Letterhead of the recruiting study center

Effects of closed-loop automatic control of the inspiratory fraction of oxygen (FiO_2-C) on outcome of extremely preterm infants – a randomized controlled parallel group multicenter trial for safety and efficacy)

Information for Parents and Guardians

For Germany - Version 4.3. / 08.06.2021

Dear Parents and Guardians,

We would like to ask for your consent to let your child participate in a clinical trial. The following pages are to inform you in detail about the study and to help you to reach a decision on your child's participation.

Despite all efforts for the well-being of extremely preterm babies, some suffer from long-term mental or neurological impairments. This study will include a total of 2240 infants in about 50-100 hospitals across Europe and aims to bring us closer to the objective of discharging home more healthy preterm babies in the future.

One of the problems when treating extremely preterm babies is their limited lung function and immature respiratory control. The lung disease of prematures is due to their immature lung structure, an inflammatory response and modified lung development, leading to an increased need for oxygen in the respiratory gas. The immature respiratory control causes apnea (the infant temporarily stops breathing) and as a result recurrent decrease in oxygen saturation in the arterial (oxygen-rich) blood.

These two problems, which are characteristic of preterm infants, cause increasing fluctuations in your baby's oxygen levels from the second week of postnatal life onwards, which will cease again spontaneously as the infant matures, around his/her "due-date" at the latest. Because of these fluctuations, the oxygen level in the respiratory gas (also called FiO_2 – fraction of inspiratory oxygen) must continuously be adjusted, up to now mainly by the nurses and doctors working in the NICU.

Recently, ventilators approved for the treatment of preterm infants have started to include a device to automatically adjust the oxygen level in the respiratory gas based on the oxygen saturation in a baby's blood.

Advantages and disadvantages of manual adjustments of the oxygen level in the respiratory gas

Until today, this is the standard method. The attending nurse or doctor not only considers the blood oxygen levels but also takes into account her/his assessment of the breathing pattern and behavior. But the nurse or doctor cannot continuously be next to each baby's incubator and thus, adjustments might be delayed. If the doctor's or nurse's assessment is not correct, the child will experience short episodes of too high or too low oxygen saturation in the blood.

Advantages and disadvantages of the automatic adjustment of the oxygen level in the respiratory gas (FiO_2-C) by the ventilator

The advantage of this method is that the ventilator can continuously monitor a baby's blood oxygen level and adjust the level in the respiratory gas accordingly.

Your baby may have to be supported by a different ventilator, and, depending on the device, an additional sensor for the automatic adjustment of oxygen levels will be attached to your baby's hand or foot. The automatic adjustment does not replace the adjustment by the doctor or nurse but is supposed to complement and support it. The automatic adjustments will always be supervised by the nurse or doctor in charge. If the program makes an error, this might lead to a short episode of too high or too low oxygen saturation (same as for the manual adjustment). In several short-term studies (up to 24 h), the automatic adjustment increased the time within the oxygen target range compared to manual adjustments. However, the expected safety in long-term application and the long-term benefit has not yet been examined and will be verified in this study.

In this study, various types of ventilators with FiO_2-C will be applied at the discretion of the local study site. All ventilators are CE-marked and applied according to their intended use.

Study Procedures

If you give your consent to participation in this study, your child will be allocated to one of two treatment groups according to a random sequence. Neither parents nor physicians are able to influence this treatment allocation (this procedure is called „randomization" and aims to allocate infants with known and unknown risk factors equally to both treatment groups).

One group (control group) is being treated according to the current standard of care and the oxygen level in the respiratory gas is adjusted by the nurse or doctor as usual.

The oxygen level in the respiratory gas of group 2 (FiO_2-C group) is being adjusted both manually by the nurse or doctor and, in addition, automatically by the ventilator. All other care will be according to current standards and is identical to the control group.

Duration of the study, discharge home, follow-up examination at the age of 2 years

The allocated treatment (manual adjustment or automated and manual adjustment of FiO_2) will be maintained as long as your baby needs respiratory support with additional oxygen or shows many fluctuations in oxygen level. It will end at the latest when your baby reaches a postmenstrual age of 36 weeks (4 weeks before the "due date" / the calculated date of birth).

Your baby will not have to stay longer in hospital because of participation in this study, but will be discharged home whenever the team treating your baby thinks that he/she is „fit enough to go home".

The study will end with a standardized neurodevelopmental assessment at 24 months of age (corrected age due to prematurity) which is mandatory in most countries for all premature infants.

Examinations within the study and data collection

Your child does not have to undergo any purely study-driven examination – unless, in particular study sites only, you may be asked for your consent to participate in additional study-driven examinations and you give the respective informed consent (see below).

However, as part of the study, the results of routine examinations and data concerning the clinical outcome shall be collected and assessed:

1. **Neurodevelopment assessment at 24 months of age:** This examination does not cause any pain or stress. It is very similar to routine check-ups by pediatricians. Your baby's mental and physical progress will be assessed as well as his/her ability to walk, to perceive pictures and to concentrate while coping with a task. Most kids have fun doing these tests. In any case, this examination is compulsory for all premature babies with less than 1500 g birth weight in many European countries. This means that you and your baby will not have to invest any additional time for this study. If this examination does not take place at your local study site, we request your permission to obtain the examination results directly from the institution / pediatrician carrying out the examination.
2. **Examination of the oxygen saturation data:** As standard of care, the oxygen saturation of the blood of all premature babies has to be monitored by means of a pulse oximeter. The 'oxygen saturation' describes the proportion of the red blood colorant, 'hemoglobin', carrying oxygen. A pulse oximeter measures the oxygen saturation non-invasively, based on the extinction of light transmitted through tissue. The data of this monitoring shall also be assessed in this study to find out whether this new technology also helps to reduce the time with too high or too low oxygen saturation on a long-term basis.

3. **Clinical Data:** As part of the study the following data are also collected: birth weight, gestational age at birth, duration of respiratory support, respiratory status at 36 weeks postmenstrual age, results of the routine eye examinations, routine cerebral and heart ultrasound examination etc.

   In study hospitals where magnetic resonance imaging of the brain around the "due-date" are routinely performed in all very preterm infants, the results of these examinations will also be collected for the study.

   In study hospitals where weekly urine samples are analyzed routinely, small aliquots of these urine samples will be stored for analysis of indicators of oxygen damage to lipids, proteins and genetic material.

   If your child is transferred to another hospital, we request your permission to obtain the study relevant data from the institution/pediatrician/eye specialist continuing the treatment for your child.

Potential additional, purely study-driven examinations at some study sites

Measurement of the brain's oxygen supply:

This examination is non-invasive and does not cause any pain or stress. By means of a device similar to a pulse oximeter (see 2 above), light is being sent into the tissue and by measuring the light which returns to the surface, the oxygen supply of the organ under the sensor can be determined. This examination is a standard procedure during cardiac and carotid artery surgery and, in this study, shall be carried out 4 times for 24 hours each during the hospital stay of your baby. In case your local hospital participates in this additional assessment, you will be asked to give your consent to this study-driven examination on the informed consent form.

Your child may benefit from taking part in this study

Your child has a 50% chance to be treated with the new technology (automated control of the oxygen level in the respiratory gas) and may benefit from an increased proportion of time within the oxygen target range of which the investigators hope that it may result in lower rates of complications of prematurity.

Potential benefits for future patients

This study will contribute valuable data and further our understanding about the optimal administration of the medication most frequently given to preterm infants: oxygen. Thereby, we hope to improve future treatment of extremely preterm infants and the new technology under investigation here.
If this technology actually brings clinical benefit for the infants, this study will contribute to a faster implementation of this technology everywhere in the world. There might be more healthy infants who can be discharged home in the future.

Fundamental risks related to the administration of supplemental oxygen in preterm infants (during the study *as well as during standard care*):

Inadequate administration of supplemental oxygen can a) in case of *too little oxygen* lead to oxygen deficiency, which may particularly affect the brain but also increase mortality, and b) in case of *too much oxygen* harm the eyes (i.e., cause retinopathy of prematurity), the lung and the brain. Hence, both, too little and too much oxygen, may impair long-term development. In the summary of product characteristics for medicinal oxygen, the rates of such adverse reactions to oxygen are described as follows: retrolental fibroplasia (the most severe degree of retinopathy of prematurity): rare (i.e., the risk for this eye disease is between "one child in every 10,000 children exposed will acquire the disease" and "one child in every 1,000 children exposed will acquire the disease"); lung injury: occasionally (i.e., the risk for lung injury caused by oxygen is between "one child in every 1,000 children exposed will be affected" and "one child in every 100 children exposed will be affected").

The study has been critically reviewed

The study has been critically reviewed and approved both by the ethics committee responsible for your hospital and the leading ethics committee in Tuebingen. It has also been approved by the German competent authority (BfArM).

The study and the participants' well-being is continuously supervised

To ensure maximum safety of all study participants and to ensure that the study will be modified or stopped early in case there will be new evidence of harm (which is not expected at all), the study is supervised at specified intervals by an independent Data Monitoring Committee.

The study is being realized by public funds

The study is funded by the German Federal Ministry for Education and Research (BMBF) after having been selected out of a large number of applications.

Who is responsible for the study?

The study is being „sponsored“ by the Universitätsklinikum Tübingen, Germany, i.e. the Universitätsklinikum Tübingen is responsible for the sound conduct of the study.

Participation in the study is voluntary

Of course, the participation in this study is voluntary. If you refuse the participation, this will not have any negative impact for you and your baby nor will your decision influence the relation to your child's doctor or nursing staff.
Your baby will still receive the best possible treatment.

Your baby can leave the study at any time

Even if you have given your consent to participation in the study, you can revoke it without prior notice and without justification. Your decision to do so will not have any negative impact on your baby's medical treatment or your relation to the medical team. In this case, the data collected up to that point of time will still be evaluated. According to the legal stipulations, your consent to the storage and use of the accumulated data cannot be revoked with retroactive effect.

If you decide to prematurely stop your child from participating in the study, you can decide if~~,~~ future examination results (as for example results from the follow-up examinations at the age of 2 years) may be further collected for the study analysis. This is very important for us because also incomplete data might contain important information that may help other babies.

If the study doctor thinks that there might be any negative impacts for your baby, he/she can terminate the study intervention in your child even without your authorization. In this case, the doctor would continue to treat your child according to the best medical knowledge and the data of your baby would be evaluated according to the study protocol.

Of course, you will be informed about any changes

You will be informed about all new results related to this study. If there are any changes concerning the study or if the risk benefit ratio has changed, we will again ask you for your consent.

Insurance

The participants of this study are insured at HDI Global SE represented by location Düsseldorf, Mr. Günther Ripphahn (Am Schönenkamp 45, 40599 Düsseldorf, Telefon: 0211 / 7482 286, Email: Guenter.Ripphahn@hdi.global, insurance number: 5701 0311 03840 390 2668001 registration number: 57 010311 03013). Maximum benefit is 500,000 € per patient. Please find attached a copy of the insurance policy as well as of the conditions resulting from the policy. If you think that there are any adverse events resulting form the study, you are obliged to inform your doctor and the insurance without delay.

Data Protection

At all times, the identity of your child will only be identifiable at the institution where your child is being cared for. After removal of the name/address of your child, so called 'pseudonymized' data (without name and address) will be transferred to the protected study database at the 'Sponsor' of the study (University Hospital Tuebingen) where it will be stored for 10 years after the end of the study. Thereafter, all data which could enable re-identification will be removed (study code, exact dates etc.). Publications of study data will exclusively rely on 'anonymized' data (which will no longer enable identification).

According to the legal requirements of the German Pharmaceutical Act, the consent you give with regard to the collection and processing of your child's data, in particular the data pertaining to your child's health, is irrevocable. Even though you can withdraw your consent to participation in the study at any time, the data collected up to that point of time can continue to be used in the study if required for the following purposes: a) to determine the effects of the studied substances (oxygen) b) to ensure that the interests of our child are protected and will be in no way affected.

The person responsible for data integrity at the sponsor of the study is the coordinating investigator Prof. Dr. Axel Franz (Email: fioc@med.uni-tuebingen.de). The contact details of the data protection officer at

the sponsor are: Datenschutzteam des Universitätsklinikums Tübingen, Calwerstraße 7/4 72076 Tübingen; phone: 07071 29-87667; Email: dsb@med.uni-tuebingen.de. The regional authority for data protection in charge of the sponsor is: Landesbeauftragte für Datenschutz und Informationsfreiheit BW (addresse: Postfach 10 29 32, 70025 Stuttgart, phone: 0711/615541-0, Fax: 0711/615541-15, Email: poststelle@lfdi.bwl.de)
The responsible person for data handling at the local study center is the local investigator, whose contact details are given below along with the contact details of the data protection officer of the local institution and the regional authority for data protection in charge of the local institution.

You have the right of appeal at one of the data protection authorities listed herein. You also have the right to claim information on your child's data being stored (including a copy of this information free of charge) as well as the right to demand correction or deletion of the data (with the legal limitations described above).

Further questions and contact details

If you have any further questions relating to this study or to your rights and duties as parents of a child that participates in the study, please do not hesitate to contact your local study doctor treating your child. You can also contact the relevant regulatory authority, Bundesinstitut für Arzneimittel und Medizinprodukt (BfArM), who has approved the study.

Investigator:		National Authority:
Name:	.....	Bundesinstitut für Arzneimittel und Medizinprodukte
Department:	.....	Klinische Prüfungen
Address:	.....	Kurt-Georg-Kiesinger-Allee 3
	.....	53175 Bonn
Phone:	.....	+49 6103 77 1811
Email:	.....	klinpruefung@bfarm.de

Data Protection Officer of the local study center:

Dept.:	.....
Address:	.....
	.....
Phone:	.....
Email:	.....

Relevant regional authority for data protection in charge for the local study center:

Naming:	.....
Address:	.....
	.....
Phone:	.....
Email:	.....

If there are any changes at the regional authority related to data protection, we refer to the following internet address of the 'Bundesbeauftragten für den Datenschutz und die Informationsfreiheit: https://www.bfdi.bund.de/DE/Infothek/Anschriften_Links/anschriften_links-node.html'

At your local study center, ventilators with automated control of the oxygen level are produced by the following manufacturer:

Manufacturer:	.....
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Address:	.....
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Website:	.....

Further questions arising from the informed consent discussion:

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