PARENT INFORMATION FORM

BeNeDuctus Trial

Study to investigate the optimal treatment of a patent ductus arteriosus (Botalli) in preterm newborn infants.

Dear Sir, Madam,

Your baby has been admitted to the Neonatology Department because it was born prematurely. All members of the medical team are currently doing their utmost to help your child get through this difficult period in the best way possible. Your physician will undoubtedly have told you that most treatment procedures we have at our disposal may not be without adverse effects. Fortunately, we know that the benefits of many therapies far surpass their disadvantages. There are also types of treatment, however, yet unproven, which are presumed to be more beneficial than detrimental. Proof for such a presumption can only be obtained by conducting research, which will enable us to continually improve the level of care we can offer premature babies.

The purpose of this letter is to inform you about an important clinical research study that is currently being carried out at all neonatology departments in the Netherlands and several departments in Belgium. Before you decide whether to agree to your child taking part we would like to inform you about the study, explain why this study is conducted and what it involves.
Please read this information form carefully and discuss it with your friend and relatives if you wish. A member of the team caring for your baby will be happy to answer any questions that you may have. There is also an independent physician available for further information, if requested. The contact details can be found on page 4.

1. Background of this study

An unborn infant does not need its lungs yet, since oxygen uptake and carbon dioxide removal occurs via the placenta. Given the fact that before birth the lungs aren't in use, blood does not need to flow through the lungs and is redirected via a specific blood vessel to the rest of the body. This vessel is called the '*ductus arteriosus*' or '*ductus*'. Directly after birth, however, is the baby dependent on an adequate lung function, since oxygen uptake and carbon dioxide removal isn't possible anymore via the placenta. After birth blood should flow through the lungs for optimal oxygen uptake and carbon dioxide removal. That is why under normal circumstances the ductus arteriosus will close after birth. This natural closure of the ductus can fail to occur in preterm infants, a well-known condition called '*patent ductus arteriosus*' (PDA).

Until recently it was thought that a PDA increased the risk of serious complications in preterm infants, such as chronic lung disease ('*bronchopulmonary dysplasia*'), cerebral bleeding, inflammation of the bowels ('*necrotising enterocolitis*') and dysfunction of the kidneys. That's why in general it is tried to close a PDA with medication. If the prescribed medication failed to close the PDA, a surgical closure could be considered.
Recent studies have shown that active closure of the PDA does not result in a decrease in the aforementioned complications. This has led to a lot of discussion in the medical community throughout the world about whether to actively close the PDA or on the contrary just wait and have a so-called expectative approach. There are centres that actively try to close the PDA and there are other centres that do not treat a PDA at all. No one can tell for sure which approach is the best. In conclusion, it is not known which treatment is best for preterm infants with a PDA. With this study we try to investigate the optimal approach.

2. What is the aim of this study?

The aim of this study is to investigate whether waiting for a spontaneous closure of the ductus (expectative approach) is as good as the prescription of medication to actively close the PDA in preterm newborn infants (less than 28 gestational weeks). When this study proves that treatment of a PDA isn't needed, the potential side-effects of the prescribed medication and the high burden of a possible surgical closure will be prevented.

3. What children qualify for participation in this study?

Babies born after a pregnancy of less than 28 weeks, in whom a PDA has been diagnosed with an echo scan of the heart in the first three days of life.

4. What precisely does this study involve?

Babies participating in this study will receive either medication to try to close the PDA or no treatment will be given specifically for the PDA in the assumption that this is not needed and the ductus will close spontaneously. Which approach will be applied is unknown in advance; it will be decided by drawing lots, so-called randomization.
Nobody has any influence on this drawing, since it is performed by a computer. If your child will participate in this study, there will be a 50 percent chance of treatment of a PDA with medication and a 50 percent chance of waiting for spontaneous closure of a PDA. There will be no difference in all other treatment of your child.

During the study, we will ask you to fill in a questionnaire at 4 separate moments to analyse whether there is a difference in burden for both the patients as parents between the two different approaches. The questionnaire will be send to you at your child's age of 4 weeks after birth, and at the age of 6, 12 and 24 months after the due date, respectively. This will take about 10 minutes per questionnaire.

As usual, your baby will be checked on a regular basis at the outpatient clinic of the neonatology department. A development test will be performed 24 months after the calculated date of birth. These data are also included in the study.

5. How will the study impact your child and what are the pros and cons?

It goes without saying that your child's health is of paramount importance, which is why your baby is closely monitored all the time. Your attending physician can decide at any time to discontinue your baby's participation in the study, if he/she thinks that a different type of treatment is required, which falls outside the scope of this study. You will, of course, be notified if such should be the case.

Possible advantages of participation: An advantage of waiting for spontaneous closure might be the avoidance of possible side-effects of the medication. These potential side-effects are: decreased blood platelets, decreased white blood cells, cerebral bleeding, lung bleeding, chronic lung disease ('*bronchopulmonary dysplasia*'), cerebral bleeding, inflammation of the bowels ('*necrotising enterocolitis*') and dysfunction of the kidneys

Possible disadvantages of participation: A disadvantage might be that no treatment of a PDA might have some influence on your child's condition and thereby increasing the risks of complications, such as chronic lung disease ('*bronchopulmonary dysplasia*'), cerebral bleeding, inflammation of the bowels ('*necrotising enterocolitis*') and dysfunction of the kidneys
As you probably noticed, the risks of both different approaches are practically identical and thereby confirming again that we truly do not know what the best choice would be for your child.

Burden for your child: When your child is treated with medication for a PDA, this will be infused directly in the blood. Because all preterm infants less than 28 weeks' pregnancy will have an infusion, there will be no need for an extra puncture for the purpose of this study.

6. What happens if you don't want your child to participate in this study?

Participation is entirely voluntary. If you don't want your child to participate in this study, it will not have any negative consequences regarding the treatment and care of your child.
It depends on in which hospital your child is born, what the regular policy will be regarding the PDA. Both strategies are applied in different hospitals. When you decide that your child will not participate in this study, he/she will be treated according the local protocol. This means that in the Radboudumc that - based on an echo scan of the heart on the second or third day of life - treatment of the PDA will be considered in some children.

7. How has this study been judged?

This study is supported by all neonatal intensive care units in the Netherlands and Belgium and everyone agrees that there is no proof that one of the two approaches is better than the other. The Radboudumc Medical Ethics Committee has given this clinical trial a favourable opinion (Commissie Mensgebonden Onderzoek Arnhem - Nijmegen). Moreover, the Board of Directors of the Radboudumc has also approved this study.

8. What do we request your permission for?

We ask your permission for your baby's inclusion in this research study. Participation in the study is entirely voluntary, which means that you can withdraw your child from the study at all times, without any consequences for the treatment and care your child will receive. If your child participates and should be transferred during the study to a hospital in your area, your consent will also involve allowing us to retrieve data on the course of your child's condition during this part of the research study.

We also check the medical record of the mother. During the study these data will also be collected, coded and stored. These data are only used for this study. You consent this when your child participates in this study. In addition, we would like to ask your permission to approach you at a later date, after the study has been completed, for additional research.
We want to start this study as soon as possible, but at the latest before the age of 3 days.

9. Confidentiality of data?

For reasons of privacy protection, all research and medical data will be recorded under code, i.e. anonymously, and thus kept fully confidential. Your baby's name will neither be used nor made visible. The identity of study subjects can only be retrieved by the researchers and attending physicians. It may be necessary, however, that certain parties be allowed to inspect medical files for trial monitoring purposes, such as representatives from the Radboudumc Medical Ethics Committee or from the study's initiator, the Radboudumc, or duly authorised government bodies. Access to the files is then granted under the responsibility of the attending physician. If you consent to your child's participation in this study, you automatically agree to such inspections. Your child's identity will never be disclosed for any other reason. The data recorded within the scope of this study will be kept by us for 15 years and then be destroyed. The anonymous data will be analyzed and presented in scientific articles.

10. Role of the patient organization

This study is supported by the Dutch Association of Parents of Newborn Patients (Vereniging van Ouders van Couveusekinderen - VOC). This patient organization has been involved in the design of this trial and advises the researchers.

11. Insurance

Radboudumc has taken out an insurance for the subjects in this clinical trial. This insurance covers losses caused by injury resulting from participation in the clinical trial, which reveals itself during the participation of the subject in the clinical trial or within four years thereafter. Further information about the insurance can be found in appendix B.

Further information

Should you have any further questions regarding this study, you can contact one of the responsible researchers at telephone number 024-3613860.
If you have any questions that you would rather not discuss directly with the researcher, you can turn to an independent physician who is not involved in the conduct of this study. In this case, the physician in question is Dr. M. Schreuder, who can be reached at telephone number 024-3614430.

On behalf of the national and local research team,

Dr. Willem P. de Boode, pediatrician-neonatologist
(principal investigator)
Department of Neonatology, Radboudumc
Phone: 024-361 44 30

Appendices

A. Informed Consent Form
B. Information about insurance
C. Brochure 'Medisch-wetenschappelijk onderzoek. Algemene informatie voor de proefpersoon'