 days safety assessment

On the initial business day after 15 days, post-discharge an investigator will contact the parent/legal guardian to ask about any AE which may have occurred following the infant's return home under any medical administrations' requirements.

7. STATISTICAL METHODS

7.1 Sample Size

Sample size calculations were done using a t-test on the primary outcome. Based on our pilot trial to obtain a power of 80% and alpha of 0.05 with a 1:1 proportion of control to intervention groups, the sample size yielded a total of 100 participants for CRS, 38 for RR, and 43 for HR. Given these sample sizes, we chose to recruit a minimum of 100 subjects. However, the final sample size was 110 patients, considering the study's longitudinal aspect (with a 10% attrition rate).

7.2 Data Analysis Methods

Categorical and continuous variables will be expressed as frequency (percentage) and median (IQR). Between groups, we will use the Mann-Whitney-U test for comparing the time of success for HR, RR, and CRS (SPSS Inc., version 25.0, Chicago, IL, USA). The longitudinal analysis part of the study will be performed non-parametrically with the Brunner Langer model for CRS conducted with a linear mixed model in a parametric way for HR and RR. Brunner Langer model (F1-LD-F1) is applied using web-based software (R software, version 3.5.2, package: nparLD, R Foundation for Statistical Computing, Vienna, Austria; http://r-project.org). The PROC MIXED procedure in the SAS software is used (Version 9.3; SAS Institute, Cary, NC, USA) to perform linear mixed models in which subjects will be included as random effects. When there is a significant interaction effect in the longitudinal analysis ($P < .1$), the time effect will be analyzed in each group, and groups will be compared at baseline and following time points (the baseline was subtracted from these time points). The proportions of the treatment failure at 4 hours, rescued patient, ICU admission, and AE are analyzed using Fisher's Exact test and given with odds ratio (OR) and 95% Confidence Interval (CI). We will perform intention-to-treat and per-protocol approaches for all outcomes. The time of success for HR, RR, and CRS outcomes will be analyzed using the PP approach. A 2-sided $P < .05$ defines statistical significance.

Statistical Analysis Plan

The biostatistician in the study, which has blinded to allocation, will perform the analysis. An interim analysis will not be performed. If substantial evidence of increased risk of harms ($p <0.001$) observed in both groups, stopping rules will be used with the biostatistician's advice. Intention to treat and per-protocol approaches will be conducted if necessary.

8. REGULATORY CONSIDERATIONS

8.1 Participant Consent

We will describe the study's nature and identified risks to the parents/legal guardians of possible recruits in a written document (Informed Volunteer Consent Form) and verbally. An Investigator will obtain written informed consent from each participant's parent/legal guardian before participation in the study under regulatory requirements.

8.2 Ethical Review

Before the study's commencement, the protocol and any amendment(s), Informed Consent Form, and Study Information Letter will be referred to the HREC of EUMF, and the Principal Investigator will keep the written approval. The approval will submit to the study by title, protocol number, and version date and provide details of the documents reviewed by the HREC. During the course, the Principal Investigator will submit to the HREC: amendments to the protocol, adverse event data, outcome, and administrative changes to the protocol. At the end of the study, the Principal Investigator will inform the HREC in writing that the course has ended. No further activities regarding this protocol will be conducted at the site. The Investigators will perform the above responsibilities under the Note for Guidance on Good Clinical Practice annotated with any adverse events comments and the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research, 2008.

8.3 Sponsor

The Director of the Scientific Research Projects of Ege University will approve the study. There is no other sponsor. Material for the trial is supplied under the Ministry of Health contract arrangements and loan items from Fisher and Paykel®.

9. STUDY ADMINISTRATION

9.1 Protocol Deviations

Protocol deviations will be reported in the publication of the results (CONSORT, 2010).

9.2 Monitoring and Auditing

Researchers will meet periodically to discuss the trial progress and review processes. The team will analyze adverse events as they are notified.

9.3 Study Documentation and Records Retention

Pediatric study documentation will be kept for a minimum of 22 years. Participant files and other essential documents (study protocol, signed informed consent forms, correspondence, and other documents relating to the study) will be securely archived in HREC of EUMF to meet these conditions. He or she must notify the Study Approver if the Researcher should want to assign the investigation documentation to another party or transfer to another position.

9.4 Publication and Use of Study Findings

Study findings will be submitted to various peer-reviewed, high impact journals depending on the report's focus, e.g., pediatric diagnostics, pathology, and respiratory disease.

10. Appendices

Appendices 1: Initial Assessment of Children According to CRS Reported by Liu and Colleagues.

	0 point	**1 point**	**2 point**	**3 point**
Respiratory rate				
<2 months		≤60	61–69	≥70
2-12 months		≤50	51–59	≥60
1-2 years		≤40	41–44	≥45
2-3 years		≤34	35–39	≥40
4-5 years		≤30	31–35	≥36
6-12 years		≤26	27–30	≥31
>12 years		≤23	24–27	≥28
Retraction	None	IC	IC and SS	IC, SS, and SC
Dyspnea				
0-2 years	Normal feeding, vocalizations, and activity	1 of the following: difficulty feeding; decreased vocalization; or agitated	2 of the following: difficulty feeding; decreased vocalization; or agitated	Stops feeding, no vocalizations, or drowsy or confused
2-4 years	Normal feeding, vocalizations, and play	1 of the following: decreased appetite, increased coughing after play, hyperactivity	2 of the following: decreased appetite, increased coughing after play, hyperactivity	Stops eating or drinking, stops playing, or drowsy or confused

≥5 years	Counts to ≥10 in one breath	Counts to 7–9 one breath	Counts to 4–6 in one breath	Counts to ≤3 in one breath
Wheeze	Normal breathing; no wheezing present	End-expiratory wheeze only	Expiratory wheeze only (greater than end-expiratory wheeze)	Inspiratory and expiratory wheeze or diminished breath sounds or both

Appendices 2: Parent Follow up Questionnaire

Infant's name		
Parent's name		
Study device	□ St-FMOT	□ HFNCOT
Has your child returned to his former health state? If the answer is no, give detail.	□ Yes	□ No
Was there any need for medical treatment after discharge? If the answer is no, give detail.	□ Yes	□ No
Are there any of the complaints as followed?	□ Fever □ Wheeze □ Cough □ Central cyanosis	□ Respiratory distress □ Shortness of breath □ Fast breathing
Has your child's nutritional status returned to the state it was in before hospitalization? **If the answer is no, give detail.**	□ Yes …….	□ No
Did you re-hospitalized after discharge? **If the answer is yes, give details about why?**	□ Yes …….	□ No
Is there anything else you would like to tell us about your child's health status?	Open-ended answer ……..	

Appendices 3: Pediatric Early Warning Score

	Age groups	**0**	**1**	**2**	**4**
Heart rate (bpm)	0 to < 3 months	> 110 and < 150	≥ 150 or ≤ 110	≥ 180 or ≤ 90	≥ 190 or ≤ 80
	3 to < 12 months	> 100 and < 150	≥ 150 or ≤ 100	≥ 170 or ≤ 80	≥ 180 or ≤ 70
	1-4 years	> 90 and < 120	≥ 120 or ≤ 90	≥ 150 or ≤ 70	≥ 170 or ≤ 60
	>4-12 years	> 70 and < 110	≥ 110 or ≤ 70	≥ 130 or ≤ 60	≥ 150 or ≤ 50
	>12 years	>60 and < 100	≥ 100 or ≤ 60	≥ 120 or ≤ 70	≥ 140 or ≤ 40
Systolic blood pressure (mmHg)	0 to < 3 months	> 60 and < 80	≥ 80 or ≤ 60	≥ 100 or ≤ 50	≥ 130 or ≤ 45
	3 to < 12 months	> 80 and < 100	≥ 100 or ≤ 80	≥ 120 or ≤ 70	≥ 150 or ≤ 60
	1-4 years	> 90 and < 110	≥ 110 or ≤ 90	≥ 125 or ≤ 75	≥ 160 or ≤ 65
	>4-12 years	> 90 and < 120	≥ 120 or ≤ 90	≥ 140 or ≤ 80	≥ 170 or ≤ 70
	>12 years	> 100 and < 130	≥ 130 or ≤ 100	≥ 150 or ≤ 85	≥ 190 or ≤ 75
Capillary refill time		< 3 seconds			≥ 3 seconds
Respiratory rate (breaths/minute)	0 to < 3 months	> 29 and < 61	≥ 61 or ≤ 29	≥ 81 or ≤ 19	≥ 91 or ≤ 15
	3 to < 12 months	> 24 and < 51	≥ 51 or ≤ 24	≥ 71 or ≤ 19	≥ 81 or ≤ 15
	1-4 years	> 19 and < 41	≥ 41 or ≤ 19	≥ 61 or ≤ 15	≥ 71 or ≤ 12
	>4-12 years	> 19 and < 31	≥ 31 or ≤ 19	≥ 41 or ≤ 14	≥ 51 or ≤ 10
	>12 years	> 11 and < 17	≥ 17 or ≤ 11	≥ 23 or ≤ 10	≥ 30 or ≤ 9
Respiratory effort		Normal	Mild increase	Moderate increase	Severe increase/any apnea
Oxygen saturation (%)		> 94	91 to 94	≤ 90	

Oxygen therapy		Room air		Any to < 4 L/minute or < 50%	≥ 4 L/minute or ≥ 50%

Appendices 4. Case report form

Case No and date							
Age (months)							
Gender	□ Male		□ Female				
Gestational age							
Body weight (gr/kg)							
Virus detected in RT-PCR	□ Yes		□ No				
If yes, which virus was detected							
Number of bronchiolitis	□ 1	□ 2	□ 3+				
Season	□ Winter		□ Autumn		□ Spring		□ Summer
Study device	□ St-FMOT		□ HFNCOT				
VARIABLES	Body temperature (℃)	Heart rate (bpm)	Respiratory rate (/min)	Arterial tension (mm/Hg)	SpO_2 (%)	Venous blood gases Ph-PCO_2	CRS
At first admission							
1 h							
2 h							
4 h							
12 h							
24 h							

2 d							
3 d							
4 d							
5 d							
6 d							
7 d							
8 d							
9 d							
10 d							
Length of oxygen requirement (h)							
Length of hospital stay (d)							
Beta2 mimetic use?	□ Yes	□ No					
If yes, how many days did it use? (d)							
Inhaler corticosteroid use?	□ Yes	□ No					
If yes, how many days did it use? (d)							
IV corticosteroid use?	□ Yes	□ No					
If yes, how many days did it use? (d)							
Inhaler hypertonic saline use?	□ Yes	□ No					
If yes, how many days did it use? (d)							
Did any complications occur?	□ Yes	□ No					

Which complications occurred?				
Transfer to ICU	□ Yes	□ No		
Did the treatment fail at the 4th hour?	□ Yes	□ No		
Laboratory findings at first admission	WBC:	ANC:	ALC:	CRP:

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