**Information for parents of newborn children for participation in a medical scientific study**

**Doxapram to treat interrupted respiration (apnoea) in premature babies**

*Official title:*

Doxapram versus placebo study in premature babies: a double-blind multicenter randomised study

**Introduction**

Dear Sir, Madam,

Your son or daughter has been admitted to the neonatology department of ………………… ………………………… …………………… (name of hospital). We kindly ask your permission for your child to participate in a medical scientific study. Participation is voluntary, it is your choice whether you wish to participate. However, your written consent is required for participation. You have received this letter because your baby was born before the full pregnancy period of 29 weeks. In premature births, breathing regulation is not yet well developed and apnoea (interrupted respiration) can occur.

Before deciding whether you want your child to participate in this study, you will be given an explanation of what it involves. Please read this information carefully and ask the researcher for an explanation if you have any questions. You can also ask the independent expert, mentioned at the end of this letter, for additional information. You can also discuss it with your partner, friends or family. Further, in Annex C you can find a link to a short online information film.

1. **General information**

This study has been set up by doctors and researchers from the Erasmus MC - Sophia Children's Hospital, Emma Children's Hospital AUMC and UZ Leuven, and is supported by the Dutch Neonatal Network (N3). It is conducted by physicians and researchers at neonatology departments in various hospitals in the Netherlands and Belgium. This study was evaluated by an independent ethics committee (UZ Leuven Ethics Committee) which issued a favourable opinion following consultation with the ethics committee of the hospital where your baby is currently being treated. In no event should you regard the favourable opinion of the Ethics Committees as an incentive to participate in this study.

1. **Aim of the study**

The aim of this study is to find out how effective and safe the drug doxapram is for the treatment of persistent interrupted respiration in premature babies. Doxapram is a drug that stimulates respiration via receptors in the neck, causing breaths to become deeper. With increasing doses, it will also stimulate the respiratory centres in the brain. Doxapram is not officially registered for use in children, but in all Dutch and Belgian centres it is already given in varying doses to premature babies (this means that it is used outside of the approved age, indication or dose), while knowledge about its long-term safety is still lacking. We will compare the effect of doxapram with the effect of a placebo. A placebo is a substance without any active ingredient, a 'fake' substance. In the study, the possible replacement of doxapram by a placebo is the only aspect of the standard care as it is currently given which will change. Doxapram appears to have an immediate beneficial effect on respiration. However, it also regularly leads to side effects such as, for example, irritability, accelerated heart rate and eating problems (see section 6, p. 4). Whether doxapram ensures a better future for premature babies is currently unknown. It is, of course, crucial to know whether this is the case, and this is precisely what we wish to find out with this study.

1. **Background to the study**

In premature births, organs such as the brain and lungs are still not fully developed. Breathing regulation also often does not function optimally. As a result, children born prematurely regularly forget to breathe, so-called interrupted respiration.

If the baby fails to breathe, artificial respiration may be necessary. However, prolonged artificial respiration can lead to serious problems in lung development and to impaired general long-term development. As such, efforts are made to limit artificial respiration as much as possible.

Support for the baby's own respiration with air and/or oxygen and the drug caffeine are given as standard to minimise the use of artificial respiration.

For some children born prematurely, this intensive treatment is still not sufficient. The drug doxapram might alleviate persistent interrupted respiration. Doxapram stimulates respiration in a different way than caffeine, and therefore likely leads to less interrupted respiration. However, the safety of doxapram and its long-term effects have never been properly researched. A total of 396 neonates will be included in this trial.

1. **What participation involves**

**During hospitalisation**

If you give permission for your child to participate in this study, and if your child is eligible for it, participants will be selected by a computer program. Half of the newborn babies will be given doxapram, the other half will be given the placebo. Which treatment your child will be given is decided at random. You and the researcher will not know which group your child is in. This is called a double-blind randomised study. If it is important to know this for your child's health, it can be looked up.

We will treat your child with doxapram or the placebo according to the guidelines for doxapram used in current practice. It is always started with administration via an infusion. Doxapram or the placebo can then also be administered by gavage. Your child will be treated until it is no longer necessary, because they are doing better, or because artificial respiration is required. If the interrupted respiration persists after starting the study medication, the treating physician will decide to switch to artificial respiration. If necessary, the drug can be restarted later.

**Neuromonitoring**

In some children, the effect of the study medication on the oxygen value of the brain (brain oxygenation), brain activity and neurological functioning will also be studied. We can do this by taking additional measurements and observations, for which there is already good experience with newborns. You can decide for yourself whether you want this. Brain oxygenation is measured with a NIRS (near-infrared spectrometer) sensor on the baby's forehead. We measure brain activity with a special monitor, a CFM (cerebral function monitor) or EEG (electroencephalogram) monitor, via small electrodes placed on your child's head. Depending on the study centre, this may be between 2 or 4 (CFM) to 9 (EEG) electrodes. The brain activity is measured 3 times during hospitalisation, namely at the start of the study medication, at the age of 32-34 weeks, and 36-38 weeks (the sum of gestational age at birth and age after birth).. We evaluate the neurological function by brief video observation of your child. This can be done during the hospitalisation (start and 72h after the start of study medication, each time for 20 minutes) and/or at the corrected age of 3 months (this is the age after the due date, recording for 5-10 minutes). This can vary from centre to centre. The research doctor will explain to you at what times this will take place for your child. In this way, we attempt to better understand what exactly doxapram does to the brain, specifically by analysing the general movements of the child.

**Visits**

As standard, all children who were born before the full pregnancy period of 29 weeks will be examined again at the age of 2 and 5 years, during a consultation in the hospital or the Centre for Developmental Disorders (COS). The location of this consultation, for the centre where your child is being treated, will be communicated to you by the treating physician. During these visits, the health and development of the children born prematurely is closely examined. This is done as standard with motor and cognitive tests and questionnaires to gauge behaviour and language development. These visits are also planned for your child. The information collected in these visits will be used in this study. When participating in this study, you and your child will also be asked to complete a number of additional questionnaires. We will try to keep the time as short as possible (maximum 10 minutes, PARCA-R questionnaire[[1]](#footnote-1)). Follow-up at the age of 8 years is only done with a questionnaire. In addition, we also ask you to note any re-admissions of your child up to the age of 2 years.

1. **What we expect from you**

For the study to run smoothly, it is important that you observe several rules after discharge from the neonatal intensive care unit (NICU). It is important that you contact the researcher:

* if your child is hospitalised or treated again in this or any other hospital.
* if your child suddenly develops unfamiliar health problems.
* if you no longer wish to participate in the study.
* if you change your contact details.
1. **Possible side effects and other adverse effects/discomfort**

Treatment with doxapram may have a beneficial effect, but can also cause side effects. In the short term, mainly agitation and irritability, and to a lesser extent nutritional problems, reduced potassium levels, accelerated heart rate, prolonged conduction time of the heart rate, elevated blood pressure or convulsions have been described. Little is known about the long-term side effects and adverse effects of doxapram in children, but these will be carefully examined in this study. In the event of side effects, in consultation with the doctor on duty, it will be examined whether it is necessary to lower the dosage or stop the study medication. When NIRS sensors are used, a very low risk (<10%) of redness on the skin has been reported in previous studies. In very exceptional cases, this can cause a small scar. This risk is now avoided by regularly changing the sensor site. The nurse can do this carefully, so that the baby is not disturbed. Although EEG measurements are completely painless and safe, preparing the skin and removing the electrodes can cause some discomfort and, in rare cases, skin irritation or injury. We will try to keep this to a minimum. We do not expect any additional side effects or other adverse effects in connection with this study.

1. **Possible advantages and disadvantages**

It is important that you carefully weigh up the possible advantages and disadvantages before you decide to let your child participate or not. The potential benefit of participating in the study is the excellent monitoring of interrupted respiration and its treatment. Blind study medication will be given in the event of interrupted respiration. If the effect is insufficient, invasive ventilation will be used. By participating in this study, your child will also help us in future to provide better treatment for premature babies with persistent interrupted respiration. Doxapram may prevent artificial respiration in the short term, but the (adverse) long-term effects are not known. Participation in the study means that there are certain rules that you must observe.

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

1. **Resistance of your child**

It may be that your child resists (does not cooperate) during the study. The researcher 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 study, this will be accepted. Before the start of the study, you will be consulted on what is considered to be resistance. We will then discuss with you whether specific examinations will be postponed or cancelled.

1. **If you do not wish to participate or wish to stop the study**

It is your choice whether your child participates in the study. Participation is voluntary. If you do not want your child to participate in the study, he or she will be treated in the usual way for the persistent interrupted respiration. Your child will always be treated with the drug caffeine and supported with air and oxygen. If the interrupted respiration persists, the usual next step depends on the centre and the treatment team. They may choose to give doxapram or to start artificial respiration in order to better support breathing.

If your child does participate, you can always change your mind and still stop, even during the study. Your child will then be treated in the usual way for the persistent interrupted respiration. You are not obliged to say why you wish to stop. However, you need to notify the researcher immediately. The data collected up to that point will be used for the study. New data will no longer be shared with the client.

If there is new information about the study that is important to you, the researcher will let you know. You will then be asked whether you will continue participating.

**10. End of the study**

Your participation in the study will end when

* all the visits as described under point 4 are completed
* you decide yourself to stop
* the researcher thinks it is better for your child to stop
* The Erasmus MC Rotterdam, the government or the evaluating ethics committee decides to stop the study.

The study will be completed when all participants have finished all trial related assessments.

After processing all the data, the researcher will inform you about the most important results of the study. This will be around 8 to 10 years after the start of your participation.

At the end of the study, the researcher can also tell you which treatment group your child was in. If you do not wish to know, you can tell the researcher. Then you will not receive this information.

**11. Use and retention of your data**

For this study, your child's personal data is collected, used and retained. These are data such as name and address and data about your child's health. The collection, use and retention of the data is necessary in order to answer the questions raised in this study and 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 give permission for us to request information about your child's illness progression during this period. You also have the right at any time to access the data collected about your child and to notify any necessary corrections to the researcher, such as, for example, a change of address. If you give your consent for your child to participate in the neuromonitoring studies, the video recordings for assessing the general movements of your child will be saved in a password-protected folder on the computer network of UZ Leuven and UMC Groningen. This means that each recording is given a number, but that the name or date of birth is not recorded. This is the same number as the study number for storing personal data. Only study staff of UZ/KU Leuven and UMC Groningen will have access to these recordings. The video recordings will not be used for other purposes.

**Confidentiality of your data**

To protect your privacy, the data has a code. Names and other information that can directly identify your child will be omitted. Data can only be traced back to your child with the key to the code. The key to the code remains safely stored in the local research facility. The data sent to the client only contains the code, but not the name or other data that can be used to identify your child. The data cannot be traced back to your child either in reports and publications about the study.

**Access to your data for verification**

Some people in your own hospital may have access to all your data, including data without a code. This is necessary in order to check that the study is carried out properly and reliably. The persons who will have access to your data for verification purposes are: the committee that monitors the safety of the study,a monitor (an independent person who monitors whether everything is progressing well) who has been appointed for this purpose, or external auditors. They will keep your data confidential. We ask you to give permission for this verification.

**Retention period for data**

The general data will be kept at the study site for 25 years. The encrypted data are also kept by the sponsor of the study. The video recordings will be kept for a maximum of 15 years.

**Retention and use of data for other research**

The study data of your child will be processed in accordance with the General Data Protection Regulation (GDPR) and the Belgian Data Protection Act of 30 July 2018[[2]](#footnote-2). The client is the data controller in this regard. The data of your child may also be important for other scientific research on premature births after this study has been completed. For this purpose, the data will be kept for 25 years after the end of the present study. For use of the data for research outside this context, a new request must be submitted to the Ethics Committee in advance.

**Information regarding unexpected findings**

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

**Withdrawal of consent**

You can withdraw your consent to the use of your child's personal data at any time. This applies to the present study as well as use for any future research. The study data collected up to the moment you withdraw your consent will still be used in the study.

**More information about your rights when data are processed**

If you have any questions about how we use your data, you can always contact your doctor-researcher. You can also contact the Data Protection Officer of the research centre. The contact details of the latter are as follows: ......................................................................(DPO contact details of the local research centre. Example for UZ Leuven: DPO - UZ Leuven, Herestraat 49, 3000 Leuven, e-mail dpo@uzleuven.be).

Finally, if you have a complaint about the processing of your data, you can contact the Belgian supervisory body that monitors compliance with the basic principles of the protection of personal data:

The Belgian supervisory body is the following:

Data Protection Authority (DPA)

Rue de la Presse 35

B-1000 Brussels

Tel. +32 2 274 48 00

e-mail:  contact(at)apd-gba.be

Website: https://www.dataprotectionauthority.be/

**Registration of the study**

Information about this study is also provided in an overview of medical scientific studies, namely (www.neonatologynetwork.eu). This does not contain any data that can be traced back to you. After the study, the website may publish a summary of the results of this study. You can find this study under DOXA trial. You can also find information on the website of the EU Clinical Trials Register https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-003666-41/NL (under the search term DOXA trial) and on the website https://clinicaltrials.gov/ct2/show/NCT04430790.

**12. Insurance for test subjects**

Any participation in a study involves risk, no matter how small. Even if they are not at fault, the client is liable for any damage suffered by the participant or, in the event of their death, their beneficiaries, which is directly or indirectly related to their participation in the study. Therefore, you do not need to prove any negligence. The client has delegated this task to UZ Leuven, which has taken out insurance for this liability for all participating Belgian centres.

We therefore ask you to report any new health problem to the doctor-researcher. They can provide you with additional information about possible treatments. If the doctor-researcher is of the opinion that there may be a connection with the study, they will inform the client of the study, who will start the claims procedure with the insurance company. If the insurer deems it necessary, it will appoint an expert to assess the connection between the new health problems of your child and the study. In the event of disagreement with the doctor-researcher or the expert appointed by the insurance company, and whenever you consider it necessary, you may make a claim on the insurer directly in Belgium (MS Amlin Insurance SE, Koning Albert II laan 37, 1030 Brussels, Belgium, policy number 299.053.700).

The law[[3]](#footnote-3) provides that the insurer may be summoned to appear either before the court of the place where the events giving rise to the damage occurred, or before the court of your domicile, or before the court of the insurer's registered office.

**13. Informing the GP and attending specialist**

We always send a letter to your GP 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, you cannot take part in this study.

**14. No remuneration for participation**

You child's treatment during the study is supported by the sponsor.. You will not be paid for participating in this study. However, we do offer a small gift for your child as a thank you for your participation.

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

If you have any questions, please contact the doctor treating your child to have them answered. You can also be referred to one of the researchers. For independent advice on participating in this study, you can contact the independent doctor. They are fully aware of the study, but are not involved in it.

If you have a complaint or question regarding the rights of your child as a participant in the study, you can discuss this with the researcher, your attending physician, or the ombuds service. A list with contact details can be found in Annex A.

**16. Signing of consent form**

When you have had enough time to reflect, you will be asked to decide whether you wish to participate in this study. If you give your consent, we will ask you to sign in writing on the corresponding consent form. Your written consent indicates that you have understood the information and consent to your child participating in this study.

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

Thank you for your attention

**17. Annexes to this information**

A. Contact details

B. Consent form parents or guardian

C. Link to a short online information film on the DOXA-trial

**Annex A: contact details for Belgian centres**

**Head researcher local study centre:**

**Name** ………………………………………….

**Address** ……………………………………….…

**Telephone number** ……………………………

**Research nurse local study centre:**

**Name** ………………………………………….

**Address** ……………………………………….…

**Telephone number** ……………………………

**Local ombudsperson patient rights:**

**Name** ………………………………………….

**Address** ……………………………………….…

**Telephone number** ……………………………

**Independent doctor:**

**Name** Prof.dr. Maissa Rayyan

**Address** Herestraat 49, 3000 Leuven, Belgium

**Function** Paediatrician -neonatologist

**Telephone number** 016 34 32 11

**Belgian Coordinating Centre: UZ Leuven**

**Contact person**: Prof. Dr. Anne Smits

**Address**: UZ Leuven, Herestraat 49, 3000 Leuven

**Telephone number** : 016 34 32 11

**Annex B: Consent form for participation of child**

**Doxapram to protect premature babies**

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

**Name and first name of the participant (child):** ……………………………………..…………..

**Date of birth:** \_\_\_ / \_\_\_ / \_\_\_\_\_

* I have read the information letter for parents/guardians. I had the possibility to ask questions. My questions were sufficiently answered. I had enough time to decide whether I wanted my child to participate.
* I am aware that participation is voluntary. I also know that I can decide at any time that my child will no longer participate. I do not have to give a reason in this regard.
* I consent to my GP and/or specialist who treats my child being informed that my child is participating in this study.
* I □ **do** □ **do not**

consent to the GP and/or specialist treating my child being informed about any unexpected findings that (may) be important for my child's health.

* I consent to the collection and use of the data for the purpose of answering the research question in this study.
* I am aware that in order to verify the study, certain individuals may have access to all my child's data. These individuals are listed in this information letter. I consent to such verification by these individuals.
* I agree to my child's participation in this study.
* I □ **do** □ **do not**

give permission for the retention and use of my child's personal data for future research in the field of premature birth and doxapram treatment in premature babies.

* I □ **do** □ **do not**

give permission for the measurement of brain activity as described in point 4, in order to better understand the effect of the study medication on the brain.

* I □ **do** □ **do not**

give permission for the measurement of brain oxygenation and neurological function as described in point 4, in order to better understand the effect of the study medication on the brain.

- I □ **do** □ **do not**give permission for my child to be approached again after this study for a possible follow-up study (>8 years).

**Email address**: ……………………….…………………………………………………………….

- I □ **do** □ **do not**
want to be informed which group my child was in. This information can only be provided after the study has been completed.

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**Name and first name of parent/guardian:**

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

**Name and first name of parent/guardian:**

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

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**Witness / Interpreter**

I declare that I was present during the entire process of informing the participant’s parent(s)/guardian(s), and I confirm that the information about the study objectives and procedures was adequately provided, that the parent(s)/guardian(s) understood the study, and consent to participate in the study was voluntarily given.

**Name, first name and qualification of the witness/interpreter:**

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

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**Researcher (or their representative):**

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

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

**Name and first name of researcher** (or their representative):

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

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Additional information is provided by:

Name and first name:

Function:

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

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

**Annex C: Link to information video DOXA-trial**

By scanning the QR code below, you can find a brief video with information about this trial. The video appears on You Tube and lasts approximately one and a half minutes.



1. PARCA-R: Parent Report of Children’s Abilities-Revised [↑](#footnote-ref-1)
2. Belgian act of 30July 2018 on the protection of individuals with the regard to the processing of personal data. [↑](#footnote-ref-2)
3. In accordance with Article 29 of the Belgian Act of 7 May 2004 on experiments on humans and the applicable royal decrees. [↑](#footnote-ref-3)