**Information for parents of a newborn baby for participation in medical-scientific research**

**Doxapram to treat breathing pauses in premature babies**

*Official title:*

Doxapram versus placebo study in premature infants: a double-blind multicenter randomized study

**Introduction**

Dear Sir/Mrs,

Your son or daughter is admitted to the neonatology department of [*name hospital*]. We ask you whether your child may participate in a medical-scientific study. Participation is voluntary; it is up to you to decide whether you wish to do so. However, your written consent is required to participate. You receive this letter because at birth your child was younger than a pregnancy of 29 weeks. After premature birth, the control of breathing is not yet well developed and episodes of breathing pauses may occur.

Before you decide whether you want your child to participate in this study, you need to know what it means. Please read this information carefully and ask the researcher if you have any questions. You can also ask the independent expert mentioned at the end of this letter for additional information. You may also talk about it with your partner, friends or family. General information about participating in medical-scientific research can be found on the website of the central government: [www.rijksoverheid.nl/mensenonderzoek](http://www.rijksoverheid.nl/mensenonderzoek).

**1. General information**

This study has been set up by doctors and researchers of the Erasmus MC - Sophia Children's Hospital, Emma Children's Hospital AUMC and UZ Leuven and is supported by the Dutch Neonatal Network (N3) and the Care4Neo parents’ association. It is carried out by doctors and researchers in the neonatology departments in various hospitals in the Netherlands and Belgium. The Medical Ethics Review Committee (METC) of Erasmus MC has approved this research. In addition, the Board of Directors of your hospital has approved the conduct of the study in your hospital. General information about the review of the investigation can be found on the website of the Central Government: www.rijksoverheid.nl/mensenonderzoek.

**2. Purpose of the study**

The aim of this study is to find out how good and safe the drug doxapram is for the treatment of persistent respiratory breaks in premature infants. Doxapram is not officially registered for children, but is already given to premature babies to a greater or lesser extent in all Dutch centers, while knowledge about long-term safety is still lacking. Doxapram can have an immediate good effect on breathing. However, it also regularly leads to side effects such as irritability, a faster heartbeat and feeding problems. Whether doxapram ensures a better future for premature babies is currently unknown. This is, of course, very important to know and that is why we want to establish this very precisely with this research.

**3. Background of the study**

After preterm birth, organs such as the brain and lungs are still immature. Also, the control of breathing often doesn't work well yet. As a result, children born prematurely forget to breathe regularly, which gives rise to what are known as breathing pauses.

Supporting one's own breathing through the nose with air and/or oxygen and the medicine caffeine are given as standard to at least prevent the breathing pauses. Despite these interventions, the breathing pauses may persist and treatment should be intensified. One of the options might be artificial ventilation. Prolonged artificial ventilation can in the long term lead to problems in lung development and to disturbed overall development. That is why attempts are being made to limit the use of artificial ventilation.

Another treatment might be administration of the drug doxapram. This drug could remedy the persistent episodes of breathing pauses. Doxapram stimulates breathing in a different way than caffeine does, and therefore probably leads to fewer episodes of breathing pauses. However, doxapram can also make children restless or unable to rest, which would be less desirable. The safety of doxapram and its long-term effect has never been well researched.

**4. What participation involves**

If you consent to your child's participation in this study, ánd if your child qualifies for the study, a computer will randomly determine which treatment your child will receive. Half of the newborns will receive doxapram, the other half will receive a placebo. A placebo does not contain an active substance. The possible replacement of doxapram by a placebo is the only thing this study will change in your child's standard of care. You, the researchers, the doctors and nurses do not know which group your child is in. If it is important for your child's health, this can be looked up.

We will treat your child with doxapram or placebo according to the doxapram guidelines used in current practice. Administration is always started via an infusion. Doxapram or placebo can later also be administered by gastric tube. Your child will be treated until it is no longer necessary because things are going better. If the breathing pauses persist after starting doxapram or placebo, your child will temporarily be put on artificial ventilation. If necessary, administration of the drug can be restarted later. General information about participating in research can be found on the website of the central government: www.rijksoverheid.nl/mensenonderzoek.

**Check-up visits**

By default, all children who were younger at birth than 29 weeks of pregnancy are invited for an outpatient check-up visit at the ages of 2, 5 ½ and 8 years. These check-ups are intended to closely examine the health and development of prematurely born children. Various questionnaires are also administered to determine the children’s IQ and quality of life. These visits are also scheduled for your child. The information that is collected will be used in this study. When participating in this study, you and your child will be asked to complete a number of additional questionnaires. We will try to limit the time spent on this as much as possible.

**5. What is expected of you?**

In order for the study to run smoothly, it is important that you adhere to a number of conditions after your child's discharge from the NICU. It is important that you contact the investigator:

* if your child is admitted again or treated in this or another hospital.
* if your child suddenly develops unfamiliar health problems.
* if you no longer wish to participate in the study.
* if your contact details change.

**6. Possible side effects and other adverse effects/discomforts**

Treatment with doxapram could have a good effect, but can also cause side effects. Restlessness and irritability are particularly common. In the long term, little is known about the side effects and adverse effects of doxapram in children, but these will be carefully considered in this study. In the case of side effects, the doctor on duty will consider whether it is necessary to reduce the dosage or stop the study medication. We do not expect any additional side effects or other adverse effects as a result of this study.

**7. Possible advantages and disadvantages**

It is important that you weigh up the possible pros and cons before you decide to participate. Your child has no benefits from participating in this study. By participating in this study, your child contributes to a better treatment of premature babies with persistent episodes of breathing pauses in the future. Doxapram possibly can prevent artificial respiration in the short term, but the (adverse) long-term effects are not known. Participating in research means that you have agreements to keep.

All these matters are described in detail under points 4, 5 and 6.

**8. Resistance of your child/the child you represent**

It may be that your child/the child you represent is resisting (not cooperating) during the study. The investigator must then of course stop the study immediately. It is difficult to describe exactly what resistance is. Suppose that your child does not feel like cooperating in the follow-up check-ups, then this will be accepted. Before the start of the study, you will be consulted on what is considered resistance. The investigator will comply with the Code of Conduct for resistance by minors ([www.ccmo.nl](http://www.ccmo.nl)).

**9. If you do not wish your child to participate, or would like to stop your child’s participation in the study**

You decide for yourself whether you want your child to participate in the study. Participation is voluntary. If you do not want your son or daughter to participate, he or she will be treated for breathing pauses as usual. Your child will always be treated with the medicine caffeine and supported with air and oxygen. If the breathing pauses persist, the usual next step will depend on the centre and the treatment team. They may also choose to give doxapram or to start artificial respiration in order to better support breathing.

If your child participates, you can always change your mind and stop participation, even during the study. Your son or daughter will then be treated as usual. You do not have to give a reason. However, you should immediately inform the investigator of your decision. The data obtained thus far will be used for the study.

If there is any new information about the study that is important for you, the investigator will inform you of this. You will then be asked if you wish to continue your child’s participation.

**10. End of the study**

Your child's participation in the study ends when

* all check-ups as described under point 4 have been completed
* you choose to stop by yourself
* the investigator thinks it's better to stop
* Erasmus MC, the government or the medical ethics review committee, decides to stop the study.

The entire study will be over when all participants have finished participation.

After all data have been processed, the investigator will inform you about the most important results of the study. This will be about 8 to 10 years after the start of your child's participation.

The investigator can also tell you at the end of the entire study which treatment group your child was in. If you do not want this, please tell the investigator. The investigator is not allowed to inform you in that case.

1. **Use and storage of your child’s data**

For the purpose of this study, your child's personal data will be used and stored. This includes data such as name and address and data about your child's health. The collection, use and storage of the data is necessary in order to answer the research questions and to be able to publish the results. We ask for your consent to the use of your child's data. If your child participates and is transferred to another hospital in your area during the study, you also consent to request information about your child's course of illness during this period.

**Confidentiality of data**

To protect your child’s privacy, his or her data will be coded. Your child’s name and other information that could directly identify him or here are thereby omitted. This information can only be encrypted with a key to the code stored securely in the hospital in question. The data that is sent to the sponsor only contain this code, but not your child’s name or other data that can identify him or her. In reports or publications about the study, the data will also not be identifiable.

**Access to data for review**

Some people at the hospital may have access to all your child's data, including data without a code. This is necessary in order to check that the study is carried out properly and reliably. Persons who have access to your data are: the committee that monitors the safety of the investigation and a monitor (independent person who sees to it if everything is going well) who has been hired for this purpose. They will keep the data confidential. We ask you to give permission for this inspection.

**Retention period of data**

The data shall be stored at the study site for 15 years.

**Storage and use of data for other studies**

Your child’s data may still be of interest after the end of this study for other clinical research in the area of premature birth. This is why your child’s data will be stored for 15 years. You may indicate on the consent form if you do or do not agree with this. If you do not consent to this, your child can still participate in the current study.

**Information about unexpected findings**

During this study, by chance, something may be found that is not important for the study but is important for your child. If this is important for your child's health, you will be informed by the treatment team. You can then discuss what needs to be done with your family doctor or specialist. You also give your consent for this.

**Withdrawal of consent**

You can always withdraw your consent for the use of your child’s personal data. This applies to this study and also for the storage and use for future research. The study data collected until the moment you withdraw your consent will still be used for the purpose of the study.

**More information about your rights concerning the processing of data**

For general information about your rights concerning the processing of your child’s personal data, please consult the website of the Dutch Data Protection Authority.

If you have any questions about your rights or your child’s rights, please contact the person responsible for the processing of personal data. For this study:

Annelies Ham

Project Manager Dept. of Neonatology

a.ham@erasmusmc.nl

If you have any questions or complaints regarding the processing of your child’s personal information, we recommend that you contact the centre where your child is being treated. You may also contact the centre’s Data Protection Officer for the institution (see contact details in Appendix A) or the Dutch Data Protection Authority.

**Registration of the study**

Information about this study is also included in a registry of medical research, i.e. www.neonatologynetwork.eu. No data that can be traced back to you or your child is included. After the study, the website may offer a summary of the results of this study. You can find this study under DOXA trial.

1. **Insurance for subjects**

Insurance has been taken out for everyone who participates in this study. The insurance covers damage resulting from the study. Not all damage is covered. In **Appendix B** you can find more information about the insurance and the exceptions. It also states who you should report damages to.

1. **Informing of family doctor and attending specialist**

We will send a letter or e-mail to your family doctor and attending specialist to let them know that your child is participating in the study. This is in the interest of your child's safety. If you do not agree with this, your child cannot participate in this study.

1. **No compensation for participation**

The treatment for your child in relation to the study costs you nothing. You will not be paid to participate in this examination. However, we do offer a small gift for your child as a thank you for participating.

1. **Do you have any questions?**

If you have any questions, please contact the doctor treating your child to answer them. You can also be referred to one of the investigators. For independent advice on participating in this research you can contact the independent doctor. He knows a lot about the study, but has nothing to do with this study. If you have complaints about the study, please discuss this with the investigator or your child's attending physician. If you prefer not to do so, you can turn to Erasmus MC's complaints committee. All details can be found in Appendix A: Contact details.

**16. Signing of informed consent form**

When you have had enough time to consider participation of your child, you will be asked to decide about participation in this study. If you consent, you will be asked to confirm this in writing on the attached consent form. With your written consent, you indicate that you have understood the information and agree to participate in the study.

Both you and the investigator will receive a signed version of this consent form.

Thank you for your consideration.

*[ondertekenen]*

**Appendices**

A. Contact details

B. Information about the insurance

C. Parental or guardian consent form

Scan for animation

**Appendix A: contact details for** [*name hospital*]

**Responsible researchers** [*name hospital*]**:**

[*name pediatrician-neonatologist*]

Pediatrician-neonatologist

[*name physician investigator*]

[*name research nurse*]

Research nurse

[*mailing address*]

Telephone: [*telephone number research nurse*]

**Neonatology Department:**

[*name hospital*]

[*internal address department of neonatology*]

[*mailing adress*]

[*telephone number secreteriat*]

**Independent physician:**

Prof. M. de Hoog

Pediatrician, head of the Intensive Care Unit for children

Telephone: + 31 (0)10 70 362 60

**For more information about your rights:**

For more information or questions about your rights, please contact the Data Protection Officer or the Dutch Data Protection Authority.

**Data Protection Officer:**

[*name contact person to protect your privacy*]

[*address*]

Telephone: [*telephone number*]

Email: [*mailing adress*]

**Complaints Committee:**

If you are not satisfied with the investigation or the treatment, you can contact the independent complaints committee.

[*address of the complaints committee*]

[*telephone number*]

[*mailing address*]

[*website*]

**Coordinating researchers DOXA-Trial:**

Dr. S.H.P. Simons

Pediatrician-Neonatologist

Intensive Care Neonatology

Erasmus MC-Sophia Children’s Hospital

PO Box 2060, 3000 CB Rotterdam

Telephone: +31 (0)10 70 360 77

Email: s.simons@erasmusmc.nl

Dr. G.J. Hutten

Pediatrician-Neonatologist

Intensive Care Neonatology

Amsterdam UMC-Emma Children’s Hospital

Box 22660, 1100 DD Amsterdam

Telephone: +31 (0)20 56 634 77

Email: g.j.hutten@amsterdamumc.nl

**Central research coordination:**

Debbie Nuytemans

Coordinator Neonatology Network Netherlands

[www.neonatologynetwork.eu](http://www.neonatologynetwork.eu)

**Appendix B: Information on insurance**

Erasmus MC has taken out insurance for everyone who participates in this study. The insurance covers damage resulting from participation in the study. This applies to damage during the study or within four years of the end of your child's participation in the study. You must report any damage to the insurer within those four years after the end of the study.

The insurance does not cover all damage. Below it is briefly stated which damage is not covered.

These provisions can be found in the *'Besluit verplichte verzekering bij medische wetenschapelijk onderzoek met mensen 2015*' (mandatory insurance for medical scientific research with people decree 2015). This decree can be found in the Legal Acts Database (https://wetten.overheid.nl).

In the event of damage, please contact the insurer directly.

The insurer of the study is:

 Name: CNA Insurance Company Europe SA

 Address: Polarisavenue 140, 2134 JX Hoofddorp

 Telephone: + 31 (0)23-3036004

 E-mail: ClaimsNetherlands@cnahardy.com

 Policy number: 10220695

 Contact: Senior Claims Handler, Esther van Herk

The insurance provides cover of € 650,000 per subject and € 5,000,000 for the entire study (and € 7,500,000 per year for all studies by the same client).

The insurance will **not** cover the following damage:

* damage due to a risk about which you were informed in the written information. This does not apply if the risk is more serious than anticipated or if the risk was very unlikely;
* damage to your child’s health that would also have occurred if your child had not taken part in the study;
* damage due to not (completely) following directions or instructions;
* damage to your child’s offspring, if any, due to a negative effect of the study on your child or his or her offspring;
* damage due to an existing treatment method when studying existing treatment methods.

**Appendix C: Child participation consent form**

**Doxapram for the protection of premature babies**

I have been asked to give permission for my child to participate in this medical-scientific study:

Child's name: Date of birth: \_\_ / \_\_ / \_\_

* I have read the information letter for the parents/carers. I was also able to ask questions. My questions have been sufficiently answered. I had enough time to decide whether I want my child to participate.
* I know that participation is voluntary. I also know that I can decide at any time that my child will not participate anyway. I don't have to give a reason.
* I give permission to inform the specialist who treats my child as well as the pharmacist that my child is participating in this study.
* I consent to the collection and use of my child's data to answer the research question for this study.
* I know that some people may have access to all my child's data for the purpose of monitoring the study. Those people are listed in this information letter. I consent to such access by these people.
* I give permission for my child's general practitioner and/or attending specialist to be informed of unexpected findings that (may) be important for my child's health.
* I □ **give**

□ **do not give**

consent to retain and use my child's personal data for a longer period for future research in the field of doxapram treatment in premature infants.

* I □ **give**

□ **do not give**

 consent to approach my child again for a follow-up study after this study.

* I □ **do**

□ **do not**

wish to be informed of which group my child was in. This information can only be provided after the entire study has been completed.

* I agree that my child will participate in this study.

Name of parent/legal representative\*\*

E-mail address: …………………………………………………………..........

Signature: Date: \_\_ / \_\_ / \_\_

Name of parent/legal representative\*\*

E-mail address: …………………………………………………………..........

Signature: Date: \_\_ / \_\_ / \_\_

---------------------------------------------------------------------------------------------------------------------------------

I hereby declare that I have fully informed the above-mentioned person(s) about the said study.

If information becomes known during the study that could influence the consent of the parent or guardian, I will inform him/her in good time.

Name of investigator (or his/her representative):

Signature: Date: \_\_ / \_\_ / \_\_

---------------------------------------------------------------------------------------------------------------------------------

Additional information was provided by:

Name:…………………………………………………………………………

Function:……………………………………………………………………..

Signature: Date: \_\_ / \_\_ / \_\_

---------------------------------------------------------------------------------------------------------------------------------

\*\* If the child is younger than 16 years, the parents exercising custody or the guardian shall sign this form.

*The parent/guardian will receive a full information letter together with a signed version of the consent form.*