Clinical Protocol Template for ClinO, Chapter 4 «Other Clinical Trials»

Effect of nCPAP-NAVA-backup mode versus standard nCPAP mode on the reduction of severe apnea in preterm infants ≤ 28 weeks – a crossover trial

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorisation:	**Risk Category A** according to ClinO Art. 61. Both nCPAP mode and nCPAP-NAVA-backup mode are routinely used as noninvasive respiratory support modalities in neonatal care units
Study Registration:	Intended registry:ClinicalTrials.gov and FOPH HumRes portal (numbers to be added).
Sponsor:	Sébastien Fau, Division of Neonatal and Pediatric Intensive Care Geneva University Hospitals and University of Geneva Bd de la Cluse 30, 1205 Genève E-mail : sebastien.fau@hug.ch
Principal Investigator	Dimitra Papasavva, Division of Neonatal and Pediatric Intensive Care Geneva University Hospitals and University of Geneva Bd de la Cluse 30, 1205 Genève E-mail : dimitra.papasavva@hug.ch
Investigated Intervention:	nCPAP-NAVA-backup mode (neurally adjusted ventilatory assist), compared with standard nCPAP mode (nasal continuous positive airway pressure), in preterm infants born at ≤28 weeks of gestational age who are at risk of apnea of prematurity, to reduce the incidence of severe apnea.
Protocol ID	NAVAPNEA Trial
Version and Date:	Version 2 (dated 22/06/2026)

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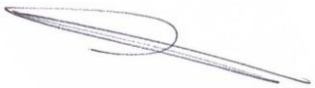
PROTOCOL SIGNATURE FORM

Study Title	*Effect of nCPAP-NAVA-backup mode Versus standard nCPAP mode on the reduction of severe apnea in Preterm infants ≤28 weeks – a crossover trial*
Study ID	NAVAPNEA Trial

The Sponsor has approved the protocol version 2.0 (dated 22/06/2026) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

Sponsor:

Name: *SEBASTIEN FAU*

Date: 22/06/2026 Signature: 

Principal Investigator:

Name: *DIMITRA PAPASAVVA*

Date: 22/06/2026

Signature:



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GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
AOP	*Apnea of prematurity*
BASEC	*Business Administration System for Ethical Committees*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
eCRF	*electronic Case Report Form*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
FOPH	*Federal Office of Public Health*
GCP	*Good Clinical Practice*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
NAVA-backup	*Neurally adjusted ventilatory assist Backup*
nCPAP	*Nasal continuous positive airway pressure*
NICU	*Neonatal intensive care unit*
NIPPV	*Non invasive Positive Pressure Ventilation*
NIV	*Non invasive ventilation*
NIV-NAVA	*Non-invasive ventilation-neurally adjusted ventilatory assist*
PDMS	*Patient data management system*
REDCap	Research Electronic Data Capture
SAE	*Serious Adverse Event*

1. STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Dr Sébastien Fau, Médecin Adjoint Division of Neonatal and Pediatric Intensive Care Bd de la Cluse 30, 1205 Genève Tel: 0795534911 E-mail : sebastien.fau@hug.ch
Study Title	*Effects of nCPAP-NAVA-backup mode versus standard nCPAP mode on the reduction of severe apnea in preterm infants ≤28 weeks – a crossover trial*
Short Title / Study ID	NAVAPNEA trial
Protocol Version and Date	Version 2.0 (dated 22/06/2026)
Study Registration	Intended registry: ClinicalTrials.gov and FOPH HumRes portal (numbers to be added).
Study Category and Rationale	According to ClinO Art. 61, this study is classified as a clinical trial with minimal risks and burdens (Category A). In accordance with ClinO Art. 2, minimal risks and burdens are defined as risks and burdens that do not exceed those encountered in routine clinical practice. The medical device used is a Servo N ventilator, approved for clinical use in Switzerland (CE0123), and will be used without any modification and within their intended indications. Both interventions investigated in this trail, nCPAP-NAVA-backup mode and nasal CPAP (nCPAP) mode are standard non-invasive respiratory support strategies that are used in Switzerland neonatal intensive care units (NICU) for the management of extremely preterm infants. Study participation does not require any additional invasive procedures beyond standard care. The crossover design involves switching between two routinely used ventilatory modes, which is common in clinical practice based on patient response. No additional risks beyond those inherent to standard non-invasive respiratory support are anticipated.
Background and Rationale	Apnea of prematurity (AOP) affects nearly all infants born at ≤28 weeks of gestation. Association with a significant hypoxemia and/or bradycardia define severe AOP. Current literature suggests an association between recurrent severe AOP and increased morbidity, notably regarding long-term neurodevelopmental outcomes, although a formal causal link remains to be established. Standard treatment of AOP includes caffeine and nCPAP, with invasive ventilation reserved for severe cases despite its associated pulmonary risks. The NAVA strategy relies on a specialized nasogastric probe equipped with electrodes designed to capture the electrical activity of the diaphragm (Edi signal), reflecting the infant's neural respiratory drive. In preterm infants, the NAVA strategy is used in the nCPAP-NAVA-backup mode : the infant receives standard nCPAP ; however, in the event of apnea, the ventilator automatically switches to a Pressure-Controlled Non-Invasive-Ventilation Backup mode until spontaneous breathing resumes. Although nCPAP-NAVA-backup mode is already used in neonatal intensive care units, its efficacy compared with standard nCPAP mode has not been evaluated in randomized studies. This study aims to assess whether nCPAP-NAVA-backup mode could reduce the rate of severe apnea in extremely preterm infants compared with standard nCPAP mode.

Risk / Benefit Assessment	Nasal CPAP (nCPAP) is the standard of care in neonatology, and nCPAP-NAVA-backup mode is increasingly used in neonatal intensive care units. This trial does not introduce any procedures or devices outside their approved clinical indications. The intervention does not exceed minimal risks or burdens compared with routine care, and all monitoring procedures are part of standard clinical practice.
Objective(s)	To determine whether nCPAP-NAVA-backup mode reduces the rate of severe apnea in extremely preterm infants ≤28 weeks' gestation compared with standard nCPAP mode.
Endpoint(s)	Primary Endpoint • Number of severe apnea episodes per 9-hour observation period, defined as an apnea associated with oxygen desaturation (SpO_2 < 85%) lasting ≥ 5 seconds and/or bradycardia (Heart rate (HR) < 100 bpm) lasting ≥ 5 seconds Secondary Endpoints • Number of isolated oxygen desaturation episodes (SpO_2 < 85% for ≥ 5 seconds, not associated with a severe apnea episode as defined above) per 9-hour observation period. • Number of isolated bradycardia episodes (HR < 100 bpm for ≥ 5 seconds, not associated with a severe apnea episode as defined above) per 9-hour observation period. • Number of hyperoxia episodes (SpO_2 > 94% for ≥ 5 seconds) per 9-hour observation period. • Percentage of time spent with SpO_2 < 85% over the 9-hour observation period. • Percentage of time spent with HR < 100 bpm over the 9-hour observation period. • Percentage of time spent with SpO_2 > 94% over the 9-hour observation period. • Number of apnea episodes requiring nurse intervention (tactile stimulation and/or increase in FiO_2) per 9-hour observation period. • Need for escalation of respiratory support during the observation period, defined as requirement for transition to non-invasive ventilation mode or endotracheal intubation. Reported as a binary outcome (yes/no) per observation period. • Infant comfort assessed using the EDIN score (Échelle Douleur Inconfort Nouveau-Né), recorded every 3 hours according to unit routine, yielding up to 3 measurements per 9-hour observation period. The mean EDIN score over each observation period will be used as the primary summary measure for this endpoint. • Gastrointestinal tolerance assessed every 3 hours according to unit routine, yielding up to 3 assessments per 9-hour observation period, and classified as follows: *Grade 1*: good tolerance — enteral feeding maintained at prescribed volume with no significant gastric residuals ; *Grade 2*: moderate intolerance — enteral feeding volume reduced due to gastric residuals or clinical concern ;*Grade 3*: poor tolerance — enteral feeding discontinued with initiation of continuous gastric suctioning. The worst grade recorded during each 9-hour observation period will be used as the summary measure for analysis.
Study Design	This is a prospective randomised, monocentric, cross-over clinical study comparing non-invasive ventilation using nCPAP-NAVA-backup mode and nCPAP mode in preterm infants born at ≤ 28 weeks of gestational age who present severe apnea

Inclusion- / Exclusion Criteria	The condition under investigation - apnea of prematurity - occurs almost exclusively in preterm infants, particularly those born at extremely low gestational ages. Consequently, the inclusion of these infants is scientifically necessary to evaluate the safety and effectiveness of those ventilatory strategies. <u>Inclusion Criteria</u> Infants must meet all of the following: • Born at ≤28 weeks gestational age • Currently receiving nCPAP mode as part of routine care • Receiving caffeine citrate at a maintenance dose of 10 mg/kg/day • An average of ≥1 severe apnea per hour over a 6-hour period (apnea associated with SpO_2<85% during ≥ 5 seconds and/or HR <100 bpm during ≥ 5 seconds) or an average of >2 severe apnea per hour over a 2-hour period • Written informed consent obtained from the legal representatives before inclusion. <u>Exclusion Criteria</u> Infants meeting any of the following will be excluded: • Major congenital anomalies (e.g., congenital diaphragmatic hernia, significant cardiac malformations) • Known genetic syndrome affecting respiratory function • Immediate indication for endotracheal intubation or noninvasive ventilation (NIV) • Parental refusal or withdrawal of consent • Previous inclusion in the study
Number of Participants with Rationale	Based on our clinical observations in a comparable population of extremely preterm infants, the mean number of severe apnea episodes under nCPAP is estimated at 18 ± 6 per 9-hour observation period. We hypothesised a clinically meaningful 25% relative reduction in the primary endpoint under nCPAP-NAVA-Back-up mode (from 18 to 13.5 episodes per 9-hour period), corresponding to an absolute mean within-subject difference of 4.5 episodes. The standard deviation of the within-subject paired difference (SD_diff) was estimated at 6 episodes, assuming a moderate intra-individual correlation of r = 0.50 between the two observation periods. This yields a standardised effect size of Cohen's *d*z of 0.75 (4.5 / 6). Using a two-sided paired t-test with a type I error rate of α = 0.05 and a statistical power of 90% (1 − β = 0.90), the minimum required sample size is 21 infants : To account for the discrete and potentially non-Gaussian nature of count data, and for an anticipated dropout or missing data rate of 15%, the sample size was inflated to 25 infants.
Study Intervention	Each infant will receive both interventions in a randomized order, serving as their own control. The total duration of the intervention will be 24h. We chose a 24-hour period as the neonate's respiratory status may vary from one day to another, to avoid influencing the study. Each intervention period will last approximately 12 hours. A washout period will be included between intervention periods to minimize potential carryover effects. Total monitoring: 24 hours per patient Crossover design: Two non-invasive ventilation modes alternating every 12 hours Randomized sequences to avoid order effects: • Sequence A: nCPAP mode → nCPAP-NAVA-backup mode • Sequence B: nCPAP-NAVA-backup mode → nCPAP mode Each intervention period: 12 hours Washout period: 3 hours at the start of each period during mode change

Control Intervention	-
Study procedures	**Day 0-X** • Verification of inclusion and exclusion criteria • Written informed consent must be presented to the legal representative. **Day X** • Verification of inclusion and exclusion criteria • Collection of baseline demographic and clinical data • Written consent obtained from the legal representative. **Study Period (24 hours)** • Patients will be randomly assigned to one of two sequences to minimize crossover order effects: - **Sequence A:** nCPAP mode → nCPAP-NAVA-backup mode - **Sequence B:** nCPAP-NAVA-backup mode → nCPAP mode Each of the two intervention periods lasts 12 hours A 3-hour washout period will be observed at the start of each intervention period (during each change of ventilation mode) **End of Study (Hour 24)** • Completion of data collection • Ventilatory management will continue according to clinical judgment
Study Duration and Schedule	The total duration of the main investigational plan is estimated to be **24 months**. Following completion of the main investigational phase, an additional **12 months** will be dedicated to data cleaning, statistical analysis, manuscript preparation, and publication of the study results. Planned 11/2026 of First-Participant-In Planned 11/2028 of Last-Participant-Out **Planned completion of study reporting and publication activities:** 11/2029
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Study Center(s)	Division of Neonatal and Pediatric Intensive Care Geneva University Hospitals and University of Geneva
Statistical Considerations	Continuous data will be expressed as median [interquartile range] and categorical data as counts and percentages. Endpoints will be test as within-subject difference. Continuous data will be analysed using a Wilcoxon signed-rank test (non-parametric paired test), appropriate for the discrete and potentially non-Gaussian nature of count data in small samples. Binary data will be analyzed using McNemar's test. A potential period effect (systematic difference between the first and second observation period regardless of treatment) will be explored descriptively by comparing outcomes according to the allocated sequence. All analyses will be conducted on a per-protocol basis as the primary analysis, and on an intention-to-treat basis as a sensitivity analysis. A two-sided p-value < 0.05 will be considered statistically significant.
Data privacy	All collected data will be coded and stored securely, in accordance with Swiss data protection regulations. Only authorized study investigators will have access to identifiable data.
Ethical consideration	This study addresses an important gap in the management of apnea of prematurity. Although nCPAP-NAVA-backup mode is widely used in neonatal intensive care, there is limited controlled evidence of effectiveness in reducing clinically significant apnea events in extremely preterm infants compared with nCPAP mode. Generating high quality data on this question has direct clinical relevance and may improve respiratory support strategies for this vulnerable population. The cross-over design is scientifically justified because each infant serves as their own control, reducing inter-individual variability and increasing statistical power in a small population. Alternating 12-hour periods with washout phases allows a fair comparison between the two ventilation modes under similar clinical conditions. A 24-hour period was chosen as the neonate's respiratory status may vary from one day to another, to avoid influencing the study. Continuous automated monitoring ensures objective, high- resolution data collection and minimizes observer bias. The risks of participation are minimal and do not exceed routine neonatal care. Both interventions are standard noninvasive ventilation modalities already used in daily practice. No additional invasive procedures or blood sampling are required. Continuous monitoring ensures immediate detection of any adverse events, and infants can be withdrawn at any sign of intolerance. Potential benefits include improved respiratory stability, fewer apnea related desaturation and bradycardia episodes, and reduced need for escalation of respiratory support. The study includes vulnerable participants, specifically preterm infants who are incapable of judgment. Their inclusion is scientifically necessary because apnea of prematurity occurs exclusively in this population, and the research question cannot be answered in non vulnerable groups. Parents or legal representatives provide informed consent, and all interventions remain within the boundaries of standard clinical care, ensuring ethical acceptability.
GCP Statement	This study will be conducted in full compliance with the approved protocol, the current version of the Declaration of Helsinki, the International Council for Harmonization – Good Clinical Practice (ICHGCP) guidelines, the Swiss Human Research Act (HRA), and all other applicable local legal and regulatory requirement.

2. BACKGROUND AND RATIONALE

Apnea of prematurity (AOP) is a frequent condition in preterm infants and represents a clinical manifestation of an immature control of breathing. Its incidence is inversely related to gestational age and affects nearly all infants born before 28 weeks' gestation (9,10). AOP is characterized by recurrent respiratory pauses that may be central, obstructive, or mixed, and are frequently associated with oxygen desaturation and bradycardia. There is currently no consensus regarding the duration of apnea that should be considered pathological, nor agreement on the degree of oxygen desaturation or the severity of bradycardia required to define a clinically significant apnea episode conventionally named severe apnea (11,12). The pathophysiology of AOP is multifactorial and related to immaturity of the central respiratory control system, altered chemosensitivity to carbon dioxide and hypoxia and reduced pulmonary oxygen reserves due to a low lung functional residual capacity (13,14). These factors predispose preterm infants to intermittent hypoxemia during respiratory pauses. Clinically significant apnea-related events associated with desaturation, bradycardia, increased need for respiratory support may occur repeatedly. Recurrent exposure to intermittent hypoxia has been associated with neonatal morbidity and adverse neurodevelopmental outcomes, although causal relationships are difficult to establish due to confounding factors (15,16,17,18).

Standard management of AOP includes methylxanthine therapy, particularly caffeine, that stimulates respiration through antagonism of adenosine receptors, and non-invasive respiratory support, most commonly nasal continuous positive airway pressure (nCPAP). All preterm infants with a gestational age ≤ 28 weeks routinely receive such respiratory support 24 hours per day, irrespective of the presence of apnea, as part of standard clinical care. This approach aims to maintain lung recruitment, improve oxygenation, reduce apnea episodes, and decrease the work of breathing, while avoiding invasive mechanical ventilation (13,14).

The NAVA strategy relies on a specialized nasogastric probe equipped with electrodes designed to capture the electrical activity of the diaphragm (Edi signal), reflecting the infant's neural respiratory drive. In preterm infants, the NAVA strategy can be used either in nCPAP (nCPAP-NAVA-backup mode) or in NIV (NIV-NAVA mode). In nCPAP-NAVA-backup mode, the infant receives standard nCPAP ; however, in the event of apnea, the ventilator automatically switches to a Pressure-Controlled NIV Backup mode until spontaneous breathing resumes. In NIV-NAVA mode, the infant receives proportional pressure support for each spontaneous breath, while the ventilator provides the same Backup function during apnea episodes.

The majority of studies currently available in the literature focus on NIV-NAVA mode, whereas clinical data regarding the nCPAP-NAVA-backup mode remain more limited.

Several studies, including systematic reviews and randomized controlled trials, have demonstrated that NIV-NAVA mode improves patient–ventilator synchrony and may reduce treatment failure compared to nCPAP mode or Non Invasive Positive Pressure Ventilation (NIPPV mode), particularly post-extubation (19, 20). NIV-NAVA mode has been shown to reduce inspiratory pressures, oxygen requirements, and the frequency of desaturation events (21,22). However, the certainty of evidence remains low.

There is a lack of randomized studies specifically evaluating nCPAP-NAVA-backup mode on the reduction of severe apnea of prematurity (22). Despite its increasing use in neonatal intensive care units, nCPAP-NAVA-backup mode is currently applied in clinical practice for apnea management without a robust evidence base. Therefore, a controlled and systematic evaluation of its effects is scientifically justified.

The research question of this study is whether nCPAP-NAVA-backup mode reduces the rate of severe apnea compared to nCPAP in extremely preterm infants. This question addresses an important unmet clinical need in a vulnerable population and focuses on clinically meaningful outcomes. Equivalent knowledge cannot be obtained through non-human research or observational data alone, as the intervention requires real-time physiological interaction with the neonatal respiratory control system.

This study is designed to generate new, generalizable scientific knowledge by providing the first prospective randomized cross-over trial evaluating the effect of nCPAP-NAVA-backup mode on clinically significant consequences of apnea of prematurity. The findings will inform evidence-based clinical practice, support rational use of advanced ventilation modes, and contribute to the design of future multicenter trials.

The intervention consists of nCPAP-NAVA-backup mode delivered via an Edi catheter. Ventilator settings (including PEEP and backup parameters) are adjusted according to unit standards and clinical assessment. Participants will undergo a cross-over comparison between nCPAP-NAVA-backup mode and standard nCPAP mode, with predefined wash-out periods, under continuous cardiorespiratory monitoring.

Sex and gender dimensions are not considered relevant to this study, as apnea of prematurity is primarily determined by gestational age and neurological immaturity, with no established sex- or gender-specific differences affecting the intervention or outcomes.

According to ClinO Art. 61, this study is categorized as a Category A study (minimal risk and minimal burden). The intervention uses a CE-marked medical device approved for neonatal use (ServoN ventilator) and already applied in routine clinical practice. All procedures, including ventilatory support, cardiorespiratory monitoring, and caffeine treatment, are part of standard neonatal care. The additional burden is limited to the study design (cross-over and data collection), without deviation from accepted clinical standards. No additional risks beyond those inherent to standard non-invasive respiratory support are anticipated. Therefore, the study fulfills the criteria for minimal risk and burden as defined in ClinO Art. 2

3. STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and primary objective

Our hypothesis is that nCPAP-NAVA-backup mode reduces the frequency of severe apnea (clinically significant apnea events) in extremely preterm infants (≤28 weeks gestation) compared with standard nCPAP mode. Because nCPAP-NAVA-backup mode delivers automatic backup pressure-controlled ventilation during apnea, it is expected to improve respiratory stability and reduce desaturation and bradycardia episodes.

Our objective is to determine whether nCPAP-NAVA-backup mode reduces the rate of severe apneas compared with nCPAP mode in preterm infants ≤28 weeks' gestation.

3.2 Primary and secondary endpoints

Data collection

All physiological data (SpO_2, heart rate, respiratory rate, FiO_2) will be continuously recorded and extracted from bedside monitors (intellivue MX 800 ®, Philips, Eindhoven, Netherlands) throughout the entire study period. Cardiorespiratory events will be automatically detected by the monitoring system and systematically verified by manual review of monitor waveforms and

diaphragmatic electrical activity (EAdi) signal. Clinical decisions regarding gastrointestinal tolerance and escalation of respiratory support will be prospectively documented in the medical records. All run-in periods (3 hours preceding each observation period) will be considered as washout period and excluded from all analyses.

Outcomes will be analyzed by time blocks, comparing the first 9 hours with the second 9 hours.

Primary Endpoint

Number of severe apnea episodes per 9-hour observation period, defined as an apnea associated with oxygen desaturation (SpO_2 < 85%) lasting ≥ 5 seconds and/or bradycardia (HR < 100 bpm) lasting ≥ 5 seconds

Secondary Endpoints

- Number of isolated oxygen desaturation episodes (SpO_2 < 85% for ≥ 5 seconds, not associated with a severe apnea episode as defined above) per 9-hour observation period.
- Number of isolated bradycardia episodes (HR < 100 bpm for ≥ 5 seconds, not associated with a severe apnea episode as defined above) per 9-hour observation period.
- Number of hyperoxia episodes (SpO_2 > 94% for ≥ 5 seconds) per 9-hour observation period.
- Percentage of time spent with SpO_2 < 85% over the 9-hour observation period.
- Percentage of time spent with HR < 100 bpm over the 9-hour observation period.
- Percentage of time spent with SpO_2 > 94% over the 9-hour observation period.
- Number of apnea episodes requiring nurse intervention (tactile stimulation and/or increase in FiO_2) per 9-hour observation period.
- Need for escalation of respiratory support during the observation period, defined as requirement for transition to non-invasive ventilation mode or endotracheal intubation. Reported as a binary outcome (yes/no) per observation period.
- Infant comfort assessed using the EDIN score (Échelle Douleur Inconfort Nouveau-Né), recorded every 3 hours according to unit routine, yielding up to 3 measurements per 9-hour observation period. The mean EDIN score over each observation period will be used as the primary summary measure for this endpoint.
- Gastrointestinal tolerance assessed every 3 hours according to unit routine, yielding up to 3 assessments per 9-hour observation period, and classified as follows: *Grade 1*: good tolerance — enteral feeding maintained at prescribed volume with no significant gastric residuals ; *Grade 2*: moderate intolerance — enteral feeding volume reduced due to gastric residuals or clinical concern ;*Grade 3*: poor tolerance — enteral feeding discontinued with initiation of continuous gastric suctioning. The worst grade recorded during each 9-hour observation period will be used as the summary measure for analysis.

Baseline Factors

The following baseline characteristics may influence outcomes and will be recorded:

- Gestational age at birth
- Postnatal age at the time of enrollment
- Birth weight
- Severity of the underlying respiratory disease (e.g., oxygen requirement)
- Exposure to antenatal corticosteroids
- Postnatal corticosteroid treatment
- Surfactant administration

3.3 Study design

This is a prospective randomized monocentric, open label, crossover clinical trial conducted in the neonatal intensive care unit of the University Hospitals of Geneva.

Each participant undergoes two consecutive 12-hour intervention periods (total duration of 24 hours), alternating between nCPAP mode and nCPAP-NAVA-backup mode using a Servo N ventilator. A 3-hour washout period is included at the beginning of each new modality to minimize carryover effects.

Randomization

Participants are randomized into one of two sequences to control for order effects:

- Sequence A: nCPAP mode→ nCPAP-NAVA-backup mode
- Sequence B: nCPAP-NAVA-backup mode → nCPAP mode

Participants will be randomly assigned to one of two treatment sequences (AB or BA) in a 1:1 ratio according to a crossover design. To ensure numerical balance between groups while preventing selection bias, the randomization sequence will be computer-generated using the validated **REDCap (Research Electronic Data Capture)** system, employing permuted blocks of variable sizes (4 and 6). This procedure will ensure that the sequence of allocation remains unpredictable to both the participants and the clinical staff throughout the inclusion period.

Blinding

The study is open-label due to the nature of the interventions; blinding of the clinical team is not feasible as the ventilation modes require distinct settings and monitoring. Investigators may also act as attending physicians and be involved in patient care. However, to minimize the risk of assessment bias, most outcomes are based on objective data automatically extracted from monitor and ventilator records. Furthermore, the statistical analysis will be conducted by a blinded investigator, unaware of the treatment sequence allocation.

Bias Minimization

- Crossover design ensures that each infant serves as its own control.
- Study duration minimizes bias related to variability in the infant's respiratory status.
- Randomized sequence allocation minimizes order effects.
- Objective, automated data collection reduces assessement bias.

3.4 Study Intervention

As mentioned the study intervention consists of nCPAP-NAVA-backup mode facilitated by an orogastric feeding tube measuring the electrical activity of the diaphragm (Edi catheter). The Edi catheter will also serve as the feeding tube; no additional feeding tube will be used in participating patients.

Eligible participants are preterm infants receiving standard nCPAP mode support and treated with caffeine at the maximal standard dose used in the unit (10 mg/kg/day), who present recurrent clinically significant apnea events according to unit standards.

After inclusion in the study, an Edi catheter will be inserted according to the manufacturer's instructions and routine clinical practice. Participants will be randomized to one of two ventilation sequences in a randomized cross-over design. Each participant will receive both non-invasive ventilation modes (nCPAP-NAVA-backup mode and nCPAP mode) during a total observation period of 24 hours using a Servo N ventilator. Ventilation modes will be alternated every 12 hours.

A washout period of 3-hour will be observed at the beginning of each intervention period following a change in ventilation mode, to minimize potential carryover effects.

Ventilator settings, including positive end-expiratory pressure (PEEP), and back-up ventilation parameters, will be set and adjusted according to unit standards and routine clinical assessment. During the intervention PEEP will be kept constant throughout all study periods and will not be modified during the intervention phases in order to avoid confounding effects on respiratory outcomes. No experimental settings or deviations from standard clinical practice will be applied. Throughout the study period, participants will be continuously monitored in accordance with standard neonatal intensive care unit practice. Recorded parameters include oxygen saturation (SpO_2), heart rate (HR), respiratory rate (RR), and transcutaneous carbon dioxide ($TcpCO_2$). At the end of the 24-hour study period, non-invasive respiratory support will be continued using the ventilation mode deemed most appropriate by medical team in charge of the patient, independently of study allocation.

Both ventilation modes used in this study are established and routinely used in neonatal intensive care. Participation in the study does not delay, replace, or restrict any clinically indicated treatment.

3.5 Patient and Public Involvement

No formal patient or public involvement was conducted in the design of this study due to the neonatal population and the specialized nature of the intervention.
However:

- The research question arises directly from clinical challenges observed by neonatal care teams.
- The outcomes selected reflect clinically meaningful events that impact infant stability and parental experience.

4. STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

Study Population

The study population consists of preterm infants born at ≤28 weeks of gestational age who are hospitalized in the neonatal intensive care unit of Geneva University Hospital and currently managed with nasal CPAP (nCPAP), a noninvasive respiratory support mode. These infants represent the most affected group by apnea of prematurity, with almost universal occurrence of clinically significant events. Because apnea of prematurity is exclusive to preterm infants, the inclusion of this vulnerable population is scientifically necessary and ethically justified. Moreover, the interventions studied (nCPAP mode and nCPAP-NAVA-backup mode) are standard of care treatments already used in this population. The study does not introduce any additional procedures beyond routine clinical care. Legal representatives (parents or guardians) provide informed consent.
Sex and gender are not expected to influence the incidence, severity, or treatment response of AOP. Both male and female infants will be included without restriction.

Inclusion Criteria

Infants must meet all of the following:

- Born at ≤28 weeks gestational age.
- Currently receiving nCPAP mode as part of routine care.
- Receiving caffeine citrate at a maintenance dose of 10 mg/kg/day.

- An average of ≥1 severe apnea per hour over a 6-hour period (apnea associated with SpO_2<85% during ≥ 5 seconds and/or HR <100 bpm during ≥ 5 seconds) or an average of >2 severe apnea per hour over a 2-hour period
- Written informed consent obtained from the legal representatives before inclusion.

Exclusion Criteria

Infants meeting any of the following will be excluded:

- Major congenital anomalies (e.g., congenital diaphragmatic hernia, significant cardiac malformations).
- Known genetic syndrome affecting respiratory function.
- Immediate indication for endotracheal intubation or NIV-mode.
- Parental refusal or withdrawal of consent.
- Previous inclusion in the study

4.2 Recruitment, Screening and Informed Consent Procedure

Recruitment Location and Process

Recruitment will take place in the Neonatal Intensive Care Unit of the University hospitals of Geneva. Eligible infants will be identified by the investigator team.
No advertisements, flyers, or external recruitment tools will be used.

Screening Procedures

Screening includes:

- Review of gestational age.
- Verification of current respiratory support (nCPAP mode).
- Confirmation of caffeine therapy.
- Assessment of apnea frequency and severity using monitor data.
- Evaluation of clinical stability for participation (no need of immediate endotracheal intubation or NIV-mode).

All screening procedures are part of routine clinical care.

Informed Consent Procedure

The informed consent process follows HRA Art. 7, 16–18 and ClinO Art. 7–9.

- Upon the child's admission to intensive care, legal representatives (parents or guardians) would receive advance information about the study, both written and oral, with no obligation to respond at that stage. If the child subsequently meets the inclusion criteria, parents who have already been informed could then give their consent without any additional waiting period. In cases where the parents have not yet been informed when the criteria are met, the information would be provided to them and sufficient reflection time would be granted, adapted to the situation.
- Participation is voluntary, and refusal does not affect clinical care.
- Consent is documented using the approved consent form, signed by both the legal representative and the investigator.
- A copy of the signed form is provided to the parents and another is stored in the study file.
- The consent process is documented in the infant’s medical record.

Special Considerations for Vulnerable Participants

- Only legal representatives may consent.
- No genetic testing or procedures with incidental findings are included.
- No emergency inclusion procedures are required.

The investigator or the sponsor notifies the Ethics Committee of the first study participant, in accordance with art 62 lit. c ClinO, resp. art 38 ClinO. If the first participating person is not included

in the trial within two years following the issuance of the authorization, the trial is considered interrupted (art. 23a ClinO). The clinical trial may not be started until an application for an extension of the time limit has been approved. The application for the extension is submitted to the CEC as a substantial amendment.

4.3 Study Procedures

Each enrolled infant will participate in the study for a total of 24 hours.

No additional follow-up is required after the 24-hour intervention period

Recruitment period: approximately 24 months, depending on the number of eligible infants admitted to the NICU

Total study duration: 24 months from first participant in to last participant out, plus time for data cleaning, analysis, and reporting (estimated additional 12 months). Total of 36 months

Planned Intervention

The study compares two standard noninvasive ventilation modalities used in the management of apnea of prematurity:

A. nCPAP mode: Nasal Continuous Positive Airway Pressure

- Standard nasal CPAP mode, classicaly use in our unit
- Using a Servo N Ventilator
- Delivered via nasal prongs or mask through a double limb circuit
- PEEP and FiO_2 will be managed according to standard clinical practice
- No additional procedures beyond standard care

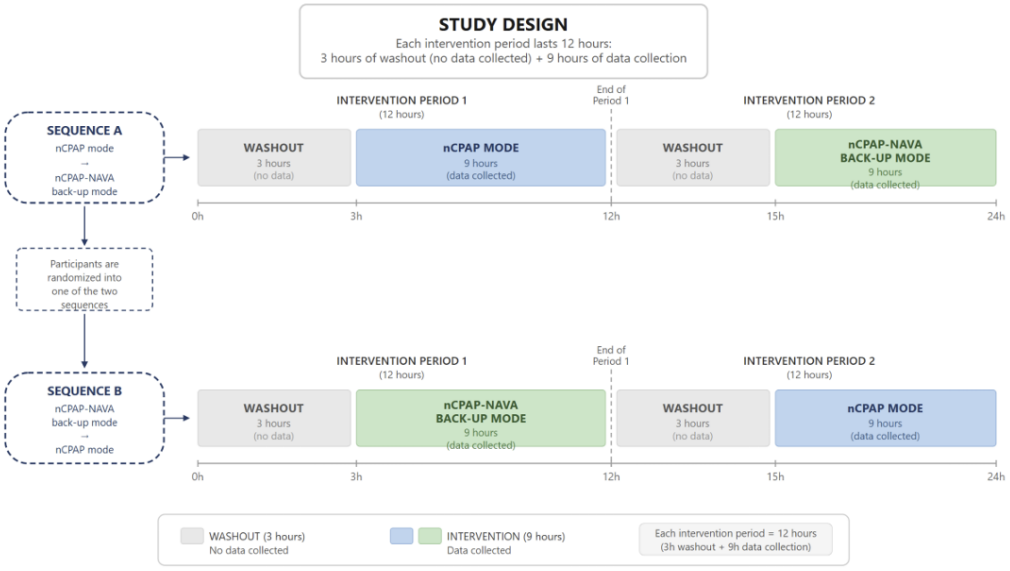
B. nCPAP-NAVA-backup mode: nCPAP with NAVA-backup mode

- Outside of apnea episodes, standard nCPAP is delivered using the same ventilator, circuit, patient interface and settings
- Electrical Activity of the Diaphragm (Edi signal) is monitored via a specific orogastric feeding tube measuring continuously the electrical activity of the diaphragm (NAVA Edi catheter). The Edi signal allows for a highly reliable diagnosis of apnea episodes.
- The Backup function consists of pressure support ventilation triggered in case of an apnea duration exceeding the pre-set apnea time. The backup parameters (respiratory rate, inspiratory time and inspiratory pressure) set according to unit standards

Crossover structure

Each infant undergoes two 12-hour intervention periods (3 hours of washout without collecting data and 9 hours of collecting data), alternating between nCPAP mode and nCPAP-NAVA-backup mode:

- **Sequence A:** nCPAP mode → nCPAP-NAVA-backup mode
- **Sequence B:** nCPAP-NAVA-backup mode → nCPAP mode



Washout periods

At the beginning of each new ventilation mode, a 3-hour washout period is observed. Data from washout periods are recorded but excluded from primary analysis to minimize carryover effects.

No additional invasive or noninvasive procedures are required beyond routine clinical care.

Continuous monitoring

The following parameters are continuously monitored and automatically recorded via the Patient Data Management System (PDMS):

- Heart rate
- Oxygen saturation (SpO_2)
- Respiratory rate
- Ventilator parameters (PEEP, backup activation, backup parameters)
- Desaturation and bradycardia episodes
- Duration of desaturation et bradycardia episodes
- Transcutaneous carbon dioxide ($TcCO_2$) measurements

Clinical documentation

- Apnea events requiring stimulation
- Comfort scoring using a validated neonatal comfort scale (e.g.EDIN) every 3 hours
- Changes on the volume of enteral feeding. Decision will be made by the medical and nursing team responsible for the patient, according to the unit's standard practice. There is no established algorithm. The decision is based on the presence of gastric distension, the volume and appearance of gastric residuals, and the patient's comfort and general condition.
- Need for continuous gastric suctioning. Decision will be made by the medical and nursing team responsible for the patient, according to the unit's standard practice. There is no established algorithm. The decision is based on the presence of gastric distension, the volume and appearance of gastric residuals, and the patient's comfort and general condition.
- Need for escalation of respiratory support to mechanical ventilation (NIV mode via a mask or mechanical ventilation via an endotracheal tube)

Material sampled

No biological samples (blood, urine, saliva, etc.) are collected or stored for this study.

Schedule of Assessments

A complete Schedule of Assessments is provided in Appendix 1, including:

- Timing of each intervention period (T0–T24h)
- Washout phases
- Continuous monitoring parameters
- Comfort scoring time points
- Documentation of apnea, desaturation, and bradycardia events
- Data extraction from PDMS

Expected Biases and Measures to Reduce Them

1. Clinical variability over time
    - Infant respiratory stability may change during the 24 hours period.
2. Observer bias
    - Manual documentation of stimulation events may vary between caregivers.
3. Handling differences
    - Variability in caregiving practices may influence apnea frequency.

Measures to reduce bias

- Randomized crossover design: each infant serves as their own control, minimizing interindividual variability.
- Study duration minimizes bias related to variability in the infant's respiratory status.
- Random allocation to Sequence A or B: balances order effects.
- Objective automated data capture: continuous PDMS recording reduces observer bias.
- Standardized definitions: clear criteria for apnea, desaturation, and bradycardia events.
- Consistent clinical environment: all procedures occur in the same NICU with standardized care protocols.

4.4 Withdrawal and discontinuation

A participant will be withdrawn from the study intervention in any of the following situations:

- **Withdrawal of consent** by the legal representatives at any time, without need for justification.
- **Clinical deterioration** requiring either intubation and invasive ventilation or non-invasive ventilation
- **Serious adverse event** judged to be possibly, probably, or definitely related to the study intervention.

If a participant is withdrawn:

- The reason for withdrawal and the time point relative to the 24 hour protocol will be documented in the medical record and study forms.
- Safety related information (e.g., adverse events) up to the time of withdrawal will continue to be collected and reported as required.
- Data will be analysed until the time of withdrawal.

5. STATISTICS AND METHODOLOGY

5.1 Statistical analysis plan and sample size calculation

Sample size calculation

Sample size calculation was performed in R (version 4.3.1; R Core Team, 2023) using the *pwr* package (version 1.3-0).

The study follows a randomised paired crossover design. Each infant will be exposed to both ventilation modes in a randomised sequence. Each observation period of 9 hours will be preceded by a 3-hour washout period under the allocated ventilation mode, allowing clinical steady state to be reached before outcome measurement begins. The total per-infant protocol duration is therefore 24 hours (3h washout + 9h observation + 3h washout + 9h observation). This washout period was selected to ensure full physiological stabilisation following the onset of each ventilation mode and to eliminate any clinically relevant carry-over effect from the preceding period.

Sequence allocation (nCPAP-first vs. nCPAP-NAVA-Back-up first) will be performed using a computer-generated randomisation list created and managed within REDCap (Research Electronic Data Capture; Harris et al., 2009), hosted at HUG.

Based on our clinical observations in a comparable population of extremely preterm infants, the mean number of severe apnea episodes under nCPAP is estimated at 18 ± 6 per 9-hour observation period. We hypothesised a clinically meaningful 25% relative reduction in the primary endpoint under nCPAP-NAVA-Back-up mode (from 18 to 13.5 episodes per 9-hour period), corresponding to an absolute mean within-subject difference of 4.5 episodes. The standard deviation of the within-subject paired difference (SD_diff) was estimated at 6 episodes, assuming a moderate intra-individual correlation of r = 0.50 between the two observation periods. This yields a standardised effect size of Cohen's *dz* of 0.75 (4.5 / 6).

Using a two-sided paired t-test with a type I error rate of $\alpha = 0.05$ and a statistical power of 90% ($1 - \beta = 0.90$), the minimum required sample size is 21 infants : To account for the discrete and potentially non-Gaussian nature of count data, and for an anticipated dropout or missing data rate of 15%, the sample size was inflated to 25 infants.

Statistical analysis

Continuous data will be expressed as median [interquartile range] and categorical data as counts and percentages.

Endpoints will be test as within-subject difference. Continuous data will be analysed using a Wilcoxon signed-rank test (non-parametric paired test), appropriate for the discrete and potentially non-Gaussian nature of count data in small samples. Binary data will be analyzed using McNemar's test.

A potential period effect (systematic difference between the first and second observation period regardless of treatment) will be explored descriptively by comparing outcomes according to the allocated sequence.

All analyses will be conducted on a per-protocol basis as the primary analysis, and on an intention-to-treat basis as a sensitivity analysis. A two-sided p-value < 0.05 will be considered statistically significant. No interim analysis is planned. All analyses will be performed using R (version 4.3.1).

Given the short duration of the study (24 hours) and close monitoring in a neonatal intensive care setting, missing data are expected to be minimal. No formal imputation will be performed; analyses will be conducted on available data (complete case analysis).

Sex and Gender Considerations

Sex and gender dimensions are not of primary interest for this study. Descriptive reporting of sex distribution will be provided.

Deviations from the Statistical Analysis Plan

Any deviation from the predefined statistical analysis plan will be documented, justified, and reported in the final study report.

Stopping Rules

The study may be prematurely terminated in case of:

- unexpected safety concerns,
- significant protocol violations,
- decision by the sponsor or ethics committee,
- clinical judgment that continuation is not in the best interest of the participants.

5.2 Handling of Missing Data and DropOuts

Missing data may occur due to technical issues (PDMS recording interruptions) or potential withdrawals. Longer gaps will be treated as missing and excluded from rate calculations.
If a participant withdraws before completing all two intervention periods, data collected up to the point of withdrawal will be included in the analysis unless legal representatives request deletion.

6. REGULATORY ASPECTS AND SAFETY

6.1 Local Regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements

6.2 (Serious) Adverse Events and Notification of Safety and Protective Measures

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavorable or unintended finding, symptoms, or disease temporally associated with a trial procedure, whether related to it or not.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

Both Investigator and Sponsor make a causality assessment of the event to the trial intervention. Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Both Investigator and Sponsor make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)

All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor of the study.

If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation (i.e., the SAE is definitely, probably, or possibly related to the intervention), the Investigator reports it to the Ethics Committee via BASEC within 15 days.

A serious adverse event related to the intervetion is highly unlikely in this low-risk study (A). Nasal CPAP (nCPAP) is the standard of care in neonatology, and nCPAP-NAVA-backup mode is increasingly used in neonatal intensive care units. This trial does not introduce any procedures or devices outside their approved clinical indications.

Follow up of (Serious) Adverse Events

Patients experiencing severe adverse events will be followed up for a minimum of 7 days, in order to assess any potential consequences. The necessary follow-up will be evaluated on a case-by-case basis depending on the adverse event. Follow-up will rely exclusively on information obtained through routine clinical care, without requiring any additional procedures beyond standard NICU practice. The investigator will document the clinical course, outcome, and any relevant interventions in the source documents and the study records. All followup information will be recorded in accordance with institutional policies and regulatory requirements.

Notification of safety and protective measures (see ClinO, Art 62, b)

If immediate safety and protective measures must be taken during the conduct of the study, the investigator notifies the Ethics committee of these measures, and of the circumstances necessitating them, within 7 days.

6.3 Periodic Reporting of Safety and General Progress of the Clinical Trial

Once a year, the investigator submits to the Ethics Committee a list of the safety events including the severity of the events, their causality to the intervention and the safety of the study participants. The investigator also informs the Ethics Committee about the general progress of the clinical trial (ClinO, Art. 43).

6.4 Radiation

Not applicable.

6.5 Pregnancy

Not applicable.

6.6 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of participants may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

A list of all non-substantial amendments will be submitted once a year to the competent EC together with the safety report / general study progress report.

6.7 Notification and Reporting Upon Completion, Discontinuation, Interruption, and Resumption of the Study

Upon regular study completion, the Ethics Committee is notified via BASEC within 30 days (ClinO, Art. 38).

Twenty four hours after the inclusion of the last study participant is defined as the end of the trial.

The Sponsor may terminate the study prematurely according to certain circumstances, e.g.

- Ethical concerns,
- Insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice that make the continuation of the study unwise
- Early evidence of harm or benefit of the experimental intervention

The investigator reports the premature termination, interruption or resumption of the study, including reasons thereof, to the Ethics Committee within 15 days. An interruption lasting more than two years is considered a premature termination (Article 38 ClinO).

All health-related data are anonymised upon end of data analysis.

A final report is submitted to the Ethics Committee via BASEC within a year after completion or discontinuation of the study, unless a longer period is specified in the protocol (ClinO, Art. 38).

6.8 Insurance

This study is classified as **Risk Category A** under ClinO Art. 61.

In the event of study-related damage or injuries, the liability insurance of the University Hospitals of Geneva provides compensation.

7 FURTHER ASPECTS

7.1 Overall Ethical Considerations

This study addresses an important clinical question in the management of apnea of prematurity, a condition that affects all infants born before 28 weeks of gestation. Nasal CPAP is the standard of care in neonatology, and nCPAP-NAVA-backup mode is increasingly used in neonatal intensive care units. This trial does not introduce any procedures or devices outside their approved clinical indications. The intervention does not exceed minimal risks or burdens compared with routine care, and all monitoring procedures are part of standard clinical practice.

The ethical justification for this study is based on:

- **Clinical relevance:** Apnea related desaturation and bradycardia events are associated with short term instability and potential long-term neurodevelopmental consequences. Identifying the most effective noninvasive ventilation strategy is of high clinical importance.
- **Minimal risk:** Both interventions are already used in daily practice. The study does not expose infants to risks beyond those of standard care.
- **Vulnerable population:** Inclusion of preterm infants is scientifically necessary because apnea of prematurity occurs exclusively in this group. No alternative population can provide the required data.
- **Informed consent:** Legal representatives receive full written and oral information and provide written consent before participation.
- **Right to withdraw:** Parents may withdraw consent at any time without affecting the infant's clinical care.
- **Safety monitoring:** Continuous monitoring ensures immediate detection of adverse events, and infants can be withdrawn at any sign of intolerance.

The study respects the principles of the Declaration of Helsinki, the HRA, and ClinO, ensuring that the rights, safety, and wellbeing of participants are protected at all times.

7.2 Risk–Benefit Assessment

Both ventilation modalities (nCPAP-NAVA-backup mode and nCPAP mode) are routinely used in neonatal intensive care units. Since premature infants routinely require a feeding tube, the NAVA Edi catheter will serve this purpose**.**The Edi catheter is a clinically approved device used regularly in the NICU. The risks associated with participation are minimal and comparable to routine clinical care.

Potential benefits include:

- improved respiratory stability during nCPAP-NAVA-backup mode
- fewer apnea related to desaturation and bradycardia events
- reduced need for tactile stimulation
- possible reduction in escalation to NIV mode or invasive ventilation
- the study may contribute to improved respiratory management strategies for future preterm infants

Given that the overall risk–benefit ratio is favorable.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality Measures

Quality assurance in this study relies on standardized clinical procedures, continuous automated monitoring, and strict adherence to the protocol.
All investigators and clinical staff involved in the study will be trained on the protocol, study procedures, definitions of apnea events, and documentation requirements.
Continuous monitoring via the Patient Data Management System (PDMS) ensures objective, high resolution data collection with minimal risk of transcription errors. Any protocol deviations will be recorded, assessed for impact, and included in the final study report. All study documents will be maintained in an organized Investigator Site File (ISF).

For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential

8.2 Data Recording and Source Data

Study data will be recorded in a secure electronic Case Report Form (eCRF) using a validated electronic data capture system (REDCap®), hosted by the institution and compliant with applicable data protection and data security requirements. The eCRF includes an audit trail that automatically records all data entries, modifications, and deletions, including the date, time, and user identification. For each participant, a dedicated CRF will be maintained throughout the study. Participants will be identified exclusively by a coded identification number. The CRF will not contain any directly identifying personal data such as name, date of birth, or hospital identification number. Participant coding will follow the recommendations of swiss ethics, with the allocation list linking the participant code to personal identifiers kept separately, securely stored at the investigator's site, and accessible only to authorized study investigators. All study data will be traceable from the CRF to the original source documents. Data consistency and completeness will be ensured through regular monitoring and data validation procedures. Access to source data and documents will be granted to authorized monitors and regulatory authorities in accordance with applicable legal and ethical requirements.

Routinely Collected Clinical Data (Source Documents)

These data are generated as part of routine clinical care and documented in the participant's medical record:

- Continuous monitoring data (SpO_2, heart rate, respiratory rate)
- Transcutaneous carbon dioxide ($TcCO_2$) measurements
- Ventilator settings and parameters

- Oxygen supplementation (FiO_2)
- Records of clinically significant apnea, bradycardia, and desaturation events
- Medication records (including caffeine citrate dosing)
- EDIN scale
- Patient comfort, including gastrointestinal tolerance

These data remain part of the participant's medical file and are transferred into the eCRF for study purposes.

Study-Specific Data (Source Data)

The following data are collected specifically for the study and recorded directly in study documents:

- Study eligibility and inclusion/exclusion checklist
- Randomization sequence and cross-over allocation
- Documentation of wash-out periods and ventilation mode changes
- Study-defined outcome variables and event counts

8.3 Confidentiality and Coding

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

The investigator has appropriate knowledge and skills in the areas of data security and data protection or is able to ensure compliance by calling in appropriate expertise (Art. 6, ClinO).

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited.

Trial and participant data will be handled with the utmost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number.

Each participant will be assigned a unique study code. The coding list linking identifiers to study codes will be stored separately in a secure, access restricted location. The analysis dataset will contain coded data only, with no personal identifiers.

Access to study data is restricted to the Sponsor, to the principal investigator and authorized study team members. Electronic data will be stored on secure, password protected hospital servers with restricted access rights. Paper documents (e.g., consent forms) will be stored in secured cabinets within the NICU research office. No data will be transferred outside the institution without appropriate safeguards (e.g., encryption, secure transfer protocols).

8.4 Retention and Destruction of Study Data and Biological Material

The investigator retains all documents necessary for the identification and follow-up of the trial participants and all other original data for at least twenty years after completion or discontinuation of the clinical trial in the NICU of University hospital of Geneva. After the retention period, data will be destroyed securely. Electronic data will be permanent deleted from servers and backups. Paper documents will be shredding or certified destructed. No biological samples are collected or stored in this study.

9 MONITORING AND REGISTRATION

The monitoring will be organized by the Geneva Clinical Trial Unit.

The monitoring strategy has been defined by the Clinical Trial Unit as low-risk, according to the SCTO guidelines and the Risk-Based Monitoring (RBM) Score Calculator published on https://ctu-bern.shinyapps.io/rbmc/.

A site initiation visit will be conducted after the study has been approved and will be followed by a green-lighting process for recruitment.

During routine monitoring visits, the verifications will be carried out according to the monitoring plan, verification of key data — including eligibility criteria, the primary outcome and safety parameters/SAEs — performed for 50% of participants, including the first enrolled participant; review of randomisation procedures for 50% of participants; review of the allocation of intervention (50% of the participants) and review of the Trial Master File.

A close-out visit will be conducted before archiving the documents.

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

This study is obtained funding support from the institution of the University hospitals of Geneva (Projets de Recherche et Dévelopement, PRD): 46'500CHF. A funding application has been submitted to Meissner foundation and Prim' Enfance foundation and is pending approval. The funding will be used exclusively to support study-related activities (monitoring, data collection, analysis, and administrative costs). The funding body will have no role in the study design, data collection, data analysis, data interpretation, or manuscript preparation. The investigators declare no conflicts of interest related to this study, including financial, intellectual, proprietary, or other competing interests.

The investigators retain full independence over the conduct of the study and the publication of its results. There are no contractual restrictions on publication. Authorship will follow the International Committee of Medical Journal Editors (ICMJE) criteria. All investigators will have access to the final study dataset, and raw data will be available to the study team upon reasonable request, in accordance with applicable data protection regulations.

Data sharing will comply with institutional policies and applicable regulations (including GDPR, where relevant). De-identified data may be shared with other researchers upon justified request and after approval by the appropriate institutional or ethical authorities.

The sponsor enters and publishes a summary of the trial results in a public register in accordance with ClinO Art. 65a, within one year of completion or discontinuation of the trial. An interruption lasting more than two years is considered a discontinuation of the trial.

For the purpose of publication in the public register the sponsor also ensures that a lay summary of the trial results is entered in BASEC within one year of completion or discontinuation of the trial. The entry is made at least in the national languages of Switzerland in which the study participants were recruited. The investigator will provide each study participant with the lay summary of the trial results at the end of the study, directly.

Study results will also be submitted for publication in peer-reviewed scientific journals and may be presented at national and international scientific meetings, regardless of the nature of the findings. If sex- and/or gender-related effects are observed, these findings will be reported and discussed in the final study report and in any resulting publications. If analyses are performed and no sex- and/or gender-related effects are identified, this will also be explicitly stated in the final study report and publications, in accordance with principles of transparency and scientific rigor.

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Annexe

Assessment	***T0***	***WashOut (first 3h of Period 1)***	***Period 1 (3–12h)***	***WashOut (first 3h of Period 2)***	***Period 2 (15–24h)***	***End of Study***
Eligibility check						
Informed consent	*X*					
Randomization	*X*					
Allocation of sequence	*X*					
Ventilation mode applied/Intervention		*X (new mode)*	*X*	*X (new mode)*	*X*	
Continuous monitoring (HR, SpO_2, RR)	*X*	*X*	*X*	*X*	*X*	
Ventilator data capture (PDMS)	*X*	*X*	*X*	*X*	*X*	
Apnea/desaturation/bradycardia event recording		*X*	*X*	*X*	*X*	
Documentation of tactile stimulation or increase FiO2			*X*		*X*	
Comfort scoring (EDIN)			*X (every 3 hours)*		*X (every 3 hours)*	
Adverse event assessment		*X*	*X*	*X*	*X*	*X*
Data extraction (PDMS)						*X*