Safety and feasibility of Predictive Intelligent Control of Oxygenation (PRICO) on the Neonatal Intensive Care Unit (NICU)

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Coordinating investigator/project leader	**Dr Andre A. Kroon** **Room SP-4455** **Wytemaweg 80 3015 CN Rotterdam tel: 010 70 36581 email: a.a.kroon@erasmusmc.nl**
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	**Dr Andre A. Kroon** **Room SP-4455** **Wytemaweg 80 3015 CN Rotterdam tel: 010 70 36581 email: a.a.kroon@erasmusmc.nl**
Local Primary Investigator **MMC Veldhoven**	**Dr Hendrik J Niemarkt** **De Run 4600, 5504 DB Veldhoven** **Postbus 7777, 5500 MB Veldhoven** **Tel: 040-8889350** **E-mail: hendrik.niemarkt@mmc.nl**

Sponsor (in Dutch: verrichter/opdrachtgever)	***Erasmus MC*** **Dr Irwin K.M. Reiss** **Room SP-4459** **Wytemaweg 80 3015 CN Rotterdam tel: 010 70 36077 email: i.reiss@erasmusmc.nl**
Subsidising party	***Not applicable***
Independent expert (s) **Erasmus MC**	***Dr. Enno D. Wildschut*** **Room SK-3234** **Wytemaweg 80** **3015 CN Rotterdam tel: 010 70 36189** **email: e.wildschut@erasmusmc.nl**
MMC Veldhoven	**Dr. P. van Runnard Heimel De Run 4600, 5504 DB Veldhoven tel: 040-8889350 Sein:7184**
Laboratory sites	***Not applicable***
Pharmacy	***Not applicable***

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor or legal representative: ***Prof. Dr Irwin K.M. Reiss*** ***Professor of Neonatology*** ***Head division of Neonatology*** **Head of Department:** ***Prof. Dr Edmond H.H.M. Rings*** ***Head of Paediatrics***	 	26-02-2018 March 5, 2018
[Coordinating Investigator/Project leader/Principal Investigator]: ***Dr Andre A. Kroon*** ***Neonatologist***		20-2-2018

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
$cSrO_2$	**Cerebral Regional Oxygen Saturation**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
FTOE	**Functional Tissue Oxygen Extraction**
FiO_2	**Fraction of inspired oxygen**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
NICU	**Neonatal Intensive Care Unit**
NIRS	**Near Infra Red Spectroscopy**
NO	**Nitrous Oxide**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
SpO2	**Saturation if Oxygen measured by pulse oximetry**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**

SUSAR Suspected Unexpected Serious Adverse Reaction Vte Exhaled Tidal Volume Wbp Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens) WMO Medical Research Involving Human Subjects Act (in Dutch: Wet Medischwetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Supplemental oxygen is given to preterm infants to ensure that they have an adequate arterial saturation (SpO_2). Fluctuations in the SpO_2 mean that the fraction of inspired oxygen (FiO_2) needs to be adjusted, a challenging and time consuming task. During the recovery of a desaturation there is often an overshoot, resulting in a period of hyperoxia. Hyperoxia interferes with vascular development of the lungs and eyes, and there is growing evidence that hyperoxia may be equally damaging to the developing brain.

An observational study conducted on our Neonatal Intensive Care Unit (NICU) has shown that infants on average spend only 54% of the time within the SpO_2 limits and 71 adjustments to the FiO_2 are made each day.

An automated controller (PRICO) has been developed that adjusts the FiO_2 based on the SpO_2. A study in a preterm lamb model has shown the effectiveness of this closed loop controller: less periods of desaturation and hyperoxia were demonstrated.

Objective: To test the safety and feasibility of a closed loop controller of the FiO_2 based on the measured SpO_2 in a NICU setting.

Study design: Neonates that are included will start with an 8 hour block of manual adjustment of the FiO_2. After completion of this block they will be switched to the automated control of the FiO2 for another 8 hours. After that they are switched back for another 8 hours of manual control, which is used to correct for any changes of the state of the neonate during the trial. For each ventilation type (high frequency , invasive and non-invasive) 24 patients will be included.

Study population: Neonates admitted to the NICU in the Erasmus MC, Rotterdam and Máxima Medical Centre, Veldhoven that are receiving respiratory support and a FiO_2 of more than 21%.

Intervention (if applicable): Automated control of the FiO_2 based on the measured SpO_2 during 8 hours.

Main study parameters/endpoints: The main parameter during the study is the time the SpO_2 spend within the target range. Secondary outcomes are the number of hyper and hypoxic events, average maximum and minimum SpO_2 during these events, number of FiO_2 adjustments (manual and automated) and cerebral oxygen saturation.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There is no burden to the patient, and the risk is minimal. The same patient monitoring is used during the study as during routine care. The closed loop

algorithm is implemented in to the Acutronic Fabian HFO ventilator, so that no additional equipment is needed at the bedside.

The controller is designed so that it checks the input signals, the validity of the pulse oximetry and the quality of the ventilation. If any of the checked parameters is not within the specified limits the controller will not adjust the FiO_2 and give an alarm.

1. INTRODUCTION AND RATIONALE

Supplemental oxygen is given to preterm infants to ensure that they have an adequate arterial saturation (SpO_2), and is one of the most common therapeutic interventions in the neonatal intensive care unit (NICU) [1]. Fluctuations in the SpO_2 are dealt with by adjusting the fraction of inspired oxygen (FiO_2), a challenging and time consuming task. During the recovery of a desaturation there is often an overshoot, resulting in a period of hyperoxia. Both hypoxia and hyperoxia must be avoided because of their detrimental effects on morbidity and mortality in these children. While hypoxia may lead to direct and indirect cellular damage, hyperoxia has been associated with oxygen toxicity, oxidative stress [2], and chronic diseases of preterm infants such as bronchopulmonary dysplasia (BPD) [3] and retinopathy of prematurity (ROP) [4]. And there is growing evidence that hyperoxia may be equally damaging to the developing brain.

Large deviations from SpO_2 targets during routine NICU care of preterm infants have been observed in clinical observational studies, where SpO_2 target ranges are met during 50% of the time, and 71 adjustments to the FiO_2 are made each day. [5, 6]. Meeting SpO_2 targets affects morbidity and mortality, depending on the target range chosen [7-9]. Beside overall SpO_2 targets, variability of oxygenation influences outcome of preterm infants [4, 10, 11]. A promising solution to optimize oxygen therapy is the employment of an automatic „closed loop" system for regulation of FiO_2 based on SpO_2. Several clinical trials with different devices have proven feasibility of automated closed loop FiO_2 control in the NICU for various modes of ventilation, mixed populations, and by using different algorithms [5, 12-17]. In addition, an overall reduction of manual interventions during automated control was found in these studies, indicating facilitation of caretakers and nursing staff in clinical routine [18, 19]. However, at least one study raised concerns about safety, as time within target range was accompanied by an increase in time spent below saturation target range [16].

An automated controller (PRICO) has been developed by our research group that adjusts the FiO_2 based on the SpO_2. A study in a preterm lamb model has shown the effectiveness of this closed loop controller: less periods of desaturation and hyperoxia were demonstrated [20]. This new algorithm distinguishes itself from previous (published) algorithms by being faster, using a predictive model based on the trend of the SpO_2, and having a variable step size based on the current FiO_2. This study was specifically preformed in preterm lambs because of their similar physiology compared to preterm neonates. The transitional phase and incomplete development of the lungs are a key aspect to the fine tuning of the algorithm.

This algorithm is tailored specifically to neonates. This patient group suffers more frequent changes in their saturation and require many adjustments of the oxygen therapy they receive. In addition their poor defence against oxygen free radicals means that they are more susceptible for too much oxygen, resulting in a very small target SpO_2 range. This range is different from almost all other patients because it targets a high saturation of only 95%. Because the high target is less than 100% is the actual reason that closed loop control based on SpO_2 is possible. Otherwise, when 100% SpO_2 is accepted, it is impossible to detect when too much oxygen is given. These lower SpO_2 targets also effect the actual uptake and transport of the oxygen, through the oxygen desaturation curve. This curve describes the relation between partial pressure of oxygen and the oxygen saturation, and is influenced by a number of factors. Fetal-haemoglobin, pH, temperature and CO_2 levels all effect the amount of oxygen that is actually transported by the blood at a certain saturation.
Besides this the actual lung volume compared to the circulated blood volume and cardiac output determine the timing of the closed loop controller. Combined with the narrow saturation target and the limited capacity of neonates it results in a very fast reacting but highly unstable system.

When a similar closed loop system would be developed for another patient group, both timing step size and gain would need to be tailored to their need. And a solution should be found when target saturation come close to or include 100% SpO_2 in order to detect and prevent overshoot.

We hypothesize that fully automated FiO_2 control conducted by this algorithm will keep SpO_2 within a predefined target range more time and with less deviation then during routine standard clinical care.

2. OBJECTIVES

Primary Objective: To test the safety and feasibility of a closed loop controller of the FiO_2 based on the measured SpO_2 in a NICU setting. This is determined by the time spend within the SpO_2 target range, and the number of times the SpO_2 was above and below the target.

Secondary Objective(s):
Track the usage of the fraction of inspired oxygen (FiO_2) during the periods. A higher oxygen use is only acceptable when it results in an improvement of the time spend within the oxygen saturation target range without a rise in hyperoxia. In all other cases a lower FiO_2 is preferred.
The respiratory support is analysed, to see if any changes were made to the ventilation settings. Changes to the pressure or timing can influence the need for additional oxygen.

Reduction in manual FiO_2 adjustments. Although the FiO_2 is adjusted automatically, it is still possible to adjust the FiO_2 by hand. This can be done on clinical indication. For example before an alteration to the respiratory support is made, before suctioning, or before respiratory support is halted for another reason.

When the infants are monitored with near infrared spectroscopy (NIRS) to monitor their cerebral oxygenation, this data will be analysed in order to see if automated oxygen control improves the stability of their cerebral oxygenation.

3. STUDY DESIGN

Neonates that are included will start with an 8 hour observational block to determine the baseline fluctuations during manual FiO_2 adjustment. After the first 8 hours they are switched to automated FiO_2 adjustment. During this time the FiO_2 is primarily controlled by the algorithm based on the measured SpO_2. Manual override is possible at all times, and logged. After the 8 hours of automated control (16 hours since the start) the neonate is switched back to manual control, and all parameters are again recorded for 8 hours. This second observational block is to make sure that the condition of the patient did not significantly change during the study period.

The care takers are not blinded to the intervention. During manual control FiO_2 is adjusted as it is during routine clinical care. During automated control the changes of the FiO_2 are clearly displayed on the screen of the Fabian HFO ventilator (Acutronic Medical GmbH, Hirzel, Switzerland), and the physicians are still able to adjust the FiO_2 manually (manual changes will be logged). The SpO_2 sensor (Masimo, Irvine, USA) for the adjustment of the FiO_2 is placed in addition to the routine pulse oximeter sensor (Masimo) that is connected to the patient monitoring system (Dräger M540, Lübeck, Germany). The routine pulse oximeter will provide the normal monitoring/alarming function.

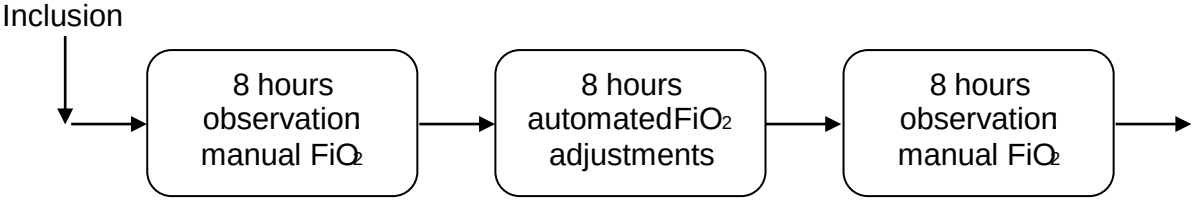

Figure 1: Study time line

The included patients are stratified based on the ventilation mode that they receive at the time of inclusion. This can be high frequency oscillatory ventilation (HFOV), mechanical ventilation with an endotracheal tube (intubated patients) or patients

receiving non-invasive ventilation. Non-invasive ventilation consists of Continuous Positive Airway Pressure (CPAP) and can be given by a mask or bi-nasal prongs.
This stratification is done because the effectiveness of closed loop control is dependent on the efficiency of the ventilation. High frequency ventilation theoretically has the highest efficiency with the shortest transition times, followed by intubated patients receiving mechanical ventilation. Non-invasive ventilation is more dependent on the patient's own respiratory drive.
All modes use the flow sensor and ensure that ventilation occurs with adequate volume. Alarms are set to ensure that the clinical staff is warned when changes occur, and the PRICO algorithm is disabled when the alarm is triggered. Frequent apnea's can influence the results, but should be handled by the apnea back-up function. This function ensures adequate ventilation even during apnea's. Another variable during all ventilation modes is the amount of leak. Due to the un-cuffed tubes that are used in neonatology this is even the case in intubated patients. The amount of leak will be reported and analysed to ensure that there is no significant change between the different periods.

4. STUDY POPULATION

4.1 Population (base)

Patients admitted to the NICU and receiving ventilation and additional oxygen.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

Neonates admitted to the NICU in the Erasmus MC, Rotterdam and Máxima Medical Centre, Veldhoven that are receiving respiratory support and a FiO_2 of more than 21% while having SpO_2 of 95% or less. No plans to change ventilation mode within the next 24 hours.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

Infants with any known congenital or chromosomal defects will be excluded from this study. When there is a plan to transfer the patient within 24 hours or change the ventilation mode within the next 24 hours the patient will not be included at that time.

4.4 Sample size calculation

The sample size calculation is based on the area under the curve for the SpO_2. Giving a value that has a unit of [%SpO_2*min]. A value of 30 can be reached by a SpO_2 of 30% outside of the target during 1 minute, or 30 minutes a SpO_2 that is 1% outside of the target. Values are normalized per hour.

During the animal trial conducted with this algorithm a reduction in the average of the area under the curve was found from 21 to 3 [%SpO_2*min per hour], with a standard deviation of 30 [%SpO_2*min per hour]. We accepted a significance level of 5% and a power of 80%. Because of the study design, each patient is its own control. Because of that only 22 patients are needed (Stata, StataCorp LP, USA). Because we want to show that the algorithm works in all 3 strata of ventilation we need three groups of 22 patients, and we expect a 10% dropout rate due to withdrawal or improvement in ventilation up to the point that additional oxygen is no longer needed, resulting in a total sample size of 72 patients.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Automated control of the FiO_2 based on the measured SpO_2 during 8 hours. The algorithm, named PRICO, that is used to control the FiO_2 is integrated into the Fabian HFO ventilator (Acutronic Medical GmbH, Hirzel, Switserland) and has a CE certificate. Saturation data is fed into the system through an integrated Masimo (Irvine, USA) pulse oximeter. For this purpose an additional pulse oximeter sensor is placed on of the infants extremities during the automated control of the FiO_2.

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Predictive intelligent control of oxygenation (PRICO) a closed loop algorithm that adjust the fraction of inspired oxygen (FiO_2) based on the oxygen saturation measured by pulse oximetry (SpO_2). This algorithm is integrated into the Acutronic Fabian HFO (Acutronic Medical GmbH, Hirzel, Switzerland) neonatal ventilator. This ventilator is equipped with its own Masimo Setline (Masimo Corporation, Irvine, USA) pulse oximeter. Both these devices are CE certified.

6.2 Summary of findings from non-clinical studies

When twenty two preterm lambs were ventilated with the PRICO closed loop algorithm, the time within the SpO_2 target range (90-95%) significantly better than manual control [20].

Animals were stabilized within the first half hour of life (median 33:11 min:sec, IQR (30:01–39:47 min:sec)). During the subsequent stable ventilation phase, time spend within the target range was significantly higher when the automated controller was used (93.2% (80.6–98.9%) vs. 84.0% (63.8–89.4%), $P < 0.05$, Figure 3a), and time outside the target range, depicted as area under the curve (SpO_2*sec per hour) was significantly lower (Figure 3a). The number of episodes outside the target range per hour was also significantly lower in the automated group (Table 3).

When comparing hypoxic and hyperoxic episodes, animals ventilated with automated control had significantly less episodes below the lower target saturation of 90% and showed a trend toward less hyperoxic episodes per hour ($P = 0.065$, Table 3). We observed only a small number of short hypoxic (<85%) and severe hypoxic (<75%) episodes in our model, and number of these episodes did not differ between groups. This was also reflected in the low average deviation of saturation from the median target saturation in both groups (Table 3). The duration of hyperoxic, hypoxic and severe hypoxic episodes did no differ significantly between groups.

Compared to manual control, the number of FiO_2 adjustments per hour was 2.3 times higher in the automated group, although this difference was not significant (median 13.0, IQR (3.0– 16.4) vs. 5.7 (2.3–9.8), $P = 0.243$). Applied FiO_2 did not differ significantly between groups, and we observed a heterogeneous need for oxygen within the groups (Figure 3b). Animals in the manual group were outside target range longer with higher oxygen need, however correlation between time outside target range and average FiO_2 was not significant (R^2 linear = 0.614, $P = 0.889$). In the automated group, average FiO_2 and time outside target range did not correlate (R^2 linear = 0.229, $P = 0.136$).

This algorithm has only been tested on intubated animals. Due to the mandatory sedation these animals have no respiratory drive of their own, so synchronised and non-invasive ventilation cannot be tested.

From this trial we speculate that in a clinical scenario where not only SpO_2 but also clinical evaluation of the patient influence oxygen therapy, the combination of automated and manual control might even imply better results.

6.3 Summary of findings from clinical studies

PRICO the algorithm developed within the Erasmus MC has not yet been tested during a clinical trial.

Other automatic „closed loop" system for regulation of FiO_2 based on SpO_2 have been used during several clinical trials. Different devices have proven the feasibility of automated closed loop FiO_2 control in the NICU for various modes of ventilation, mixed populations, and by using different algorithms [13, 16, 21-25]. Different algorithms have been tested on different patient groups consisting of both intubated an non intubated patients, receiving different ventilation modes. In addition, an overall reduction of manual interventions during automated control was found in these studies, indicating facilitation of caretakers and nursing staff in clinical routine [26, 27]. However, at least one study raised concerns about safety, as time within target range was accompanied by an increase in time spent below target range [16]. Only high frequency ventilation has not yet been tested. Why is unclear, but might be due to the limited number of devices that are available on the market. From an engineering and physiological standpoint this mode should behave just as well or better than normal mechanical ventilation given through an endotracheal tube.

6.4 Summary of known and potential risks and benefits

There are no known potential risks.

The benefit shown in pre-clinical trials include an improvement of the time spend within the oxygen saturation target range, a reduction in both hyper and hypoxia.

6.5 Description and justification of route of administration and dosage

6.6 Dosages, dosage modifications and method of administration

6.7 Preparation and labelling of Investigational Medicinal Product

6.8 Drug accountability

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

7.1 Name and description of non-investigational product(s)

7.2 Summary of findings from non-clinical studies

7.3 Summary of findings from clinical studies

7.4 Summary of known and potential risks and benefits

7.5 Description and justification of route of administration and dosage

7.6 Dosages, dosage modifications and method of administration

7.7 Preparation and labelling of Non Investigational Medicinal Product

7.8 Drug accountability

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The main study parameter is the oxygen saturation measured with a pulse oximeter (SpO_2). The goal is to stay within the SpO_2 target range. The range is dependent on the gestational age (GA) of the neonate:

Table 1: Oxygen saturation targets form the Erasmus MC - Sophia (2015)

- Prematuren <37 weken met zuurstoftoediening 89-95%
- Prematuren <37 weken met NO-toediening 92-98%
- A term neonaten met zuurstoftoediening 92-96%
- A term neonaten met NO-toediening 92-98%

The main parameter is the area outside of the SpO_2 target range. This gives an indication of both the time outside of the target range as well as the deviation from the target. The number of times the SpO_2 is above and or below the target range is logged, as is the duration of the event and the average deviation from the target.

8.1.2 Secondary study parameters/endpoints (if applicable)

The other important parameter is the fraction of inspired oxygen (FiO_2). Although it is acceptable to have a higher FiO2 during a period, this is only acceptable if it results in an significant improvement in the time spend within the target range, and not cause a significant rise in the time spend above the target range.

The number of manual changes of the FiO2 are logged during both routine and automated control. And the number of times that the PRICO algorithm disables due to insufficient ventilation or problems with the pulse oximeter are logged.

8.1.3 Other study parameters (if applicable)

All ventilation and patient monitor parameters are recorded (see table 2). Ventilation support is checked for changes due to pressure, volume and timing changes, because these can influence the need for oxygen. Because the interaction is too complex to adjust for, it will be mentioned in the analysis, but only in a descriptive manner.

When the patients cerebral oxygenation is monitored with NIRS this data will be recorded as well and analysed to see if automated control of the FiO_2 will lead to an improved stability (lower SD) of the cerebral oxygenation.

Table 2: Measured parameters during the study

PARAMETER	ABBREVIATION	SAMPLE RATE	DEVICE
Gestational age	GA	Ones	
Age	Age	Ones	
Birthweight	Bw	Ones	
Weight	Weight	Ones	
Gender	Gender	Ones	
Ventilation Measurements			
Oxygen saturation	SpO_2	1 Hz	Fabian HFO
Pulse rate	Pulse	1 Hz	Fabian HFO
Fraction of inspired oxygen	FiO_2	1 Hz	Fabian HFO
Inspired tidal volume	Vti	1 Hz	Fabian HFO
Expired tidal volume	Vte	1 Hz	Fabian HFO
Air leak	%Leak	1 Hz	Fabian HFO
Positive end expiratory pressure	PEEP	1 Hz	Fabian HFO
Peak inspiratory pressure	PIP	1 Hz	Fabian HFO
Respiratory rate	RR	1 Hz	Fabian HFO
Inspiratory time	Ti	1 Hz	Fabian HFO
Expiratory time	Te	1 Hz	Fabian HFO
End tidal carbon dioxide	$EtCO_2$	1 Hz	Fabian HFO
Patient monitoring			
Oxygen saturation	SpO2		M540
Pulse rate	Pulse		M540
Respiratory rate	RR		M540
Non-invasive blood pressure	Nbp		M540
Heart rate (if available)	ECG		M540
Extra during HFO ventilation			
Mean airway pressure (HFO only)	Pmean	1 Hz	Fabian HFO
Pressure amplitude (HFO only)	Pamp	1 Hz	Fabian HFO

Additional parameters if available			
Cerebral regional oxygen saturation	cSrO2	1/5 Hz	Invos
Hero Score (Heart rate variability)	Hero	1 Hour	Hero
Transcutaneous Oxygen	TcO2	1 Hz	Sentec
Transcutaneous CO2	TcCO2	1 Hz	Sentec

8.2 Randomisation, blinding and treatment allocation

This study is not randomised nor blinded. It is impossible to safely blind the care giver for the given intervention. The patients are used as their own control to limit the variation and thus the number of patients that have to be included.

Each neonate included in the study will be monitored for 8 hours while receiving routine care. The patient then receives 8 hours of automated control of the FiO_2. After the intervention there will be another 8 hour observational period during routine care is given. With this setup we can correct for patients that are worsening or improving during the time of the observations.

8.3 Study procedures

Routine care

FiO_2 is controlled by the care givers as normal

SpO2 is monitored by both the Acutronic Fabian HFO ventilator and the Dräger M540 patient monitor, but only the M540 gives alarms. All parameters measured by both devices is measured continuously, a complete list can be found in Table 2 together with the sample rates.

Alarms are set as normal.

Automated FiO_2

Alarms are set as normal, and the clinical staff is instructed to provide standard care. SpO_2 is monitored by both the Fabian HFO and the Dräger M540, but only the M540 gives alarms. All parameters as listed in Table 2 are logged.

The FiO_2 administered is controlled by the Fabian HFO with the PRICO algorithm.

The clinicians are able to manually adjust the FiO_2 at any time they feel it is needed. The PRICO algorithm disables when either the ventilation is insufficient, or there is a problem with the pulse oximeter.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

When patients improve and no longer need additional oxygen, they will drop out of the study, if it occurs before the completion of the automated FiO_2 phase.

8.4.1 Specific criteria for withdrawal (if applicable)

8.5 Replacement of individual subjects after withdrawal

Patients that are withdrawn from the study before its completion will not be replaced.

Ten percent extra patients are included to compensate for withdrawal or premature

drop-out due to an improvement of ventilation and no need of oxygen therapy (FiO_2=21%)

8.6 Follow-up of subjects withdrawn from treatment

Subjects that are withdrawn will not be followed.

8.7 Premature termination of the study

The study will be halted when there are any problems with the closed loop controller reported by the clinical staff. Problems are defined as frequent fluctuations around the target range, in ability to correct the saturation to within the intended target range (excluding the cases when it runs into the minimum or maximum allowed FiO_2 as set by the clinical staff). When it is determined that the problem is caused by the algorithm or the implementation of the algorithm with in the Fabian HFO ventilator, the study will be terminated prematurely.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs:

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for

SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC. The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

A DSMB or Safety Committee is not needed.

10.STATISTICAL ANALYSIS

All analysis will be done on a intention to treat, with reporting on the time that the automated algorithm was disabled and the number of manual adjustments to ensure that the algorithm was doing the fast majority of the adjustments. Every time the algorithm disables the reason is recorded and will be reported. All manual adjustments that are

performed during the automated control period will be assessed and the possible reason reported.

Because analysis are performed on a per time basis, missing data does not affect the outcome. The amount of missing data, if any, will be reported.

10.1 Primary study parameter(s)

The efficiency of the PRICO algorithm will be assessed by comparing the time spend outside and deviation from the SpO_2 target range. This is done with the area under the curve, normalized to a one hour period [SpO_2*min per hour]. It is calculated by taking the SpO_2 value from the patient monitor, logged once every second and, when it is outside the SpO_2 target range, subtract the target. The absolute value of all deviations is added together and divided by the length of all the recorded data in hours. The significance will be tested with a repeated measurement ANOVA.

The number of collected data points per period will be reported to show any possible bias due to unmeasurable SpO_2 levels, malfunctions or other events. This will be reported as a percentage of time recorded.

When there is a significant difference between the first and last period, the argument will be made that the patient changed overtime. In that case the automated period will be compared with the best of the two observational periods.

10.2 Secondary study parameter(s)

The FiO_2 administer during the three different periods of the study is tested a repeated measurement ANOVA. Additional oxygen is only exactable when it results in a significant improvement in the stability of the SpO_2.

Manual FiO_2 changes are compared, and data is analysed to check for the reason of manual intervention during the automated FiO_2 period. Periods when the algorithm is turned off are reported, both in length, total period and average duration per period and total number of times that the algorithm was stopped. Normally the algorithm turns of when there are problems with either the SpO_2 measurement or the ventilation.

10.3 Other study parameters

All other parameters listed in Table 2 will be assessed for significant changes over time with repeated measurement ANOVA. Because the changes that are made to the ventilation can influence the need for additional oxygen, changes made to any relevant parameters will be described in the analysis. But the results cannot be corrected based on the changes. Cerebral saturation will be analysed if there is a significant improvement during the period of automated FiO_2 control.

10.4 Interim analysis (if applicable)

Not applicable

11.ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted in accordance to the principles of the Declaration of Helsinki [28] and in accordance with the Medical Research Involving Human Subjects Act (WMO) [29].

11.2 Recruitment and consent

Parents or care givers of neonates that meet the requirements and can potentially be included into this study will be approached by one of the members of the research team. They will inform patients of the study, give them the information letter and answer all question they have regarding the study. They will be given at least 24 hours to consider their decision.

11.3 Objection by minors or incapacitated subjects (if applicable)

The Code of conduct relating to expressions of objection by minors participating in medical research is applicable. Both parents, care givers or all legal representatives must give consent for the inclusion of the neonate into this study.

11.4 Benefits and risks assessment, group relatedness

There is no additional risk for the patients included in this study. During the automated control period that patients will have the same patient monitoring and alarms as during routine care. A member of the clinical staff is always present to intervene whenever needed.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the

WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

There are no incentives and no compensations given to either the neonates or their parents when they are approached for this study or when they participate.

12.ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data is stored on a dedicated password protected computer that is connected to the patient network. This computer is not accessible from the outside and is positioned on the NICU. As soon as data logging is completed the data is made anonymous and copied to a secure data server located at the Rotterdam Internet eXchange and hosted by the Erasmus Medical Centre. All data is kept for the duration of the study and at least 15 years thereafter. Only anonymized data is stored, making it impossible to later relate any outcome to a specific patient.

12.2 Monitoring and Quality Assurance

< If monitoring of the conduct of the study takes place, please describe who will monitor, what will be monitored, frequencies etc. One can refer to a monitoring plan for details >

12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

<The following text is applicable for studies <u>with</u> an investigational medicinal product.> The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 Public disclosure and publication policy

Full public disclosure is allowed and planned, no restrictions are applied.

13.STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

The mechanism between Oxygen and oxygen saturation is known, but the timing and reaction to a certain step size differ between patients.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

Not applicable

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Not applicable

d. Selectivity of the mechanism to target tissue in animals and/or human beings Not applicable

e. Analysis of potential effect

Not applicable

f. Pharmacokinetic considerations

Not applicable

g. Study population

This study needs to be performed in neonates because of the state of their lungs and circulation. These will affect the timing and affectedness of the algorithm. Because the algorithm is developed specifically for neonates, we expect optimal performance in this patient group.

h. Interaction with other products

Patients that are receiving nitrous oxide (NO) may react different to the administered FiO2. The algorithm is inherently stable, so even if timing is suboptimal it should keep the patient within the intended target oxygen saturation range. The patient monitoring will ensure alarms are raised when this is not the case.

If these patients are included, the data of these patients will be used to examine if they do in fact react different because of the NO.

i. Predictability of effect

We expect a similar but exaggerated effect as seen in the animal, because during manual control there is no dedicated person for the manual adjustments.

j. Can effects be managed?

Not applicable

13.2 Synthesis

The intervention given during the study is the closed loop control of the FiO_2 according to the PRICO algorithm based on SpO_2. FiO_2 is given clinically as part of the standard of care. The targets used during the trial are the same as during routine care and the minimum and maximum FiO_2 that the algorithm can give is limited by the user.

All patients are fitted with two pulse oximeters, one for the closed loop while both are used for monitoring and alarming the clinical staff.

The FiO_2 can be manually adjusted at all time. When ventilation is sub optimal (as indicated by the clinical staff) PRICO will disable and an alarm will sound. PRICO will also disable when the pulse oximeter fails to measure or when the signal quality is insufficient. The entire point of an automated algorithm for the FiO_2 adjustments is the time it normally takes to respond to an alarm. When PRICO fails the routine care is there as a back up to ensure that FiO_2 is adjusted. The biggest residual risk is that PRICO is to aggressive in its adjustments resulting overshoot, short periods of either hyper or hypoxia opposite to the direction that caused the adjustment.

It is necessary to asses PRICO in neonates because it was developed especially for them. The physiology and related timing makes that it cannot be tested or used in other patient groups without adapting it.

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