# Subject information for participation in medical scientific research

**What is the best treatment for children with a congenital cystic lung disease ( CPAM) who do not show symptoms after birth?**
*Official title: the COllaborative Neonatal NEtwork for the first CPAM Trial – a randomized controlled trial (CONNECT trial)*

## Introduction

Dear Parent(s)/Guardian(s),

We would kindly ask your permission for your son or daughter to participate in scientific research. Participation is voluntary. You are receiving this letter because your child was born with a congenital cystic lung abnormality, or CPAM (Congenital Pulmonary Airway Malformation). In this document you can find information on the study, what participation involves for you and your child, and what the advantages and possible disadvantages are. It's quite a lot of information. Please, would you be so kind as to read the information and decide whether you want to participate?

### Ask your questions

You can make your decision with the information you will find in this information letter. In addition, we recommend that you do this:

- Ask the researcher who gives you this information.
- Talk to your partner, family or friends about this study.
- Ask questions to the independent expert, [*name*] – see underneath for contact details.
- Read the information on www.rijksoverheid.nl/mensenonderzoek.

### 1. General Information

This study was set up by the Erasmus MC Sophia Children's Hospital and is being carried out by doctors and researchers from various hospitals in Europe. These doctors and researchers often work together and discuss things. A total of 180 children will participate in this study. This research has been approved by the medical ethics review committee. This is a special committee that assesses whether a study is safe for the participants and whether the rights of the these participants are guaranteed. General information about this assessment can be found in the brochure 'Medical scientific research'.

### 2. What is the purpose of the study?

In this study, we are investigating which treatment gives the best results for patients with a congenital cystic lung abnormality who do not have any symptoms after birth. We compare an operation with a wait-and-see policy consisting of periodic checks.

### 3. What is the background of the study?

A congenital cystic lung abnormality is a rare congenital defect in the lungs that leads to one or more cavities in the lungs that are filled with fluid and/or air.

If the child has complaints after birth such as shortness of breath, infection or oxygen support, surgery is often opted for, so that the child can develop unimpeded afterwards. However, most children have no complaints after birth (are asymptomatic) and can therefore be discharged from the hospital quickly. Two types of treatment are possible for this group of children: surgery or a wait-and-see policy with check-ups. In this study we will find out which of these treatments gives the best results at the age of 5 years.

**4. What does the study entail?**

*How long does the study take?*

Do you decide that your son or daughter will participate in the study? Then your child will be followed until the age of 5 years old.

*Step 1: is your child suitable to participate?*

Your son or daughter can participate in this study if he/she does not have any complaints in the first months of life that could be consistent with the congenital lung defect. In addition, the diagnosis should have been confirmed with a CT scan at the age of 3-9 months. This CT scan is part of the standard treatment, but we do ask permission to use these images for the research.

*Step 2: the treatment*

For this study we make 2 groups:

- Group 1. The children in this group undergo an operation to remove the lung abnormality. This surgery will take place at age 6-9 months.
- Group 2. The children in this group do not undergo surgery.

Both groups are monitored in the same way up to the age of 5 years.
This study has a so-called randomized design, which means that it is randomly determined which child will be in which group, so no one within the study has any influence on this. The chance of falling into each of these groups is the same, so 50% versus 50%.
If your child has not been operated on, but during the course of the study still develop symptoms that may be consistent with the congenital lung abnormality? Then you and the treating doctor determine which steps to take. These choices are not affected by participation in this study.

*Step 3: research and measurements*

For the study it is necessary that you take your child to the hospital four times during the 5 years that the study is running. Namely if your child is 6 months, 1 year, 2.5 years, and 5 years old. A visit takes 1 to 3 hours. These visits are part of the standard treatment for children with a congenital lung defect, and also will take place if your child does not participate in the study. However, an extra CT scan will be made when he/she is 2.5 years old, and your child will be asked to perform a fitness test when he/she is 5 years old. We will also ask you to complete a number of questionnaires at various times during this study. Below you will find a chronological progression per hospital visit, regardless of which treatment group your child has been assigned to.

<u>1) Visit at age 6 months</u>

- Your child will receive a drip for the administration of contrast medium, after which a CT scan will be performed. This scan takes about 10-20 minutes.

- Physical examination. For example, the researcher listens to your child's heart and lungs and measures the blood pressure and oxygen saturation in the blood. Your child will also be measured and weighed.
- You fill in a number of questionnaires with questions about quality of life and the impact of any complaints on your life and that of your child. Completing these questionnaires takes approximately 20 minutes.

2) Visit at age 1 year
- Physical examination. For example, the researcher listens to your child's heart and lungs and measures the blood pressure and oxygen saturation in the blood. Your child will also be measured and weighed.
- You fill in a number of questionnaires with questions about quality of life and the impact of any complaints on your life and that of your child. Completing these questionnaires takes approximately 40 minutes.

3) Visit at age 2.5 years
- Physical examination. The examiner listens to your child's heart and lungs, and measures blood pressure and oxygen saturation in the blood. Your child will also be measured and weighed.
- A CT scan is performed on your child. This scan takes about 10-20 minutes.
- You fill in a number of questionnaires with questions are about quality of life and the impact of any complaints on your life and that of your child. Completing these questionnaires takes approximately 40 minutes.

4) Visit at age 5 years
- Physical examination. The examiner listens to your child's heart and lungs, and measures blood pressure and oxygen saturation in the blood. Your child will also be measured and weighed.
- You fill in a number of questionnaires with questions are about quality of life and the impact of any complaints on your life and that of your child. Completing these questionnaires takes approximately 50 minutes.
- Your child will undergo a fitness test, where he/she will be asked to continue walking on a treadmill for as long as possible while gradually the speed and incline of this treadmill are increased.

*Blood collection for genetic research*
At 6 months of age, a CT scan will be performed to confirm the diagnosis. This is therefore before the official start of the investigation. If you give permission for this, we will at the same time draw some blood from your child for genetic testing. We are doing this at the moment because a drip is now being placed to administer the contrast for the CT scan. This way your child only needs to be injected once. If you are the biological parent, we will also draw a blood sample from you, provided you have given your consent for this, as this provides more information for the genetic test.

*If your child is randomized to undergo operation:*
1) Operation at age 6-9 months
The operation will take place in the hospital where your child is being treated. After the operation, your child will stay in the hospital until he/she has recovered enough to go home.

2) Postoperative check-up appointment
Four to six weeks after the operation, your child will undergo an extra check-up, including a general physical examination and a wound check. The pathological results of the tissue test will also be discussed with you.

*What is different from regular care?*
A large part of the care for your child during this study is the same as in the normal situation. A number of issues are specific to this study, which are listed below.

- Questionnaires: we ask you as parents to complete a number of questionnaires 4 times during the study. Completing these questionnaires takes approximately 20-40 minutes each time.
- CT scan at 2.5 years of age, which is in addition to normal treatment, but can give us valuable information about the development of the lung and the abnormality over time.
- Fitness test at the age of 5, which will take approximately 10-20 minutes.

**5. What agreements do we make with you?**
We want the research to go well. That is why we make the following agreements with you:

- You come with your child to every visit.
- You complete the questionnaires during/before each appointment as accurately and truthfully as possible.
- You contact the researcher or treating doctor in these situations:
    - Your child is admitted or treated in a hospital.
    - Your child has complaints that may be related to the lung abnormality / any operation performed.
    - You or your child no longer wish to participate in the study.
    - Your telephone number, address or e-mail address changes.

**6. What side effects, adverse effects or discomforts may your child experience?**
The therapy being investigated may have adverse effects on your child. Since we compare 2 types of treatment in this study, we will discuss the 2 groups separately.

<u>1) Operative group</u>
Lung surgery in a young child is regarded as a relatively major operation with relatively good outcomes. However, there is a risk of complications. Complications can include infection, bleeding, or a long-term need for a chest drain (a tube in the chest that drains air and/or fluid). A complication can also mean that your child has to stay in the hospital longer for medication and/or supplemental oxygen. Based on the literature, we estimate the chance of a complication after surgery to be 3-20%. These complications rarely lead to long-term consequences and are often easy to treat. It is important to mention that in many centres around the world, children with cystic lung disease without complaints are still operated on as standard, with fairly good results. The procedure is therefore considered relatively safe.

<u>2) Waiting group policy</u>
The children in this group will not undergo surgery. They are, however, monitored at fixed times during the study, as mentioned above. During the period that your child

participates in this study, he/she may develop complaints that are the result of the lung abnormality. In this case, please contact the treating physician, who will determine the best management in consultation with you. It is important to also inform the researcher about this. It is possible that your child's complaints are so serious that surgery is needed. You make this choice together with the treating physician. Therefore, this is not influenced by participation in this study.

CT scan at age 2.5 years

At the age of about 2.5 years, your child will have a CT scan, regardless of which treatment group he/she is in.
In order to extract as much information as possible from the CT scan, we make this scan with contrast agent that is injected through a drip. Your child will be slightly dazed during the scan, as the examination requires your child to lie still and this is very difficult to explain at this age.

Radiation load

During this scan, your child will receive approximately 0.6 mSv of radiation. By way of comparison: the 'ordinary' radiation that everyone in the Netherlands receives anyway is about 2.5 mSv per year. It does not do any harm to undergo an examination or treatment with radiation for a medical reason.

- Does your child often have an examination involving radiation? Then discuss with the researcher whether it is wise for you to participate.
- The radiation amount we use can damage your child's health. But this is a small risk. We do, however, advise you not to let your child participate in a scientific study involving radiation again in the near future.

**7. What are the advantages and disadvantages of participating in the study?**

Participating in the study can have advantages and disadvantages. Below we list them. Think about this carefully, and talk about it with others.

If your child participates in this study, it does not mean that your child will suffer less from the congenital lung defect. But with your child's participation you help in the search for better treatment of congenital cystic lung disorders.

*Participating in the study may have these disadvantages:*

- Your child may experience the side effects or adverse effects of the surgery, as described in section 6.

*What are the possible inconveniences of measurements during the research?*

- Your child's participation in the study will cost you some extra time: you will have to visit the hospital more often, and you will be asked to complete questionnaires.
- Your child will undergo a CT scan at the age of approximately 2.5 years. The scan takes 10-20 minutes and can be exciting for your child.
- Your child will undergo a fitness test, where he/she will be asked to continue walking on a treadmill for as long as possible while the speed and incline of this treadmill are gradually increased. This test could be tiring for your child.

It is possible that something is accidentally discovered from the genetic test or the CT scan that is not directly relevant to the study, but is important for the health of your child or that of you or your relatives. In this case, your own GP or specialist will

discuss with you what needs to be done further. The costs of this are covered by your own health insurance.

*Don't want to participate?*
Should you decide not let your child participate in the study, your child will receive the treatment for cystic lung disorders as determined by the attending physician in consultation with you. The attending physician can tell you more about the treatment options available and their advantages and disadvantages.

*Objection from your child/the person you represent*
It may happen that your child does not cooperate (resists) at some point during the study. The researcher must then stop immediately. It is difficult to define exactly what resistance is. Before the start of the investigation, we will discuss with you what we see as resistance. The researcher will adhere to the Code of Conduct for minors' resistance.

**8. When does the research end?**
The researcher will let you know if there is new information about the study that is important to you. The researcher will then ask you if you will continue to participate.

In the following situations, the study will stop for your child:
- All examinations according to the schedule are over after the last hospital visit has taken place at the age of approximately 5 years
- You want to let your child stop yourself. That is allowed at any time. Report this immediately to the researcher. You don't have to tell the reason. Your child will then receive the usual treatment for cystic lung abnormalities.
- The researcher or the treating physician thinks it is better for your child to stop. The researcher will still invite your child for a follow-up check.
- The medical ethics review committee, the government or the Erasmus Medical Center decides to stop the whole study.

*What happens if your child stops with the study?*
The researchers use the data and body material (tissue, blood tests, fitness tests) collected up to the moment of stopping.
The entire study ends when all participants are finished.

**9. What happens after the study?**
*Do you get the results of the study?*
About 2 years after your child's participation, the researcher will inform you about the main results of the study.

**10. What do we do with your child's data and bodily material?**
Will your child participate in the study? Then you also give permission to collect, use and store bodily material from your child.

*What data do we store?*
We store this information about your child
- Sex
- Date of birth
- (medical) Data that we collect during the research

*What human material do we store?*
We store tubes of blood from you and your child if you give separate permission for this (see the Information Letter and the Consent Form for the genetic determinations separately). We also store pieces of tissue if an operation has taken place

*Why do we collect, use and store data and human material from you and your child?*
We collect, use and store data and bodily material from your child and you in order to answer the questions of this study, and to be able to publish the results.

*How do we protect your privacy?*
To protect your privacy, we assign a code to your and your child's data and material. We put only this code on all data and all material. We keep the key to the code in a secure place in the hospital. When we process data and human material, we always only use that code. Also in reports and publications about the research, no one can deduce that it was about you or your child.

*Who can see your data?*
Some people can view your name / your child's name and other personal data without a code. These are people who check whether the researchers conduct the research properly and reliably. These persons can access your data:

- Members of the committee that monitors the safety of the research.
- An inspector hired by the study initiator.
- National supervisory authorities. For example, the Health and Youth Care Inspectorate.
  These persons will keep your data secret. We ask you to give permission for this inspection.

*How long do we store your and your child's data and bodily material?*
We keep the data of you and your child for 20 years in the hospital and 20 years with the study initiator.
We store the bodily material in the hospital where your child is being treated. The material will be kept for 20 years in order to be able to make new determinations related to this research. As soon as this is no longer necessary, we destroy the bodily material.

*Can we use the data and body material for other research?*
After this study, your and your child's data may also be important for other scientific research into the condition and its treatment. To this end, this data and bodily material will be stored in the hospital for 20 years. In the consent form you indicate whether you agree with this. Do you not give permission? Then your child can still participate in this study, and will receive the usual care.

*What happens with unexpected discoveries?*
During the study, we might find something that is important to the health of you or your child, or the health of your family members. The researcher will then contact your general practitioner or specialist. You will then discuss with your general practitioner or specialist what needs to be done. By signing the consent form you give us permission to inform your general practitioner or specialist.

*Can you withdraw your consent to the use of the data?*
You can withdraw your consent to the use of your and your child's data at any time. This applies to use in this research and to use in other research. But please note: if you withdraw your consent, and the researchers have already collected your and your child's data, they may still use this data. The researchers will destroy the collected bodily material after you have withdrawn your consent. Still, if your or your child's bodily material already have been analysed, the results may still be used.

We send information about you and your child to countries outside the European Union.
In this study, we also send encrypted data from you or your child and bodily material to countries outside the European Union. When data is provided to countries outside the EU (so-called 'third countries'), such as the US, it is not possible to achieve exactly the same level of protection as within the EU. We make every effort to protect your child's data as well as possible outside the EU. In any case, only encrypted data (i.e. no name, address and date of birth) is passed on. If you object to this, your child will unfortunately not be able to participate in the study.

*Would you like to know more about your privacy?*
- Would you like to know more about your rights when processing personal data? Check out www.autoriteitpersoonsgegevens.nl.
- Do you have questions about your rights? Or do you have a complaint about the processing of your personal data? Please contact the person responsible for the processing of your personal data. For your study, this is Erasmus MC. Please see Appendix A for the contact details.
- If you have any complaints about the processing of your personal data, we recommend that you first discuss them with the research team. You can also apply to the Data Protection Officer of Erasmus MC, or submit a complaint to the Dutch Data Protection Authority.

*Where can you find more information about the research?*
In the future, a website will be created which contains additional information about this research. However, you can already contact the independent researcher who knows a lot about this research. For details, see section 14.

**11. Will you receive compensation if you participate in the study?**
The additional tests for the study do not cost you anything. You will also not receive any compensation if you participate in this study. You will, however, be reimbursed for your (additional) travel expenses.

**12. Is your child insured during the study?**
Insurance has been taken out for everyone who participates in this study. The insurance pays for damage caused by the study. But not for all damage.

**13. We will inform your general practitioner and/or treating specialist and/or pharmacist**
The researcher will send a letter to your and/or your child's general practitioner/treating doctor to let them know that your child is taking part in the study. If necessary, we can contact his/her doctor, for example about medical history or

about any complaints that are of interest in the context of this research. By signing this document, you consent to this.

**14. Any questions?**
Questions about the research can be put to the research team. Do you want advice from someone who is not directly involved in this study? Then go to [*name*, *e-mail*]. He/she knows a lot about the study, but does not participate in this research.
Do you have a complaint? Then discuss this with the researcher or the doctor who is treating your child. Would you rather not? Then apply to the hospital's complaints officer.

**15. How do you give permission for the research?**
You can first think calmly about this research. Then tell the researcher if you understand the information and whether or not you wish your child to participate. If so, please complete the consent form enclosed with this information letter. You and the researcher will both receive a signed version of this consent form.

Thank you for your time.

Dr. J.M. Schnater
Paediatric and Lung Surgeon
Principal Investigator CONNECT Trial
Department of Pediatric Surgery
Erasmus MC Sophia Children's Hospital

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**16. Appendixes enclosed:**
A. Contact information
B. Insurance details
C. Schematic overview of study actions and measurements
D. Consent form parents or guardians

# Appendix A: contact information Erasmus MC – Sophia Children's Hospital

| | |
|---|---|
| *Primary researcher*: | Dr. J.M. Schnater |
| Email: | connect@erasmusmc.nl |
| Phone number: | 06-47772362, 010-7036242 (secretariaat Kinderchirurgie) |
| Availability*:* | Monday through Friday during office hours |
| | |
| *Independent expert:* | Gert van den Berg |
| Email: | g.vandenberg.1@erasmusmc.nl |
| Phone number: | 0107039270 |
| Availability*:* | Monday through Friday during office hours |
| | |
| *Complaints*: | Complaint coordination Erasmus MC – Sophia Children's Hospital |
| Telefoon: | 010-7033198 |
| Availability*:* | Monday through Friday during office hours |
| | |
| *Data protection*: | |
| Functie: | Coordinator Data protection Erasmus MC. |
| Email: | functionaris.gegevensbescherming@erasmusmc.nl |
| Phone number: | 010-7034986 (secretariaat Afdeling Juridische zaken) |
| Availability*:* | Monday through Friday during office hours |

# Appendix B: Insurance details

Erasmus MC has taken out insurance for everyone participating in the study. The insurance pays for the damage you have suffered because you participated in the investigation. This concerns damage that you incur during the research, or within 4 years after the research. You must report damage within 4 years.

Have you suffered damage as a result of the investigation? Report this to this insurer:

| The insurance for this study is: | |
|---|---|
| Name: | *Centramed* |
| Address: | *Maria Mostessorilaan 9, 2719DB Zoetermeer* |
| Phone number: | *070 301 70 70* |
| E-mail: | *info@centramed.nl* |
| Reference number: | *624.100.042* |

The insurance pays a maximum of € 650,000 per person and € 5,000,000 for the entire study (and € 7,500,000 per year for all studies of the same client).

Please note: the insurance does not cover the following damage:

- Damage due to a risk about which we have given you information in this letter. But this does not apply if the risk turned out to be greater than we thought beforehand. Or if the risk was very unlikely.
- Damage to your health that would also have occurred if you had not participated in the study.
- Damage that arises because you did not follow directions or instructions or did not follow them properly.
- Damage to the health of your children or grandchildren.
- Damage due to a treatment method that already exists. Or by the study of a treatment method that already exists.

These provisions are set out in the 'Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015'. This decision can be found in the government's law database (https://wetten.overheid.nl).

# Appendix C: Schematic overview of study actions and measurements

| | Study course → | | | | |
|---|---|---|---|---|---|
| | 6 months | 6-9 months | 1 year | 2.5 years | 5 years |
| Hospital visit | - Natural history<br>- Physical examination<br>- Weight<br>- Length | - Surgery [2]<br>- Post-operative check-up [2] | - Natural history<br>- Physical examination<br>- Weight<br>- Length | - Natural history<br>- Physical examination<br>- Weight<br>- Length | - Natural history<br>- Physical examination<br>- Weight<br>- Length |
| Questionnaires | Questionnaires:<br>- VAS-A<br>- ITQOL | | Questionnaires:<br>- VAS-A<br>- ITQOL<br>- iMCQ | Questionnaires:<br>- VAS-A<br>- ITQOL<br>- iMCQ | Questionnaires:<br>- VAS-A<br>- ITQOL<br>- iMCQ<br>- CHU9D |
| Imaging | - CT-scan with intravenous contrast | | | CT-scan without intravenous contrast | |
| Material | Drawing of blood from child + parents * | Resected tissue [2] | | | |
| Physical testing | | | | | BRUCE treadmill test ** |

Table 1 – Overview of CONNECT-trial study procedures
VAS-A = Visual Analogue Scale for Anxiety (duration ±1min)
ITQOL = Infant and Toddler Quality of Life questionnaire (duration ±20min)
iMCQ = Medical Consumption Questionnaire (duration ±20min)
CHU9D = Child Health Utility Index 9D (duration ±2min)
[2] Only in case child is randomised for the surgical treatment arm
* Only in case you give specific permission
** Standardised physical endurance test, according to the BRUCE protocol, under direct supervision of a qualified paediatric physical therapist.

# Appendix D: Consent form parents or guardians

## What is the best treatment for children with a congenital cystic lung disease (CPAM) who do not show symptoms after birth?

I have been asked to provide consent for my child to participate in medical scientific research:

Name participant (child): …….. Date of birth: …./ …../ …..

- I have read the information letter for the subject/parents/guardians. I could also ask questions. My questions have been answered well enough. I had enough time to decide if 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. I don't have to give any reason in this case.

- I give the researcher permission to inform the general practitioner/specialist(s) who treat my child that my child is taking part in this study.

- I give the researcher permission to request information from the general practitioner/specialist(s) who treat my child about complaints related to the condition that is central to the study.

- I give the researcher permission to provide my child's general practitioner and/or specialist with information about unexpected results of the research that are important for my child's health.

- I give the researchers permission to collect and use my child's data and bodily material. The researchers only do this to answer the research question in this study.

- I know that some people may have access to all of my child's data for the purpose of checking the research. Those people are listed in this information letter. I give these people permission to view my child's data for this check.

- I know that my child's encrypted data will be sent to countries outside the EU. The privacy rules of the EU do not apply here and exactly the same level of protection cannot be achieved as within the EU.

- Do you want to tick yes or no in the table below?

| | | |
|---|---|---|
| I give permission to keep my child's data to use it for other research, as stated in the information letter. | Ja ☐ | Nee☐ |
| I give permission to store the (leftover) bodily material of my child to use it for other research, as stated in the information letter. The body material is stored for another 20 years after the end of the study. | Ja ☐ | Nee☐ |
| I give permission to ask my child if he/she wants to participate in a follow-up study after this study. | Ja ☐ | Nee☐ |

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

Name parent/guardian **: ……

Signature: …… Date: …./ …../ …..

Name other parent/guardian**: …….

Signature: …… Date: …./ …../ …..

I declare that I have fully informed the person(s) above about the mentioned research.

In case information becomes known during the research that could influence the consent of the parent or guardian? Then I will let him/her know in time.

Name of researcher (or his representative): ……

Function: ……

Signature: …… Date: …./ …../ …..

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Additional information was provided by:

Name: ……..

Function: ……

Signature: ……. Date: …./ …../ …..

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* Please cross the option that is not applicable.
** If the child is under 16 years of age, the parents exercising custody or the guardian will sign this form. Children aged 12 to 15 who can make independent decisions (mentally competent) must also sign a form themselves

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