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CLINICAL INVESTIGATIONAL PLAN

A NEW MEDICAL DEVICE FOR NEONATAL RESPIRATORY SUPPORT DURING RESUSCITATION

A RANDOMISED CONTROLLED TRIAL OF DELIVERY ROOM INTUBATION RATES COMPARING A NEW SYSTEM AND T-PIECE RESUSCITATION SYSTEM FOR INITIAL STABILISATION OF INFANTS BORN <28 WEEKS

Protocol short Name:	CORSAD: Comparison Of Respiratory Support After Delivery on infants born before 28 weeks gestational age
Protocol version & status	1.0 EPN, 25 May 2015 1.1 Updated 7 June 2016 1.2 Updated 5 October 2017 1.3 Updated 22 November 2017 1.4 Updated 5 December 2017 1.5 Updated 28 February 2018 1.6 Updated 12 December 2018 Details in section 26
Investigational Medical Device	Inspiration Health Care resuscitation system (CE-marked)

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Coordinating Investigator	Baldvin Jonsson, MD, PhD, Coordinating Investigator, Karolinska Institutet and Karolinska University Hospital, Astrid Lindgrens Childrens Hospital, Neonatal Unit
Principal Investigator at Karolinska University Hospital	Marco Bartocci, MD, Principal Investigator, Karolinska University Hospital, Astrid Lindgrens Childrens Hospital, Neonatal Unit.
CIP revision History	1.0 EPN reviewed and approved by EPN Stockholm Updated 1.1-1.6 (section 26)
Clinical Development phase	Product will be CE-marked before trial starts. The trial is not intended for regulatory purposes or company funded.
Study Management	Thomas Drevhammar, MD, PhD student, Karolinska Institutet. Study Coordinator Lars Söderström, Biostatistician, Data management and statistics (retired 2018, replacement to be decided).
Started	3 March 2016
Planned completion	Q4 2019

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1 Protocol Summary (Synopsis)

Study Title	Randomised Controlled Trial of a New Respiratory Resuscitation System
Study Clinical Development Phase	Product will be CE-marked before the study starts. (The trial is not intended for regulatory purposes and is not company funded)
ID of Investigational Medical Device (IMD)	Inspiration Healthcare resuscitation system (rPAP, CE-marked)
Classification of Investigational Medical Device (IMD)	IIb
ID of Reference Device	T-piece resuscitation systems (CE-marked, several options)
Trial Objectives and Outcomes	The primary objective is to compare the frequency of delivery room intubation rates for initial respiratory resuscitation between - new system (low imposed work of breathing and prongs) and - standard treatment with T-piece resuscitator system (high imposed work of breathing and face mask). The primary outcome is delivery room intubation or death. The secondary outcomes include time to intubation, use of surfactant, use of positive pressure ventilation, respiratory support at 72 hours and temperature on intensive care admission. Safety variables include pneumothorax, intraventricular haemorrhage and problems with ventilation and equipment.
Subject population	250 Infants will be randomised. <u>Inclusion criteria are:</u> 1) <28 weeks gestational age at university hospitals. 2) Delivery can be vaginal or with caesarean section and steroid prophylaxis to mother can be complete, incomplete or not given.

	Exclusion criteria are: 1) Decision on treatment limitations before randomisation, 2) Decision to intubate infant made before delivery (for example local routine for infants born before 23 weeks GA). 3) Known airway, pulmonary, cardiac, gastro-intestinal tract malformations, 4) Known neuromuscular disease 5) No study neonatologist available
Trial Design (include: number of visits, duration and follow-up)	Two arm randomised comparison of two systems (T-piece device and the new system) for respiratory support after delivery of an infant <28 weeks GA. The interventions cannot be blinded. Randomisation will be stratified on centre, gestational age and antenatal steroid treatment. This multicentre trial will start at Karolinska Hospital and other sites can join throughout the study period. Screening for eligibility and consent will be performed on mothers with threatening delivery of an extremely premature infant. The intervention is respiratory support for the first 10-30 minutes of life and will begin after birth when the infant is transferred to the resuscitation team. The intervention ends 1) when an infant is intubated (primary outcome), 2) after a minimum of 10 minutes support, with the randomized system, the patient is stable and breathing adequately, 3) at 30 minutes when the respiratory support can continue as decided by the clinicians (cross-over not allowed). After 72 hours the patient records will be reviewed.
Assessment	Apart from the system used for respiratory support all patients will receive standard care. No

	assessments or investigations of the trial subjects are planned. Data will be reported by the resuscitation team and collected from records.
Statistical methods and calculations	All analysis will be on intention to treat and $p<0.05$ considered statistically significant. The primary outcome variable (delivery room intubation or death) will represent a 2x2 cross table and analysed with Pearson chi-square test. The secondary outcomes include Kaplan Meier analysis of time to intubation and comparisons of means for continuous variables.
Risk and benefits of IMD	The new device (IMD) has been designed for neonatal resuscitation and CE-marked for this intended use. The device is operated/handled in a similar way to existing devices and can provide support according to resuscitation guidelines. Benefits: During spontaneous breathing the CPAP provided with the new system is more pressure stable and has low imposed work of breathing. The benefits of decreased imposed work of breathing during resuscitation have not previously been investigated. The new system has the option of using prongs as the patient interface. Prongs have shown promising results in trials and have theoretical benefits. We hypothesis that the combined use of prongs and low imposed work of breathing could reduce the number of infants that need mechanical ventilation. Risks: There are no known or foreseen medical risks with the device related to the low imposed work of breathing and the use of prongs (short duration). There is an increased risk when using a new device related to user error and malfunctioning. To reduce this risk, the IMD is CE marked and developed

	according to the European Medical Device Directive and its Essential Requirements. This means e.g. reducing the risks by fulfilling the requirements of the Risk Management standard (ISO 14971 Medical devices -- Application of risk management to medical devices) and the standard for Quality Management (ISO 134 85 Medical devices -- Quality management systems -- Requirements for regulatory purposes) The risk will be further reduced by training and using experienced investigators. If there are problems with the IMD there are always backup systems ready for use.
Independent Data Monitoring Committee	The independent DMC report to the sponsor/coordinating investigator and consist of a senior neonatologist (chairman) and two more clinicians. They will ensure the safety of the participants, the overall quality and the integrity of the trial by periodic reviews (details in appendix). The DMC will compare blinded data for the two intervention groups. Safety variables, primary outcome, protocol adherence, rescue treatment and the quality of the data will be examined. Stopping criteria (benefit, harm and futility) will be on the primary outcome and safety variables.
Schedules of events	1) Continuous screening of mothers with threating extremely premature infant delivery 2) Antenatal visit including informed consent and inclusion 3) Randomisation when delivery is imminent 4) Intervention and delivery room report 5) Clinical notes follow up after 72 hours
First Subject In	March 2016

Last subject In	Q4 2019
Last subject out	Q4 2019

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71 # 2 Abbreviations

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Abbreviation	Explanation
AE	Adverse Event
ADE	Adverse Device Event
APGAR	Scoring system for infants after delivery
ASADE	Anticipated serious adverse device events (are specified in risk analysis report)
CE	Conformité Européene
CPAP	Continuous Positive Pressure Ventilation
DMC	Data Monitoring Committee
DR	Delivery Room
eCRF	Electronic Case Report Form
GA	Gestational Age
IB	Investigator's Brochure
IEC	Independent Ethics Committee
ILCOR	International Liaison Committee on Resuscitation
IMD	Investigational Medical Device
ISO	International Organization for Standardization
ISO 14155:2011	Clinical Investigation of Medical Devices for human subjects – Good Clinical Practice
ISO 15223-1	ISO for labelling device
IVH	Intra Ventricular Haemorrhage
iWOB	Imposed Work of Breathing
MEDDEV	Commission Guideline relating to medical devices directives (European)
MPA	Medicinal Product Agency
NCAR	National Competent Authority Report
NCPAP	Nasal Continuous Positive Airway Pressure
NICU	Neonatal Intensive Care Unit
PPV	Positive Pressure Ventilation
RDS	Respiratory Distress Syndrome

SAE	Serious Adverse Event
SNQ	Swedish Neonatal Quality Register
SpO2	Peripheral capillary oxygen saturation
UE	User error
UID	Unique Identifier
USADE	Unanticipated serious adverse device event

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3 Principal Investigator endorsement page

I, the undersigned, am responsible for the conduct of the following title study: CORSAD, Clinical Investigational Plan (CIP version at footer) and agree to the following:

- ✓ I understand and will conduct the clinical trial according to the CIP, any approved amendment to CIP, the ISO-14155:2011, the Declaration of Helsinki and all applicable national laws.

- ✓ I will not deviate from the CIP without prior written permission from the Sponsor and prior review and written approval from the IEC, except where necessary to prevent any immediate danger to patients.

Principal Investigators signature	**Date**
_____	_____
PI name, signaute and site	

4 Administrative Information

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5 Background Information

Plain language summary

After birth the infant needs to start breathing, expand the lung and clear the airway of fluids. The extremely preterm infant has immature lungs and the transition to breathing is often difficult. The initial respiration after birth can be absent, inadequate or gradually failing. Several respiratory support treatments are used to aid this transition.

The infants who do not breathe need to be ventilated with positive pressure. The infants that breathe on their own receive a continuous positive airway pressure (CPAP) that supports the opening of the previously closed lungs. Infants that cannot establish a stable spontaneous breathing have to be intubated and ventilated with a mechanical ventilator.

Intubating and ventilating an infant is associated with higher morbidity compared to the infants that can breathe on their own with CPAP support. A key objective with resuscitation and stabilization is therefore to increase the number of infants that can be treated without intubation and mechanical ventilation. This approach has contributed to increased survival with less respiratory sequelae among extremely premature infants. There are several trials that have investigated treatments aimed at further reducing the need for intubation and mechanical ventilation. The presented trial is in line with this tradition.

Introduction

The initial management of premature infants have been evolving towards less invasive management.[1] The benefit of non-invasive management was first noted in observational studies and then in a randomized trial, the COIN trial.[2] Less invasive care has been further studied in trials such as the VON, CURPAP and SUPPORT trials.[3] The European guidelines for the treatment of RDS recommend using NCPAP in combination with surfactant and trying to avoid intubation and mechanical ventilation.[4]

In the preterm infant population the most important factor for needing invasive ventilation is gestational age and for the smallest infants mechanical ventilation is the most common support. The intubation rate for patients born in Sweden before 28 weeks of gestational age was 60% during 2012 and 2013 (data from Swedish Neonatal Quality register (SNQ)).

The international guidelines on resuscitation (ILCOR) give several options for respiratory support after

delivery.[5] The algorithm aims at establishing stable spontaneous breathing and includes positive pressure ventilation (PPV) if the infant is not breathing and the option to use continuous positive airway pressure (CPAP) to facilitate breathing or ventilation. The guideline also allows use of nasal prongs instead of a face mask as the patient interface. The effect of different CPAP systems, the CPAP level and the effect of using different patient interfaces have been insufficiently studied.[6]

Effect of CPAP

The provision of CPAP during resuscitation has been suggested to be beneficial and is used in several clinical trials.[5] However, when supporting a breathing infant with CPAP, the infant will be challenged with the additional workload that is needed to breathe through the support system (imposed work of breathing). The imposed work of breathing (iWOB) has been suggested to be an important factor for treatment failure and subsequent need for intubation. In our previous ex-vivo study the standard system for resuscitation (T-piece) has been shown to have high iWOB.[7] A method for providing ventilator support with CPAP and with lower iWOB might reduce treatment failure and subsequent need for intubation.

Effect of Patient Interface

There has been one trial comparing nasal prongs and face mask that showed better results for the nasal prong interface.[8] Still the standard care has remained using a face mask. There are no more published trials using bi-nasal prongs but an observational study with historical controls including 124 patients was presented at the PAS meeting in Vancouver 2014.[9] The delivery room intubation rates were 23/67 for face mask and 11/57 for bi-nasal prongs (p=0.061) for infants with an gestational age of 26+4 and 27+0 weeks. They had no safety problems.

Clinical experience with new system

A clinical feasibility trial was started in 2012 at Karolinska University Hospital for delivery room support of infants 27-34 weeks gestational age. The trial had three treatment arms (T-piece resuscitation system, the new system with face mask and the new system with prongs) and randomisation was balanced to 12 patients in each arm. The main outcome was usability and the trial did not have power to detect differences in intubation rates or variables related to stabilisation of breathing. The trail was performed under the regulatory framework of non-CE marked, own produced equipment (National Board of Health and Welfare).

The trial finished April 2015 with 36 patients recruited. The new system has worked well and there have been no technical problems. The results will be submitted as an abstract to a scientific meeting (jENS,

16-20 September 2015, Budapest)

Research question

For infants born <28 weeks of age, can initial respiratory resuscitation with new system (low imposed work of breathing and prongs) reduce the frequency of delivery room intubations compared to standard treatment with T-piece resuscitator system (high imposed work of breathing and face mask)?

6 Investigational Device

6.1 The Reference Device – the T-piece Resuscitation System

The T-piece resuscitator system can be used for PPV as well as CPAP. The T-piece is provided with a constant fresh gas flow. PPV is provided by occlusion of the patient device and adjusted with a pressure limiting valve at the driver. CPAP is generated by outflow obstruction (an adjustable resistor) at the patient device. The T-piece resuscitation system can be connected to a facemask or an endotracheal tube.

6.2 The Investigational Medical Device - the new system

The investigational medical device (the new system) is handled in a similar way to the T-piece resuscitator system. The IMD is provided with a fresh gas flow equivalent to the T-piece resuscitator system. PPV is provided by occlusion of the patient device and adjusted with a pressure limiting valve at the driver. It has the same PPV performance as a T-piece resuscitator system in terms of peak pressure and inspiratory rise time. CPAP is generated in the patient by turbulent flow opposing expiration and aiding inspiration (technology from the Infant Flow generator). The level of CPAP is adjusted at a bedside driver and not at the patient device (different compared to T-piece resuscitator systems). The IMD has an imposed work of breathing measured ex-vivo at the same level as the most pressure stable variable flow NCPAP generators and significantly lower compared to T-piece resuscitator systems. The IMD can be used with prongs or a standard connector to a facemask or an endotracheal tube. Switching between prongs and facemask requires changing a connector at the patient interface side of the device. The design of the prongs has been used for more than twenty years

The IMD was developed in Östersund and at the Karolinska University Hospital. The invention has been licence for production and commercialization to a UK company that is certified for production of medical

devices (ISO 13485). The product will be CE marked and the letter of conformity will be appended to the CIP.

7 Objectives

7.1 Primary Objective (Efficacy)

The primary objective is to compare delivery room intubation rates for two types of respiratory resuscitation systems in extremely premature infants.

The new system has low imposed work of breathing and in this trial, use prongs as the recommended patient interface. The use of prongs and the low imposed work of breathing are expected to improve respiratory support and increase the number of infants that can achieve stable spontaneous breathing.

7.2 Secondary Objectives

The secondary objective is to compare the safety between the treatments. This includes (but are not limited to) death, intra ventricular haemorrhage, pneumothorax, airleaks, need to change system used for respiratory support, failed ventilation and problems with use or devices.

The other secondary objective is to compare the two treatments and the effects of initial respiratory support other than delivery room intubation rates. This includes the time of intubation after delivery, the time needed for initial stabilisation, the use of surfactant, the use of PPV, respiratory support at 72 hours of age and temperature on admission to the intensive care unit.

The study will also include hypothesis generating and explanatory variables including background information on mother and infant, reason for intubation, summary of other events and use of surfactant.

8 Endpoints

8.1 Primary Endpoints

The primary outcome is delivery room intubation or death.

Death has to be included in the primary outcome since patients that die may not always be intubated.

8.2 Secondary Endpoints

The safety endpoints are:

1. Death
2. Intra ventricular haemorrhage grade III or more
3. Airleaks and pneumothorax
4. Failed ventilation
5. Device problems or malfunction

The secondary endpoints are:

1. Time to primary outcome (intubation or death) up to 72 hours of age
2. Surfactant use in DR and NICU (<72 h). Method to deliver surfactant, time to treatment and repeated dosage. Three modes of surfactant delivery will be recorded: After intubation, intratracheal installation on NCPAP failure with or without short episode of mechanical ventilation (for example MIST and INSURE) and nebulized.
3. The use of PPV in delivery room
4. Use of sustained inflation (not recommended)
5. Reason for DR intubation
6. APGAR at 1, 5 and 10 minutes
7. Time to stable breathing
8. Oxygen level, SpO2 and level of CPAP support at 5 and 10 minutes
9. Patient temperature on NICU admission
10. Reason for NICU intubation
11. Mechanical ventilation at any time <72 h
12. Mechanical ventilation or mode of non-invasive support at 72 h
13. Decisions on treatment limitations during resuscitation
14. Withdrawal or withholding treatment

9 Trial Design

9.1 Outline

The study is a two arm randomised comparison of two systems for respiratory support after delivery. The comparison is between the use of a T-piece resuscitation device (standard intervention) and the new system (new intervention). The interventions cannot be blinded.

Justification of the trial design

A randomised controlled trial is the golden standard of investigating the possible benefits of a resuscitation system with low imposed work of breathing and resuscitation by prongs.

Justification of patient population

Gestational age is the most important predictor for respiratory failure and subsequent need for intubation. The range of gestational age for the study population has been selected at a balanced intubation rate. Intubation rate goes from 37% at 27 weeks to 94% at 23 weeks for national Swedish data (2012-2013). This may vary between centres and at the Karolinska University Hospital in 2013, no infants at 27 weeks (0/8) were intubated and all infants 23 weeks (9/9). The GA where half of the infants were intubated can be found at 25-26 weeks for both Swedish national and Karolinska University Hospital data.

Infants >28 weeks GA have not been included since they have a very low incidence of intubation and would be less likely to show an effect on the primary outcome variable.

A lower limit gestational age is difficult to set and instead infants with a decision to intubate prior to delivery should be excluded. This exclusion criteria aims to avoid conflicts with local routines to intubate the smallest infants. Even if a very high proportion of the smallest infants are intubated there are no foreseen risks of using the new technique compared to the T-piece technique before these patients are intubated. The hypothesised benefits of support using prongs and pressure stable CPAP also apply to this patient group even if all patients would be intubated.

9.2 Assessment of Efficacy and Safety

The assessment of efficacy and safety will be based on data after delivery room management, as reported in eCRF by the attending resuscitation team. Data will also be collected after 72 hours from patient records. The collected variables are discussed in section 14 and listed in the Variable list appendix.

Safety will be assessed by secondary outcomes (section 14.2) and by reporting problems with equipment (errors, deficiency, malfunction) and adverse events (section 16.3). The sponsor/coordinating investigator will rely on the independent DMC to compare safety and efficacy between the two treatments during the trial.

A high incidence of safety variable events is expected in both groups. Respiratory and other medical complications will be common, irrespectively of the respiratory support systems used. Historical data from Sweden indicates that approximately 20% of the patients will not survive.

9.2.1 Schedule of Investigational Events

Please see section 27.1 for a table with the scheduled investigational Events.

The investigational events are:

1. Screening will be of all patients admitted with threatening preterm labour of an extremely premature infant.
2. An antenatal visit to the mother (and father when possible) including consent, inclusion and exclusion criteria. The antenatal visit by neonatologist is a routine part of standard care. The visit usually includes information of delivery room management (resuscitation, intubation and respiratory support systems) and intensive care. Informing about the trial will require additional time for the antenatal visit (typically below 30 minutes).
3. Randomisation will be on hold until delivery is imminent.
4. After delivery the infant will receive the intervention (randomised respiratory support system) for 10-30 minutes.
5. Data from patient records will be collected after 72 hours.

The collected variables are discussed in section 14 and listed in the Variable list appendix.

9.3 Investigational Medical Device – training of staff at participating centres

Staff on the participating centres will be trained on the device, usage and the study protocol before start (site initiation). Adequate training will be documented for PI (documented GCP training required) and members of the site investigational team. An abbreviated CV of investigators with focus on neonatal training and resuscitation will also be included. This will be recorded in a log including names, initials, signature, function and authorization before access to eCRF and randomisation is given. New members can be added to this log and investigators that are not active shall be inactivated. This is the responsibility of the Principal Investigator at each site and will be checked by the monitor at site initiation. The coordinating investigator is responsible for providing support for teaching and training before start and as needed during the trial. Examples of training are on site visit with demonstrations, simulations and usage on patients not included in the trial.

The need for training after starting the trial could be identified by the staff on the participating centre, by monitoring, by the independent DMC or by the coordinating investigator. Request for training is encourage and contact details to Baldvin Jonsson or Snorri Donaldsson can be found in section 4.

Training by usage outside the trial

The System is CE marked and can be used outside the trial.

Run-in patients

Participating centres have an option to include the first three patients as pilot patients. Data from these patients will be included in the data provided to the DMC and for the halfway interim analysis but they will not be included in the final analysis. The aim of using pilot patients is to reveal problems and allow centres to test the protocol before enrolling true patients.

10 Risk to Benefit Rational of the Device and Clinical aspects

The new device (IMD) has been designed for neonatal resuscitation and CE-marked for this intended use. The device is operated/handled in a similar way to existing devices and can provide support according to resuscitation guidelines.

Benefits: During spontaneous breathing the CPAP provided with the new system is more pressure stable and has low imposed work of breathing. The benefits of decreased imposed work of breathing during resuscitation have not previously been investigated. The new system has the option of using prongs as the patient interface. Prongs have shown promising results in trials and have theoretical benefits. We hypothesis that the combined use of prongs and low imposed work of breathing could reduce the number of infants that need mechanical ventilation.

Risks: There are no known or foreseen medical risks with the device related to the low imposed work of breathing and the use of prongs (short duration).

Reducing the risks

With any new device there is an increased risk related to user error and malfunctioning.

This risk has been reduced by using an IMD that is CE marked and developed according to the European Medical Device Directive and its Essential Requirements. This means e.g. reducing the risks by fulfilling the requirements to the Risk Management standard (ISO 14971 Medical devices -- Application of risk management to medical devices) and the standard for Quality Management (ISO 134 85 Medical devices - Quality management systems - Requirements for regulatory purposes)

The trial will further reduce the risks by training and using experienced investigators. Using experienced investigators and personnel is important for recognising problems with equipment or usage.

Limiting the consequences of unforeseen risks and problems

If there are problems with the IMD there are always backup systems ready for use. Immediate access to backup systems is routine in areas used for resuscitation.

The participating centres have capacity for intensive care and are experienced in treatment of the known problems that can occur during resuscitation and respiratory support.

Adverse events, deficiencies, malfunctioning will be processed according to ISO 141 55 (Clinical Investigation of medical devices for human subjects - Good Clinical Practice). This will be reported by eCRF according to section 15. In case of uncertainty the sponsor/coordinating investigator can use the independent DMC for advice. Any problems will also be reported to the manufacturer according to the medical Device Vigilance System (see section 15), local authorities and ethical review board as appropriate.

If needed, stopping the trial by disabling randomisation is fast and no infants should be at risk of being treated if there are concerns with safety.

Summary

For the participating patients the risks are small compared to the possible benefits.

Risks have been assessed and reduced by the manufacturer following regulations and standards of Medical Devices product development and manufacturing (please see above). The trial is designed to handle problems or concerns with safety efficiently and in a structured way according to Good Clinical Practice (ISO 141 55).

11 Selection and Withdrawal of Subjects

11.1 Inclusion Criteria

Approximately 250 infants will be randomised with an estimated enrolment period of three years time. The Inclusion criteria are:

- <28 weeks gestational age at university hospitals.
- Delivery can be either vaginal or with caesarean section and steroid prophylaxis to mother can be complete, incomplete or not given.

11.2 Exclusion Criteria

The exclusion criteria are:

- Decision on treatment limitations before randomisation
- Decision to intubate infant made before delivery (for example local routine for infants born before 23 weeks GA).
- Known airway, pulmonary, cardiac, gastro-intestinal tract malformations
- Known neuromuscular disease
- Fetal hydrops
- No study neonatologist available

11.3 **Criteria and procedures for dealing with 'Withdrawal'**

Withdrawal of consent:

Withdrawal of consent before randomisation will be reported and the patient will receive standard treatment. Patient will not be asked if data can be collected.

Withdrawal of consent after randomisation but before delivery will be reported and the patient will receive standard treatment. The parent will be asked if data can be collected as intended. They should be offered an explanation of intent to treat analysis.

Withdrawal of consent during treatment will be reported and the patient will receive standard treatment. This is likely to be rare since the intervention period is very short (less than 30 minutes). The parents will be asked if data collected up to the point can be used and data can be collected as intended. They should be offered an explanation of intent to treat analysis.

If a parent withdraws consent to treatment but is still consenting to data collection, the consent will be adjusted by adding "withdraws consent to treatment but consents to collecting data", dated and signed by investigator and parent.

If the withdrawal is related to safety or performance as well as adverse events or suspected adverse events this will be reported to the DMC even if no further collection of data is allowed.

Stopping the trial temporarily (suspension) by disabling randomisation

If the trial has to be stopped temporarily (ISO 14155:2011 section 7.1.1 suspension), for example by order from authorities, manufacturer, sponsor or DMC, the randomisation process will be disabled and subjects will receive standard care. Since randomization is performed just before delivery and the intervention is short <30 minutes stopping the trial is fast and there is no process for withdrawing patients that has been randomized. If the trial is stopped the planned data collection from records will continue as planned. There are no planned investigations or events that needs to be discontinued.

Responsibility to stop the intervention for individual patients

The safety of the patient is the responsibility of the resuscitation team. Failure to provide adequate ventilation or respiratory support is a secondary outcome and expected for both treatments. If the intervention cannot provide adequate ventilation there are several options including adjustment of support (CPAP and PPV level), intubation or the use of backup systems. Crossover between the treatments is regarded as a protocol violation. Details are provided in the clinical management appendix.

The clinical management protocol provides details for how to handle equipment problems. This includes the use of back-up equipment. Back-up equipment is always available during resuscitation of infants and not specific for the patients included in the trial. The use of back-up equipment and failed ventilation is a secondary outcome.

There will be a number of infants where the clinician withdrawing or withholding treatment because of poor prognosis. This is also a secondary outcome.

11.4 Subject Study Participation and Replacement of Subjects

The antenatal visit will include the mother's participation and will require additional time for trial information and enrolment.

Each subject will receive the intervention for 10-30 minutes after birth. There are no investigations or other activities that require subject participation after this.

No replacements of subjects have been discussed. The independent DMC has an option to increase sample size based on over all event rates.

11.5 Subject Screening Log and Subject Identification

All patients screened will be registered in the eCRF with screening date, initials, date of birth and if the patient is suitable. If considered not suitable the reason for this will be recorded. No further information will be collected if patients are unsuitable. Patients suitable will be approached for consent.

For patients that do not consent to participation, no further information will be collected or registered. Patients that consent to participation will be enrolled with full name and personal identifier (social security number or personal identification number as applicable) and go through inclusion and exclusion criteria.

The eCRF allow the trial monitor to identify patients on a site to access source data in patient records. The PI at each site can identify patients on their site since this may be needed for Adverse Event reporting or queries raised by the monitor. The investigators at each site can search enrolled patients when proceeding to randomisation or when entering data in the eCRF forms.

12 Device CE-marking

The device will be CE-marked according Medical Device Directive 93/42/EEC, Class IIb by Inspiration Healthcare, UK. The intended purpose will include respiratory support during neonatal resuscitation. The CE-marking includes:

- Packaging, labelling and handling
- Traceability
- Biocompatibility
- Risk-evaluation

12.1 Device Distribution

The device is CE-marked and will be delivered to sites either through the manufacture retailer network or by the sponsor's department. The logistics of distribution will depend on national regulations and will be in place before a site starts to enrol patients.

13 Concomitant Device prohibitions and Study Compliance

No other respiratory support than the randomised system is allowed (protocol violation). Cross-over between the two treatments are not allowed (protocol violation). Use of bag and mask systems as rescue is allowed if needed and this represent a secondary outcome. Use of rescue systems will be reported to the DMC as a variable that may be linked to equipment or ventilation problems.

Compliance to randomised systems is expected to be high and non-adherence to protocol will be reported to the DMC as a variable that may be linked to equipment or ventilation problems.

Study personnel reporting in eCRF form will be automatically monitored by alerts (e-mail reminders) after randomisation. Delays in reporting (time limits for completion) will also generate alerts by e-mail.

14 Assessment of Efficacy and Safety

14.1 Clinical Efficacy Assessments

The primary efficacy variable is intubation in delivery room or death. The decision to intubate is made by the investigator responsible for resuscitating the infant.

Other efficacy variables from the delivery room are: 1) time to intubation 2) variables related to effective ventilation such as time to spontaneous breathing, need for PPV, APGAR, need for surfactant and SpO2.

The *immediate delivery report form* is reported by the investigator responsible for resuscitating the infant.

Follow-up at three days includes status on admission to NICU, any NICU intubation <72 hours or administration of surfactant.

The *delayed delivery report form and the three days follow up* are reported by study personnel at the site.

14.2 Clinical Safety Assessments

The expected safety variables that will be analysed by the DMC are:

1) Death
2) Intubation
3) Pneumothorax, airleaks and drainage
4) IVH and lung bleed

There are also more than ten variables (not counting APGAR and rare events such as chest compressions) that reflect problems or effectiveness of ventilation. These variables, or a selection, will be reviewed by the DMC (to be decided at the first DMC meeting).

There are four main variables that reflect problems with equipment and potential problems with trial design or the interventions (Management completed with randomised system; Problems with adhering to protocol; Any problems with equipment and Any adverse events).

The safety variables of the *immediate delivery report form* is reported by the investigator responsible for resuscitating the infant.

The *delayed delivery report form* and *the three days follow up* are reported by the study personnel at the site.

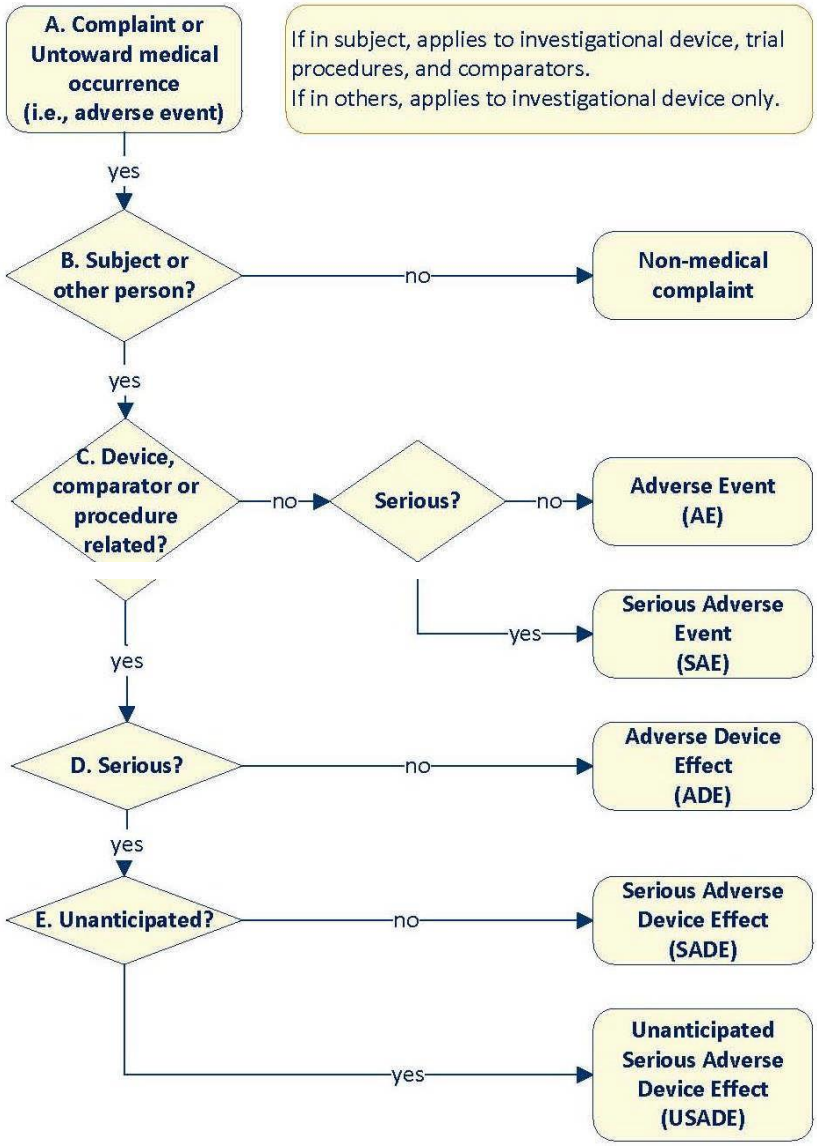
Registering an AE or problems with equipment will be handled according to Section 15: Proceedings for Adverse Events.

14.3 **Laboratory Efficacy and Safety Assessments**

There are no planned laboratory investigations.

15 Proceedings for Adverse Events

15.1 Schematic Decision Tree for Classification Adverse Events



15.3 Definitions of different types of Adverse Events and Device Deficiencies

15.3.1 Adverse Events (AE)

An Adverse Event (AE) is any untoward medical occurrence, unintended (or unfavourable) disease or injury or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device or comparator.

NOTE 1: This definition includes events related to the *procedure* involved

NOTE 2: For users or other persons, this definition is restricted to events related to investigational medical devices.

15.3.2 Adverse Device Effect (ADE)

If AE is related to the use of investigational device (or comparator) and related to investigational device or comparators *procedures or functions or intended use* it is considered as an adverse device effect (ADE).

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation or any malfunction of investigational device.

NOTE 2: This definition includes any event resulting from error use or from intentional misuse of the investigational medical device.

15.3.3 Serious Adverse Events (SAE)

Each AE is to be classified by the investigator as 'serious' or 'non-serious'. Seriousness is not defined by a medical term; it is a result or an outcome. An AE is defined as a Serious Adverse Event (SAE) if it:

a) led to death,

b) led to a serious deterioration in the health of the subject, that either resulted in

- ✓ a life-threatening illness or injury, or
- ✓ a permanent impairment of a body structure or body function, or
- ✓ in-patient or prolonged hospitalization (of existing hospitalisation), or
- ✓ medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function,
- ✓ led to foetal distress or congenital abnormality or birth defect

Please note! Planned hospitalizations for a pre-existing condition, or a procedure required by the CIP without deterioration, are not considered a serious adverse event.

15.3.4 Serious Adverse Device Effect (SADE)

An adverse device effect that has resulted in any of the consequences characteristic of a ***serious adverse event*** (see above)

15.3.5 Unanticipated Serious Adverse Device Effect (USADE)

An unanticipated Serious Adverse Device Effect which by its nature, is an incidence, severity or outcome that has ***not been identified i****n the current version of the* ***risk analysis report***.

15.3.6 Device Deficiency (DD)

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of investigational medical (or comparator) device shall be documented throughout the clinical investigation and appropriately managed by sponsor.

Device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance

NOTE: Device deficiency include malfunctions, use errors and inadequate labelling

Please note! Device deficiencies that did not lead to an adverse event but ***could have led to medical occurrence***

a) If either suitable action had not been taken
b) It intervention had not been made or
c) If circumstances had been less fortunate

shall be reported to sponsor. Sponsor is then responsible for the classification (as stated in §8.2.5 b) *to review* and determine *and document in writing* whether they could have led to a serious device effect.

15.3.7 Device Malfunction (DM)

Malfunction is the failure of the investigational medical **device to perform in accordance with its intended purpose** when it is used in accordance with the instructions for use or as intended in CIP (and does not involve a subject or any other persons (e.g. care giver, by standard) and is not lead to a medical occurrence, is considered as a 'malfunction' of device.

Please note! Do not confound with '*USE ERROR*'

15.3.8 Use Error (UE)

Use error is the act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

NOTE 1: Use error includes slips, lapses and mistakes.

NOTE 2: An unexpected physiological response of the subject does not in itself constitute a use error

15.4 **Assessment of Adverse Events**

According to ISO14155:2011 the Sponsor is responsible for the classification of adverse events and ongoing safety evaluation during the clinical investigation and shall review the investigators assessment of all adverse events and determine and document in writing their seriousness and relationship to investigational device; in case of disagreement between sponsor and the principal investigator the sponsor shall communicate both opinions to concerned parties.

Assessment of Intensity

Each AE is to be classified by the investigator as mild, moderate or severe.

Mild: Acceptable. The subject is awareness of symptoms or signs, but they are easy tolerated.

Moderate: Disturbing. The AE is discomfort enough to interfere with usual daily activity.

Severe: Unacceptable. The subject is incapacity to work or to do usual daily activities.

Assessment of Causality

Unlikely: The event is most likely related to aetiology other than the Investigational medical Device

Possible: A causal relationship is conceivable and cannot be dismissed.

Probably: Good reason and sufficient documentation to assume a causal relationship.

15.5 Methods for Eliciting Adverse Events

The investigational medical device and reference device are used during a short period directly after delivery and then transferred to intensive care. The patients are not expected to leave intensive care and will be under constant care. Any adverse event should be reported, documented and study personnel alerted. There will also be a review of records after 72 hours.

The study subjects (extremely premature infants) have a high incident of events that could be classified as adverse events and might be related to the type of randomised respiratory support system. The anticipated adverse events that are listed 15.6.3 constitute primary and secondary outcomes. These will be evaluated by the independent DMC at regular intervals. This includes (but are not limited to) death, intubation, pneumothorax, airleaks, inadequate breathing

Adverse events that are unanticipated (i.e. not reported in eCRF and under DMC review) always need to be reported and evaluated, even if the intensity was mild. Unanticipated Serious Adverse Device Effect (15.3.5) is of particular concern and should be reported and thoroughly investigated.

Any adverse events noted in the eCRF will result in e-mail alert to the Sponsor/coordinating investigator including the UID. The sponsor/coordinating investigator can review the AE and take appropriate actions (15.6).

15.6 Reporting and recording different types of Adverse Events and Device Deficiencies

15.6.1 Reporting according to the Medical Device Vigilance System

Since the Investigational Device is CE marked, the Manufacturer is responsible for reporting any adverse incident according to the Vigilance system (MEDDEV 2 12-1 rev. 8 Vigilance). The trial is academic and the Sponsor is separate from the Manufacturer. Information on adverse incidents will therefore be reported to the manufacturer.

The purpose of the Medical Device Vigilance System is to improve the protection of health and safety by reducing the likelihood of reoccurrence of incidents related to the use of a medical device. Therefore, The Medical Devices Directives provide that adverse incidents are evaluated and, where appropriate, information is disseminated in the form of a National Competent Authority Report (NCAR) with the objective of preventing repetition of such incidents through the adoption of appropriate field safety corrective actions.

Upon becoming aware that an event has occurred and that one of its devices may have caused or contributed to that event, the MEDICAL DEVICE MANUFACTURER must determine whether it is an INCIDENT. The following time lines apply in a case of:

- **Serious public health threat**: IMMEDIATELY (without any delay that could not be justified) but not later than 2 calendar days after awareness by the MANUFACTURER of this threat.

- **Death or UNANTICIPATED serious deterioration in state of health**: IMMEDIATELY (without any delay that could not be justified) after the MANUFACTURER established a link between the device and the event but not later than 10 elapsed calendar days following the date of awareness of the event.

- **Others**: IMMEDIATELY (without any delay that could not be justified) after the MANUFACTURER established a link between the device and the event but not later than 30 elapsed calendar days following the date of awareness of the event.

15.6.2 Reporting according to Good Clinical Practice

This study will also document Adverse Events according to GCP (ISO 141 55 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice). Documentation will be the basis for reporting according to the Medical Device Vigilance System when applicable.

The Medical Device Vigilance System has time limit requirements on the Manufacturer and the Investigators reports to the Manufacturer should be handled without delays.

Throughout the clinical investigation all Adverse Events will be documented on a separate report form in the eCRF (Adverse Event Form). The Sponsor / coordinating investigator will administer this report, additional documentation or investigations. Apart from the initial eCRF documentation all subsequent documentation will be on paper and filed at Karolinska University Hospital.

<u>The Sponsor/Coordinating Investigator is responsible for the classification of Adverse Events, and ongoing safety evaluation of the clinical investigation, and shall:</u>

- Review the Investigators assessment of all Adverse Events.
- Review device deficiencies and determine whether they could have led to a SADE.
- Report, or ensure reporting, all SAEs and device deficiencies that could have led to a SADE, to the IEC by the Principal Investigator(s), if required.
- Report to the Regulatory Authorities (if required), within the required time period, all SAEs and device deficiencies that could have led to a SADE.

- Report all relevant safety information to the independent DMC according to written procedures.
- In case of a multicentre clinical investigation, inform all principal investigators in writing of all Serious Adverse Events at all investigation sites that have been reported and ensure that they are reported as required by local regulations.
- Decide if randomisation should be stopped during review and reporting

The principal Investigator at each site shall:

- Record every Adverse Event and observed Device Deficiency together with an assessment in the eCRF (Case Report Form for Adverse Events and Device Defincies).
- Report to the Sponsor/Coordinating Investigator all Serious Adverse Events and Device Deficiency that could have led to Serious Adverse Device Effect, without unjustified delay (within three calendar days).
- Report to IEC all Serious Adverse Events and Device Deficiency that could have led to Serious Adverse Device Effect, if required by local/national regulations.
- Report to Regulatory Authorities all Serious Adverse Events and Device Deficiency that could have led to Serious Adverse Device Effect, as required by national regulations.

Contact for support or discussion is encouraged. Contact the Coordinating Investigator, the Principal Investigator at Karolinska University Hospital or the Study Coordinator.

15.6.2.1 Sponsor contact details:

Baldvin Jonsson, MD, PhD, Karolinska University Hospital, Astrid Lindgrens Childrens Hospital, Neonatal Unit
Email: baldvin.jonsson@ki.se
+46-851775130 (direct)
+46-8-51770000 (switchboard)
+46-8-51773053 (fax)

If the coordinating investigator cannot be reached alternatives are; the Principal Investigator at Karolinska University Hospital (Snorri Donaldsson) or the Study Coordinator (Thomas Drevhammar). Contact details in section 4 (Administrative Information).

15.6.3 List of Foreseeable Adverse Events and Anticipated Adverse Device Effects

The following events are foreseeable and anticipated. They are outcome variables and will be monitored. If the events are related to, or suspected to be related to, Device Deficiency (15.3.6), Device Malfunctioning (15.3.7) or User Error (15.3.8) they should be reported. If there are uncertainties the event should be reported.

List of events:

- Death
- Intubation
- Pneumothorax and airleaks
- IVH grade III or more
- Lungbleed.
- Problems with ventilation (variables reflecting use of rescue system, protocol violations and reason for intubation)

16 Statistics and Data Management

16.1 Data Management and Case Report Forms

Electronic Case Report Forms (eCRF) will be completed for each included patient. A separate binder will be held for the signed Informed Consent. Investigators will ensure completion and review of the eCRF. Investigators have personal responsibility for the accuracy and authenticity of all data that are entered into the eCRF.

The eCRF data will go through automatic check of range, format and inconsistencies when entered. After completion of the eCRF forms the file will be signed by the Principal Investigator at each site. To increase quality further a trial nurse or dedicated site investigator will be automatically notified if eCRF forms are not completed on time or if enrolled patients reach 28 weeks gestational age without being randomised. The notifications have no personal identifiers and will use UID. This continuous quality work does not replace monitoring and it has the aim of reducing loss of patients, encourage prompt reporting and increase quality.

Software, security and backups of the eCRF are provided by MedSciNet. After completion of the last subject data in the eCRF will be exported without personal identifiers to a master file. The master file will be screened for completeness, inconsistencies and go through statistical analysis.

During the course of the study the investigational team, and the monitor will have access to the study material (investigator binder with essential documents, Signed Informed Consent etc.). These will be kept in a locked place.

16.1.1 Entering of data into Case Report Forms

Data will be entered in the eCRF. This will be source data for many of the variables concerning respiratory support during resuscitation. Most of the other data can also be found in patient records (background information on mother and patient, standard infant reports including APGAR, weight, drugs given and post resuscitation respiratory support). Instructions on use of eCRF and definitions will be available before trial start. A dry run version for instructional use will be available.

The eCRF application includes an automated user and an event logging system. Changes or corrections are logged.

After completion of the 72 hour follow up, the eCRF will be signed off by the Principle Investigator at each site.

16.2 Statistical Analysis

The primary outcome will be evaluated as percent of events. The difference in events between the two arms will tested according to Wald, using a p-value of 0.05.

Time to primary outcome will be described according to Kaplan-Meier and the difference between the two arms will be compared using the logrank test.

Descriptive measures of primary and secondary outcomes will be tabulated for each arm and differences between the arms will be assessed using Student's t-test or Fisher's exact test, where appropriate.

Relations between the primary event and confounding variables will be investigated using a logistic regression model, and tested according to Wald.

All analysis will be made according to intention to treat using a p-value of 0.05, adjusted according to Bonferroni for multiple comparisons.

16.3 Determination of Sample Size

Baseline event rate: The intubation rates for infants <28 weeks were 60% in Sweden 2012-13 (370 of 615 patients). The delivery room death rate is difficult to estimate since deaths are unreliable (not always recorded) in SNQ.

Calculation: The calculations were performed with binary outcome superiority trial design at significance level (alfa) of 5% and power (1-beta) of 80%.

Estimated treatment effect: The effect that the new system may have on intubation rates or deaths is not known. A minimal important difference is probably an absolute reduction of around 10%, which corresponds to a number needed to treat (NNT) of 10. This would give a sample size of 770 patients, which is not feasible.

The estimated sample size for two levels of treatment effect is 195 for an absolute reduction 20% (from 60% to 40% intubation rate). This corresponds to a number needed to treat (NNT) of 5.

Adjustments: The sample size has not been adjusted for patients lost (expected to be low) and differences in baseline intubation rates after application of exclusion criteria or when death is included in the primary outcome. The sample size has not been adjusted for clustering effect of multiples receiving the same treatment.

17 Direct Access to Source Documents

The monitor and authorities (if required) must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the clinical trial. The right to access data is included in the patient information and consent. The Principal Investigator at each site will ensure that site staff completes the eCRF and that the source documents are accessible. The monitor needs to sign secrecy agreement in accordance with national regulations and hospital practice before reviewing records.

18 Quality Control and Quality Assurance

18.1 Source Data

The investigator is responsible for maintaining the eCRF and include data on all patients who were screened, provided informed consent (or rejected), were enrolled, randomized and treated.

The investigators will record the patients screened, if they were suitable, reason if they were not suitable and if the patients that are approached for consent. This will be recorded in the first part of the eCRF and constitutes the screening log. It will contain no personal information (initials and date for screening).

The patients that give consent are enrolled with personal identifiers and receive a UID in the eCRF. The UID and personal identifiers constitutes the Patient Identification Log and is accessible by the principal investigator and monitor at each site.

Paper notes or copies of the log to facilitate logistics can be inserted in the trial binder.

The medical records of each patient included will include a note of participation in the study. The note will contain

- Study title (with a short description of the study)
- Information that an informed consent form has been signed and is kept with the study documentation
- Patient study number, UID
- Length of study (Intervention 10-30 minutes of age, follow-up after 72 hours, no planned investigations or procedures)
- Medically responsible study doctor and study nurse, with contact details

The medical record of each enrolled patient will include information on antenatal care, management during resuscitation and the intensive care period. After the initial stabilisation in the delivery room there are no planned procedures related to the trial and the patient will receive standard care. Any adverse events noted should be in records as well as withdrawal before study completion.

The Source Data List for the study will define where the source data for every efficacy and safety variable is to be found.

18.2 Monitoring

Before the beginning of the trial, the Sponsor will appoint an independent monitor. Monitoring will be performed before, during and after study completion in accordance with the ISO 141 55 standard.

Study conductance, source data, device accountability, adherence to the study protocol and Good Clinical Practice (ISO 141 55) plus regulatory requirements will be monitored.

A Monitoring Plan will be developed prior to the start of the study. This document will describes the frequency and the level of detailed of monitoring. It will include the degree of source data verification, based on the design and risk of the study.

18.2.1 Query Process

The monitor will review the e-CRFs and evaluate them for completeness and consistency. The e-CRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the investigator or his/her designee. The monitor cannot enter data in the e-CRFs. Corrections to the eCRF will be audit trailed. This means that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering the clinical data into the e-CRF will be determined in advance. If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture application. The appropriate investigational personnel will answer queries in the e-CRF. This will be audit trailed by the electronic data capture application meaning that the name of investigational personnel, time, and date is logged.

19 Ethics

19.1 Independent Ethics Committee

Local independent ethical committees will review the trial. National rules apply and it is the responsibility of the Principal Investigator at each site to adhere to these standards. IEC application and review will be included in the first monitor meeting before enrolment starts. The sponsor/coordinating investigator is responsible for reporting adverse events to the IEC as appropriate.

19.2 Ethical Conduct of the Trial

The trial will be conducted according to Helsinki Declaration, Good Clinical Practice (ISO 14155), the national rules use of medical equipment and record keeping.

19.3 Subject Information and Informed Consent

All subjects will be given verbal and written information about the study before signing the informed consent and being enrolled in the study. Consent is obtained from mother (and partner when applicable). The issue of legal guardian of an unborn child may vary between countries and the consent form can be adapted to this as necessary.

The information is written in such way that it is clear that a refusal of participation incurs no penalty for the subjects and this information is approved of the local Ethics Committee. The statement shall also confirm that the subject agrees that sponsor´s representatives, regulatory authorities and IEC representatives will be granted direct access to subject medical record. The original consent will be filed and kept at each site.

20 Data Handling and Record Keeping

20.1 Record Keeping

To enable audits and evaluations by the sponsor and inspections by regulatory authorities, the investigators shall keep records (essential documents) of the trial for a minimum of 10 years after

final signed clinical trial report. This includes any original source data related to the trial and the original signed informed consent forms and e-CRF data. A copy of the eCRF database for the patients enrolled at each site will be provided and compiled data from all sites will be stored at the sponsor's/coordinating investigator's department.

The sponsor/coordinating investigator should be contacted before any trial related documentation is planned for destruction.

Medical records containing personal information are filed in accordance with routines for hospital patient records. This includes informed consent forms and documentation related to any adverse events. Unique identifiers should be used as far as possible and personal information avoided. The UID is generated by the eCRF when a patient has been enrolled. The UID key for patients enrolled at a site is accessible by the Principal Investigator and monitor at that site. The UID key for all trial subjects is accessible only by the Coordinating Investigator.

The eCRF is developed by Medscinet in Microsoft SQL deploys a validated systems that complies with Good Clinical Practice (GCP) predicate rule requirements, laws, and regulations for clinical trial conduct and FDA 21 CFR 11 for electronic record and signature use. The applications are also compatible with the rules of HIPPA, NIH and HL7 as well as the European (CENTC-251) recommendations and requirements.

The database application is protected by a username / password login with 128 bits encryption. License for a Secure Server ID is included. The application includes an automated user and an event logging system.

Security and protection from fire, damage or human mistakes are by daily back-ups and weekly back-ups with media stored in fireproof location. Back-ups are taken of both the database and the application.

21 Financing and Insurance

The trial funding will be from several institutions, funds and research support organisations. A list of applied and received grants is attached as a supplement. No company funding will be considered.

The patient insurance (Patientförsäkringen, Stockholm County Council/ Stockholms Läns Landsting) is valid for patients enrolled in Sweden.

Centres recruiting patients in other countries need to provide information on insurance policies and the requirements by the local Ethics Committee.

The manufacturer has insurances for liability.

The trial is academic with the coordinating investigator as the sponsor. The coordinating investigator does not provide liability insurance valid for clinical trials.

22 Publication Policy and Registration

The results will be presented in an abstract to a scientific meeting and as a manuscript submitted to a scientific journal. Authorship will be based on the principles of the Vancouver protocol and participating centres are invited to contribute. Publication or analysis of data, or subsets of data, from one site is not allowed before publication of results from the trial.

The study will be included in Snorri Donaldson's PhD thesis at the Department of Women's and Children's Health, Karolinska Institutet.

The trial has been registered at clinicaltrials.org (NCT02563717).

23 Supplements

23.1 Amendments

Amendments to this document should be noted below and the information at each site updated. Amendment should be approved by the sponsor/coordinating investigator and approved by IEC as appropriate. Amendments to Appendices should be recorded in the changed document.

23.2 Personnel Information

The Principal Investigator, at each site, is responsible that an investigator has sufficient knowledge and is able to perform tasks related to and needed for the trial. This should be documented in the site binder.

24 References

1. Lawn JE, Davidge R, Paul VK, et al. Born too soon: care for the preterm baby. Reprod Health 2013;**10 Suppl 1**:S5.
2. Morley CJ, Davis PG, Doyle LW, et al. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008;**358**(7):700-8.
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4. Sweet DG, Carnielli V, Greisen G, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants--2013 update. Neonatology 2013;**103**(4):353-68.
5. Wyllie J, Perlman JM, Kattwinkel J, et al. Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation 2010;**81 Suppl 1**:e260-87.
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7. Drevhammar T, Nilsson K, Zetterstrom H, et al. Comparison of seven infant continuous positive airway pressure systems using simulated neonatal breathing. Pediatr Crit Care Med 2012;**13**(2):e113-9.
8. Capasso L, Capasso A, Raimondi F, et al. A randomized trial comparing oxygen delivery on intermittent positive pressure with nasal cannulae versus facial mask in neonatal primary resuscitation. Acta Paediatr 2005;**94**(2):197-200.
9. Delivery Room (DR) Ventilatory Support Via Bi-Nasal Prongs in Extremely Premature Infants (EPI) < 29 Weeks. Observational, Two Time Period Comparative Study of Prospectively Collected Data. The Pediatric Academic Societies (PAS) Annual Meeting; 2014; Vancouver.

25 Appendices

Clinical management protocol

DMC instructions

eCRF template and database variable list

Financial grants application list

25.1 Schedule of Investigational Events

	Screening of inpatients	Antenatal visit	Anticipated Delivery	Delivery 10-30 min	Follow-up after 72h
	Continually				
Informed consent		X			
Inclusion/exclusion criteria		X			
Randomisation			X		
Initial respiratory support				X	
Clinical notes review[A]					X
Adverse events	Not applicable			Continually	
Investigations	None planned				
Blood samples	None planned				

Table 1: Schedule of Investigational events. Variables collected from records (A) are presented in Appendix: eCRF template and database variable list

26 Amendments

7 June 2016 1.0 EPN updated to 1.1

- Start date inserted
- Clinical trials registration number inserted
- Stavanger and Linköping added as sites
- DMC members confirmed
- Clinicaltrials.gov registration number added

5 October 2017 1.2

- Trial abbreviation changed from CORSAD28 to CORSAD
- Vilnius and Poznan added as sites
- PI addresses and titles updated
- CE-mark status on new resuscitation device (rPAP) corrected
- Caffein added as variable in eCRF (no change in CIP)
- Endorsment page reviewed and corrected

22 November 2017 1.3

- PI at Karolinska Hospital updated

5 December 2017 1.4

- Iceland University Hospital added as site
- Study coordinator split into management and administration

28 February 2018 1.5

- Sahlgrenska University Hospital, Gothenburg added as site

28 February 2018 1.6

- Expected completion date adjusted to Q4 2019

Lars Söderström and Helena Fenger-Krog has retired. No immediate need for contracting a new biostatistician or GCP consultant.