# Would you like to participate in the N-Forte study, in which we will compare two different protein fortifiers for breast milk?

**Dear parents,**
How can supplementary feeding of preterm infants be improved? We intend to investigate that in a research study in which we will compare two different protein fortifiers for breast milk. One of them is based on cow's milk and the other on human breast milk. The purpose of the study is to see whether the risk of contracting sepsis and inflammation in the intestines could be reduced if the necessary protein supplement that preterm infants need is coming from donated breast milk instead of cow's milk.

**Why do we want to carry out this study?**
A child that is born extremely premature is very sensitive and may suffer serious complications during the period of care. Medical development has made advancements and led to most of these children surviving and coping well.

The children's supplemental feeding and growth is an important challenge. The better we manage to handle this challenge, the better the child's health and development will be – both in the short and the long term. The aim is to give these small children the opportunity to grow just as well as they would have done inside the uterus, which is difficult. We know that breast milk is the best nutrition, including for premature infants. For that reason we always give the children a few milliliters of milk in the first 24 hours and then increase the amount progressively. After a few weeks, the child can be fed exclusively with breast milk and does not need any IV treatment. Primarily the mother's own pumped-out milk is given. If it is not enough, we give the child breast milk that has been donated to a breast milk bank, so that the child does not have to have any regular infant formula.

Children who have been born extremely premature have a larger nutritional need than children who are born following a regular term of pregnancy. Therefore additional fortifier (that contains protein, minerals, and vitamins) is added to the breast milk as routine practice in order for the children to grow as well as possible. The fortifier that is used at hospitals today is made from cow's milk, since there have not been any alternatives available.

A fortifier has now been developed that comes from human breast milk, i.e. breast milk that has been donated by other mothers, and there are some results from research that indicate that this "human" breast milk fortifier could have positive health effects. We now want to investigate whether the risk of infection and severe intestinal inflammation (NEC) is reduced if the children are given this fortifier instead of the traditional fortifier that is made out of cow's milk.

**Who can take part in the study?**
All children that are born in pregnancy week 22+0 to 27+6 and who do not have any serious abdominal condition, congenital disease, or malformations. The child cannot have had any protein supplement in the breast milk before entering the study.

**How is the study conducted?**
The child must be included in the study before we start administering additional fortifier in the breast milk, which most often occurs at 4-21 days of age, and it will be followed during the entire period of care during the newborn stage of life. We will also conduct a follow-up once your child has reached two years of age, and at 5.5 years of age. These follow-ups are made in connection with the regular follow-up that is made on all premature children.

The children who participate in the study are divided into two groups. In one of the groups, the children will be given a fortifier that is based on donated breast milk ($H^2MF^®$) until pregnancy week 34+0. If the child needs additional energy, a supplement of fat (ProlactCR®), which is also based on breast milk, will be given to the children in the group. In the other group, the children will be given the fortifier based on cow's milk that is the standard treatment at the department. If additional fat is needed, they will be given the supplement of fat that is the standard treatment at the department. The children will be randomized to one of the two groups so that half of the children will be given traditional fortifier and half will be given $H^2MF^®$. In that way we can compare and see whether the new fortifier is better than the current standard treatment. Apart from that, the children in both groups will be treated in exactly in the same way.

During the period of care, information about the child's supplemental nutrition, growth, treatments, and symptoms, as well as information about the mother that is important for the child's health, will be collected from the medical records and nutritional programs in order to interpret the results of the study correctly. Samples will be taken to investigate which mechanisms could be behind improved growth, intestinal function, and protection against infections. Blood samples will be taken from the child on four occasions during the period of care in connection with occasions when blood samples are being taken for other reasons. Samples of pumped-out breast milk will also be taken from the mother, as well as samples of feces and urine from the child. These samples will be frozen for future analyses. They will first be included in the care provider's biobank and then moved to biobank 516 of the Center of Pediatrics, Gynecology, and Obstetrics in Region Östergötland, Linköping. You may at any point request to have these samples destroyed without stating any reason.

Apart from the taking of samples and the study product, the children will not be treated any differently compared to children who do not participate in the study.

**Is it dangerous?**
The new dietary supplement ($H^2MF^®$) and the fat supplement (ProlactCR®) have been tested in several studies on extremely premature children before. There are no reports of any occurrences of an increase in the number of infections or other serious side effects. For safety's sake we will still check up on the children carefully.

**Can you withdraw from the study?**
Participation in the study is completely voluntary, and if you consent to participate but change your mind later on, you can withdraw your child from the study at any point in time. You do not have to tell us why. In such case, we will ask you whether we may still record information about the child's growth and health condition after the withdrawal. If you choose to terminate your child's participation in the study, it will not have any impact on your child's continued care. No remuneration will be paid for participating in the study. The patient insurance applies to your child, just as for all healthcare.

**Which questions would we like to have answered?**

- Could $H^2MF^®$ reduce the occurrence of serious diseases such as sepsis and inflammation in the intestines compared to cow's milk based protein fortifier?
- How long does it take before the child can handle having full meals of breast milk?
- How is the child's growth and development affected?
- Which factors could be behind the effect of $H^2MF^®$?
- Which other mechanisms lead to serious complications, poor growth and gastrointestinal function

**What do we do with the results?**
The results of the study will be presented in international scientific journals. If it turns out that $H^2MF^®$ reduces the risk of complications for prematurely born children, the intention is to offer this ~~protein~~ fortifier to all premature children. You will be informed of the results via letter.

**Processing of personal data**
The information will be taken from the medical records, and will only be used to answer the questions that we have specified above. They will be handled in accordance with the EU General Data Protection Regulation. The legal basis of the processing is the support of the General Data Protection Regulation for processing of data for research purposes. All data will be processed by group, and no unauthorized people will have access to it. It must be stored in a database for at least 10 years, and must be stored for longer if the scientific analyses are still ongoing. Region Östergötland, Region Uppsala, Region Västerbotten, the Västra Götaland Region and the Stockholm County Council have a joint responsibility as data controllers for all of the data in the saved data file. If needed, you can contact the data protection officer in Region Östergötland at the address Region Östergötland, Dataskyddsombud, 581 91 Linköping, or via email dataskyddsombud@regionostergotland.se. In study protocols, on sample tubes, and in the database, names and personal ID numbers will not be stated, but merely a specific code that is unique to your child. To be certain the all information is reported in a correct manner, a quality audit will be carried out. In independent person may then compare the forms that are filled out with the child's medical records. X-ray images may also be sent for an additional assessment to radiology specialist in another county council. For research purposes, researchers from other universities in Sweden and abroad may access data from the database. That also applies to the USA-based company Prolacta that produces the dietary supplement $H^2MF^®$. You have a right to gain access to the specific agreement that is required for data to be transferred to a company in the U.S. The Canadian company Interrand will also be given certain information that is needed when the help us with the randomization for which group the child should belong to (place of birth, if the child was born before pregnancy week 25+0, gender, and whether it is a twin or not). Names and personal ID numbers will not be sent to Interrand either. All people who have access to data are bound by professional secrecy. All results that are published in scientific journals will be presented at group level so that not individual child can be identified. You have the right to access the information about you that is processed in the study free of charge, and if needed have any errors amended. To ensure the quality of the results of the study, data collected in research studies cannot always be deleted upon your request, as stated in applicable legislation and regulations. Any complaints regarding the processing of personal data may be submitted to the Swedish Data Protection Authority

Should you have any further questions, or would like more information, please get in touch with one of us.

For the project,

[Name and title of supervising physician]

[Office location/clinic]
[Tel. No.]
[Email]

[Name and title of supervising nurse]

[Office location/clinic]
[Tel. No.]
[E-mail]

# Consent to participation

The signing legal guardians hereby consent to our child participating in the N-Forte study, which investigates whether the breast milk based protein supplement $H^2MF^®$ reduces the risk of serious complications and improves feeding and growth in extremely premature children compared to cow's milk based protein supplements. Our child will either be given $H^2MF^®$ or the cow's milk based protein supplement that is the standard treatment at the department.

We have read the written information. We have had the opportunity to ask questions and have had them answered to satisfaction.

We approve that an external person may review the study documents and compare with information in the medical records.

**Regarding storage of biological samples**
We have been informed and consent to biological samples (blood, breast milk, urine, and feces) being stored frozen in a biobank for future scientific use within the area that this project relates to. We can at any point request to have these samples destroyed without stating any reason.

We are aware that participation is completely **voluntary** and that we have the opportunity to withdraw from the study at any time, without having to state any reason.

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| …… | …… |
| The child's personal ID number | The child's last name and first name (if applicable) |
| …… | …… |
| Signature of legal guardian No. 1 | Signature of legal guardian No. 2 |
| …… | …… |
| Place and date | Place and date |
| …… | …… |
| Name in print letters | Name in print letters |
| …… | …….. |
| Home telephone number cell phone | Home telephone number cell phone |
| ……. | …… |
| ……. | Place and date |
| Supervising physician (signature and name in print letters) | |