REFERENCE VALUES FOR THYROID HORMONES IN NEWBORNS

Dear sir/madam,

With this letter, your child is invited to take part in a study called: *"Neonatal reference values for thyroid hormones and the validation dried blood spot measurements in the neonatal period".* This study was initiated to improve the newborn screening for Congenital Hypothyroidism (CH). Whether or not your child takes part is your choice. Before making this decision, it is important to know more about the subject of the study. Take your time to read this information carefully. If you have any questions after reading this letter, feel free to contact the coordinating research physician or an independent physician. You can find their contact information at the end of this information sheet.

1. What is the goal of this study?

Almost every newborn in the Netherlands participates in the neonatal screening ("heel prick") during the first week of life. Blood taken from the heel of the baby is checked for various severe diseases. Early detection of these diseases can prevent severe damage to the physical or mental development of your child.

One of these diseases is Congenital Hypothyroidism (CH). CH is in inborn shortage of thyroid hormone (thyroxin or T4). This condition is present in 1 in 1800 baby's. Thyroid hormone is important for metabolism, growth and development of both body and brain. A shortage of thyroid hormone can lead to a delay in mental and motor development. Fortunately, CH is easily treatable by immediately starting with thyroid hormone replacement therapy. If a child with CH starts this treatment as soon as possible after birth, the brain usually develops in a normal way.

In the current newborn screening for CH, the amount of thyroid hormone in blood taken from the heel of the baby is measured, compared to a daily mean value and judged as either "within the normal range" or "outside of the normal range". If a sample shows values "outside the normal range", this does not automatically mean the newborn has CH.
In case of an abnormal value, the newborn is referred to a pediatrician to examine the thyroid function. The pediatrician will measure the amount of thyroid hormone in the child's blood again, to determine whether the child has CH or not. Because the amount of thyroid hormone continuously

decreases in the first weeks after birth, the results from this second blood collection cannot simply be compared to the results from the newborn screening in the first week.

Unfortunately, it is not exactly clear which amount of thyroid hormone is normal in newborns at different moments during the first month after birth. This makes it hard to distinguish healthy children from children with CH. It is especially hard to recognize forms of CH in which there is just a subtle deviation of the thyroid hormone values. If it remains unclear whether the child has CH or not, this may lead to multiple extra blood collections, a prolonged period of uncertainty for parents and a late start of treatment for the child with CH. Each year, there are several hundreds of children with an abnormal result in the newborn screening for CH. Thus, a lot of parents go through this period of uncertainty.

With this study, we want to examine thyroid hormone values in healthy newborns on the day the heel prick test is performed (between the 3rd and 7th day of life) and on the day the child with an abnormal result would be referred to the pediatrician (two weeks after birth). Moreover, we would like to study the difference between the thyroid hormone values in blood taken from the heel and blood taken from a vein in the back of the hand ("venipuncture").

Therefore, we would like to measure thyroid hormone values in a large number of healthy children, at day 3-7 and at the age of 2 weeks, through extra blood collections. These thyroid hormone values can then be used as a comparison ("reference values") for children who might have CH. The pediatrician will then sooner be able to determine whether the child has CH or not.

In the Netherlands, the neonatal screening is performed with blood collection by a heel stick. Earlier studies found that a venipuncture is both more efficient, and less painful for the child than the heel stick. In several other European countries, the neonatal screening is therefore performed with a venipuncture. Because we want to know how parents experience both methods of blood collection, we would like to ask parents who have participated in this study to fill in a questionnaire. If from these questionnaires we can conclude parents prefer either method of blood collection, this can be taken into account when deciding whether the Dutch neonatal screening should switch to venipuncture, or not.

2. How is the study performed?

All newborn babies taking part in the standard newborn heel prick screening can participate in this study. The decision to let your child take part in this scientific study is independent from taking part in the newborn screening. Thus, if you decide not to let your child take part in this study, he or she can still participate in the newborn screening. Only if you decide not to take part in the newborn screening, your child cannot participate in this study.

If you decide to participate in this study, a physician related to this study (clinical researcher) will visit your child at home at the day the heel prick is performed. After enough blood has been collected from the heel, a small amount of blood will additionally be collected from the vein in the back of the hand. Moreover, once your child's screening results are available, we will collect your child's results for thyroid hormones. When your child is 14 days old, we will invite you for a second blood collection. This can take place in the hospital, or at home. The blood will be collected by venipuncture, again. Of course, you can choose to participate in only one of the moments of blood collection. After the last blood collection, we would like to ask you to fill out the anonymous questionnaire. With this list, we would like to gain insight in the preferences of parents regarding the method of blood collection in newborns.

Several studies revealed that giving sugar water to newborns before collecting the blood provides pain relief for the child. This method of pain relief seems more effective than pain relief achieved through anesthetic creams. Therefore, your child will be offered sugar water before each blood collection to minimize discomfort.

In case the results from your child's newborn screening are abnormal, he or she will routinely be referred to a pediatrician. Measurements in blood already collected from your child for this study will then not be included in the further analysis.
Once blood from enough newborns has been collected, their blood values will be used to determine new reference values. Research has shown that thyroid hormone values are different in various ethnic groups. The researcher will therefore ask you about you and your partner's ethnic origin. You are not obliged to answer this question. If the results from one or both measurements in your child's blood deviate strongly from these reference values, we will check if your child's values during the newborn screening were abnormal as well. The research team will also critically study your child's values. Only if your child's values differ so strongly from the reference values that a thyroid disease is

suspected **and** the results from the newborn screening were **not** abnormal, your will child be recalled for further testing by a pediatric endocrinologist.

3. What is expected from your child?

In your daily life, there are no behavioral restrictions or instructions before, during or after participating in this study.

4. Which side effects are possible?

The blood collections may be unpleasant for your child. A bruise might develop after the blood is taken.

5. What are the potential advantages and disadvantages of participating in this study?

Your child has no benefit from participating in this study. The study does, however, provide useful information for children with abnormal results in neonatal screening for CH in the future. Disadvantages of participating in this study are additional blood collections, and possibly an additional hospital visit.

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

Participation is completely voluntary. If you decide not to participate, no further action is needed. You don't have to explain why you don't want to participate. If your child participates in this study, you can always change your mind and withdraw your consent, even during the study.

7. Are you insured when you participate in this study?

Since there are no risks in participating in this study, the Medical Ethical Committee of the AMC hospital has agreed to waive the obligation for insurance for the participants of the study.

8. What happens to the data of your child?

All your child's data is kept strictly confidential by the research group. The researcher will store your child's data using a code. In reports on the study, this code will be used. Only the researcher knows which code your child has.

To check whether the study is being performed according to the guidelines, some people may access the study data without using the code. Your child's data may be seen by representatives from

the AMC and representatives for the Health Care Inspectorate (IGZ: Inspectie voor de Gezondheidszorg). They are permitted to evaluate whether the study is being carried out correctly, but they are obliged to keep these data confidential.

The data is stored for 15 years, to evaluate whether the study has been performed according to guidelines, but also in case new questions related to the research topic arise. Blood taken from your child is stored during the study. It will be destroyed immediately (i.e. after publication of the study). The paper (or: Guthrie) card used for the heel prick is routinely stored by the screening laboratory for 1 year for quality purposes. Afterwards, the card will be stored for another four years at the National Institute for Public Health and Environment (RIVM, Rijksinstituut voor Volksgezondheid en Milieu). The card is stored under a code for facilitating scientific research, unless you object. Our research team may use the cards used for the heel prick as well. If you don't agree with this, please let us know as soon as possible. If you have filled in the questionnaire, the results will be stored anonymously.

9. Will the general practitioner (and pediatrician) of your child be informed of participation?

We inform your child's general practitioner when your child participates in this study. You give your consent to contact your GP by signing the informed consent sheet.

10. Is there a financial compensation when your child participates in this study?

For your participation, you will receive a reimbursement of your travel expenses, and a compensation of €20 for each blood collection.

11. Which medical-ethical committee approved this study?

The medical-ethical committee of the AMC hospital approved this study.

12. Is there anything else you would like to know?

If you would like to receive more information about this study, you may always contact the clinical research physician: J.C. Naafs, AMC, department of Endocrinology and Metabolism. Telephone: +31(0)20-566 6791, or email: j.c.naafs@amc.uva.nl

You can also contact the principal investigator: Dr A.S.P. van Trotsenburg, AMC, department of Pediatric Endocrinology. Telephone: +31(0)20-566 8844, or email: a.s.vantrotsenburg@amc.uva.nl

Would you like an independent advice on participating in this study? You can contact our independent physician: Dr A.M. Bosch, department of Pediatrics, AMC. Telephone: +31(0)20-566 5664, email: a.m.bosch@amc.uva.nl

Yours faithfully,

J.C. Naafs, research physician

C.A. Heinen, research physician

V. van Tellingen, pediatrician, fellow pediatric endocrinology

Dr A.S.P. van Trotsenburg, pediatric endocrinologist

Dr A. Boelen, head of the neonatal screening AMC

Prof E. Fliers, internist-endocrinologist